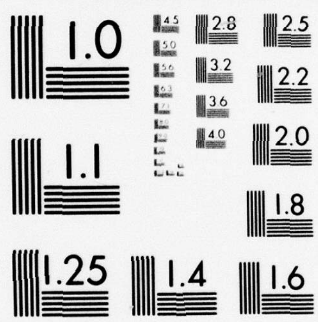
AD-A058 620   OKLAHOMA UNIV NORMAN DEPT OF CHEMISTRY   F/G 11/3
ORGANOTINS IN BIOLOGY AND THE ENVIRONMENT.(U)
JUL 78 J J ZUCKERMAN   N00014-77-C-0432

UNCLASSIFIED   TR-2   NL

1 OF 1
AD
A058620

END
DATE
FILMED
11-78
DDC



MICROCOPY RESOLUTION TEST CHART

NATIONAL BUREAU OF STANDARDS-1963-A

AD A058620

AD No. ____
DDC FILE COPY

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

(1)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER 2	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Organotins in Biology and the Environment		5. TYPE OF REPORT & PERIOD COVERED
		6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s) J. J. Zuckerman		8. CONTRACT OR GRANT NUMBER(s) N00014-77-C-0432
9. PERFORMING ORGANIZATION NAME AND ADDRESS The University of Oklahoma Department of Chemistry Norman, Oklahoma 73019		10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS NR 053-636
11. CONTROLLING OFFICE NAME AND ADDRESS Office of Naval Research Department of the Navy Arlington, Virginia 22217		12. REPORT DATE July 1, 1978
		13. NUMBER OF PAGES 19
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)		15. SECURITY CLASS. (of this report) Unclassified
		15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

LEVEL II

16. DISTRIBUTION STATEMENT (of this Report)

Approved for Public Release, Distribution Unlimited

DDC RECEIVED SEP 14 1978

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

Prepared for publication in American Chemical Society Symposium Series

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Organotin Compounds	Biomethylation of Tin
Organoelemental Environmental Chemistry	Regulation of Organotins
Biological Effects of Organotins	Environmental Transport of Organotins
Human Exposure to Organotin Compounds	Environmental Fate of Organotins

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

World consumption of tin metal is currently ca. $4x10^{11}$ lbs ($2x10^{11}$ kg) of which only 4.26% is consumed in the production of organotin compounds. Current world consumption of organotins is ca. $55x10^6$ lbs ($25x10^6$ kg) with a selling price of over $150 million, and in the USA ca. $24x10^6$ lbs ($11x10^6$ kg) whose weighted average tin content is ca. 30%. US production of organotins is rising at a rate of ca. 10% per year, with the products devoted to polyvinyl chloride polymer stabilization (66% by wt.), catalysis

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE
S/N 0102-LF-014-6601

Unclassified
SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

78 09 13 051

(21%), biocides (8%) animal health (1.2%) and miscellaneous, including export (3.3%), resulting in 2,400x10^6 lbs (1,088x10^6 kg) of organotin-containing industrial and commercial products distributed annually in the American environment. This material eventually reaches municipal incinerators, land fills and sewets, or river, ocean and estuarine water, or industrial deep-injection wells, sludge burial sites and settling ponds through disposal, leaching, weathering, evaporation, runoff, etc. This paper will review the present applications of organotin chemicals, and their economic value, their throughput to the U.S. environment by geographical area, the toxicity of selected organotins and the scientific data bearing upon the potential fate of these compounds in the environment.

BLOCK 19 (Cont.):

Chemical Degradation of Organotins
Biological Degradation of Organotins
Mercury-Tin Crossover

OFFICE OF NAVAL RESEARCH

Contract N00014-77-C-0432

Task No. NR 053-636

TECHNICAL REP[redacted]T NO. 2

TR-2

Organotins in Biology and the Environment,

by

J. J. Zuckerman

Prepared for Publication

in

American Chemical Society Symposium Series

University of Oklahoma
Department of Chemistry
Norman, OK 73019

1 Jul[redacted]78

40p.

403 980

ORGANOTINS IN BIOLOGY AND THE ENVIRONMENT

J.J. Zuckerman
Department of Chemistry
University of Oklahoma
Norman, Oklahoma 73109

ORGANOTINS IN BIOLOGY AND THE ENVIRONMENT

J.J. Zuckerman
Department of Chemistry
University of Oklahoma
Norman, Oklahoma 73019

Tin in the form of the metal and its alloys has greatly affected the course of human history (1) from the Bronze Age of antiquity to the Tin Drum (2) of today. Implements of tin alloy dating from about 3000 BC have been found at Ur, and tin is mentioned in the Bible (3). Tinplate, tinware, pewter, bronze and brass, solder, bearing, bell and type metal, and toothpaste tubes are all examples of current use, and we are in contact with tin all through our lives, from our tinplated babyfood cans through stannous fluoride-containing toothpastes and the dental amalgam in our teeth to the tinplate on our casket linings.

Introduction

Tin chemistry has been the subject of much research effort in the last few years. Elemental tin possesses two allotropic modifications, forms a wide variety of intermetallic phases and inorganic compounds, and has an extensive organometallic chemistry. Basic studies in organotin chemistry are stimulated by the obvious close analogies and interesting differences with the even more extensive chemistry of the cognate organosilicon compounds, and with the vast body of organic chemistry, and also by the success with which a large number of modern physical techniques can be applied to organotin compounds. Tin possesses, for example, two spin of one half nuclides, tin-117 and tin-119, which have become important in nuclear magnetic resonance studies of tin-proton and tin-carbon coupling constants as well as more recently in the tin chemical shifts themselves (4, 5); ten stable isotopes (the largest number for any element), which allows easy identification of tin-bearing fragments in the mass spectrometer (6); the isomeric nuclide tin-119m, which with iron-57 is one of the two easiest to observe nuclear gamma ray (Mössbauer) resonances (7); and easily assignable tin-carbon stretching frequencies in the infrared and Raman (8). Useful chemical information is routinely obtained from this battery of powerful techniques in combination with others such as X-ray and UV photoelectron spectroscopy (9). X-ray, neutron and electron diffraction techniques have been applied to solve the structures of nearly 600 inorganic and organotin compositions (10).

Tin and its compounds are found in two stable oxidation states, tin(II) and tin(IV), and assume a wide variety of structural types from the allotropic modifications of the element and its alloys to compounds in which the tin atom is two- to eight- coordinated in neutral, cationic and anionic species with intra- and intermolecular association to give dimers and higher oligomers and one-, two- and three-dimensional polymeric arrays. Tin alloys and intermetallic phases exhibit superconductivity (Nb_3Sn) (11), ferromagnetism (Cu_2MnSn) (12), and semiconductivity ($ZnSnAs_2$) (13). Polyatomic anions, the Zintl phases, have been characterized to Sn_9^{4-} (14). Organotin complex ions can be cationic or anionic, and both can exist in one crystal as in the terpyridyl complex of dimethyltin dichloride which contains both a tin-bearing anion and cation (15). Associated polymers can be one- $[(CH_3)_3SnCN]$ (16), two- $[(CH_3)_2SnF_2]$ (17, 18) and helical, three-dimensional $[(CH_3)_2Sn]_2NCN$ (19). Organotin compounds can take two- $[(h^5\text{-}C_5H_5)_2Sn]$ (20), three- $[\{[(CH_3)_3Si]_2CH\}_2Sn]_2$ (21), four- $[R_4Sn]$ (10), five- $[(CH_3)_3SnCl \cdot C_5H_5N$(trigonal bipyramidal) (22) or $[(C_6H_5)_3Sn]_3SnNO_3$(square pyramidal) (23)], six- $[[(CH_3)_2SnCl_4]^{2-}$ (24)] and seven-$[CH_3Sn(NO_3)_3$ (25)], coordinated forms. The structure of tin(II) derivatives show the effect of the stereochemically active lone pair of electrons present in this oxidation state as a space in the coordination sphere (26).

The Organotin Literature

The literature of organotin compounds is now so vast that some guidance for the interested reader is in order. Two important single-author works are available (27, 28) along with a three-volume edited work (29), but these all date from 1970-1971. Extensive reviews of the formation and cleavage of the bonds of tin to carbon (30), the halogens and the halogenoids (31) were published in 1968 and 1972, respectively. A more recent work brings together the papers delivered at a 1976 Symposium on chemistry and applications (32). The structural data for over 250 organotin compounds have been reviewed in 1978 (10). However, the definitive compilation of information on organotin compounds is to be found in the Gmelin Handbuch der Anorganischen Chemie. The first four volumes covering R_4Sn (1975) (33), R_3SnR'(1975) (34), $R_2SnR'_2$, $R_2SnR'R''$, $RR'SnR''R'''$, heterocycles and spiranes (1976) (35) and organotin hydrides (1976) (36) have been published thus far. The publishing program under the authorship of H. Schumann and I. Schumann will eventually include all compounds in which tin is bound to carbon. In the meantime, readers can keep abreast of the literature using the Annual

Surveys for each year since 1964 published in various forms associated with the Journal of Organometallic Chemistry (37-48), and using the yearly volumes on Organometallic Chemistry in the Specialist Periodical Reports of the Chemical Society of London (49-55). The manufacture and use of selected alkyltin compounds have been reviewed in 1976 in a U.S. Government report (56).

This review paper is based upon two U.S. Government commissioned reports: Criteria for a recommended standard... Occupational Exposure to Organotin Compounds, from the National Institute for Occupational Safety and Health (NIOSH), November, 1976, under the editorship of E.S. Flowers (57). The Stanford Research Institute staff developed the basic information for this report. The second report, Assessment of the Need for, the Character of, and the Impact Resulting from Limitations on Selected Organotins. Phase I. Assessment of the Need for Limitations on Organotins, from the Environmental Protection Agency (EPA), Office of Toxic Substances (OTS), July, 1977, under the editorship of R.R. Wilkinson and I.C. Smith of the Midwest Research Institute whose staff developed the basic information and wrote the report (58). The EPA-OTS project officer, P. Hilgard, has kindly given permission to quote from this preliminary draft report before its release by the agency. The author was a consultant in the preparation of these documents for the government agencies. In addition, much useful information was shared by the participants at a Workshop on Organotins organized by M.L. Good in February, 1978 under the sponsorship of the U.S. Office of Naval Research (59).

Historical

Until recently it was generally believed that organometallic compounds, which are usually air- and moisture sensitive, were purely artificial and synthetic, and a text published in 1964 stated, "The situation regarding applications may be summed up by saying that there are no organometallic compounds in nature, there seemingly being no mechanism for their formation..." (60). However, it had been recognized early in the 19th century that cases of arsenic poisoning could be traced to the use of domestic wallpapers containing Scheele's green (copper hydrogen arsenite) and Paris or Schweinfürter's green (cupric aceto-arsenite) dyes. Gmelin in 1839 described a garlic odor in rooms in which the symptoms developed (61), and it was demonstrated in 1872 that moldy green wallpaper liberated an arsenic-containing gas (62), but it was the definitive experiments of Gosio in 1897 that established this "Gosio-gas" as an organometallic compound, an alkylarsine. It remained for Challenger to identify the garlic odor component as $(CH_3)_3As$ in 1933 (64), and to coin the term "biological methylation" for its production.

Despite continued publication by Challenger (65, 66) on the subject of biomethylation, the crystal structure of the vitamin B-12 (cobalamin) coenzyme 5,6-dimethylbenzimidazolyl-cobamide in 1961, which showed the presence of a cobalt-carbon bond (67), was viewed as a curiosity at the time. Meanwhile, the tragic deaths of residents at Minimata Bay, Japan became recognized as owing to ingestion of methylmercury derivatives formed from the inorganic mercury effluent of a nearby factory (68), and in 1969 it was demonstrated that living organisms have the ability to methylate mercury (69).

Now the methylation of metals and metalloids in the environment is recognized as an important route in their mobilization. The role played by microorganisms in the biochemical transformations whereby elements are methylated is being elucidated, and some of the molecular mechanisms are beginning to be grasped (68, 70-78).

Organotins in the Environment

Production. The annual world consumption of tin in all forms was ca. 200,000 tons (ca. 400 million lbs. or ca. 180 million kg) in 1976, but of this total only ca. 55 million lbs. (ca. 25 million kg) was in the form of organotin compounds. These compounds were composed of a weighted average of ca. 31% tin, and so only ca. 17 million lbs. (ca. 7.7 million kg) of tin or 4.26% of the annual world production of tin is produced in this form. The U.S. consumption of organotin compounds was ca. 24 million lbs. (ca. 11 million kg) in 1976. Midwest Research Institute forcasts call for an 11-13% annual growth for the next ten years (58).

Table I lists the estimated U.S. production of selected aklyltin compounds for the period 1965 to 1976. The total weight of these organotin compounds produced in this country during this 12-year period is ca. 185 million lbs. (ca. 84 million kg).

Use. Over two-thirds of the total world annual production of organotin compounds is devoted to the thermal stabilization of polyvinyl chloride (PVC) plastics (79). The mechanism of PVC breakdown is not entirely clear at present, but the most commonly accepted view is that the decomposition is related to a dehydrochlorination reaction at an allylic or tertiary chlorine site with the formation of a double bond. As the degradation continues, conjugated unsaturated systems are formed which diminish optical clarity and lend undesirable color to the plastic. As little as 0.1% decomposition can lead to blackening. The dehydrochlorination process is autocatalytic, and in the processing of unplasticized PVC resin, temperatures well in excess of those required for the initiation of the degradative process are attained (>200°C). The mode of action of the effective stabilizers is not completely known, but probably

TABLE I. Estimated Annual U.S. Production of Selected Alkyltin Compounds (Million Pounds Per Year)

Year	Bu IOMA	Me IOMA	Bu LM	Bu Maleate	Oct. IOMA	Oct. Maleate	Mixed metals	DBTDL	DBTH	TBTO®	TBTF	Total
1965	2.3	-	1.0	0.22	-	-	-	0.6	-	0.86	-	5.0
1966	4.6	-	1.0	0.22	-	-	-	0.9	-	0.93	-	7.6
1967	4.9	-	0.9	0.48	-	-	-	1.2	-	1.20	-	8.7
1968	6.2	-	0.9	0.52	0.16	0.02	-	1.6	-	1.32	-	10.7
1969	7.1	-	0.9	0.57	0.20	0.03	-	2.0	-	1.50	-	12.3
1970	8.3	0.7	1.1	0.59	0.32	0.05	-	2.4	-	1.67	0.01	15.2
1971	8.2	1.4	1.1	0.62	0.37	0.06	-	2.8	-	1.97	0.02	16.6
1972	10.5	2.9	1.3	0.26	0.56	0.08	-	2.5	0.8	1.61	0.05	20.6
1973	10.1	4.0	1.3	0.22	0.62	0.08	0.8	3.0	0.9	1.09	0.08	23.0
1974	9.3	4.5	1.3	0.21	0.37	0.07	0.5	3.5	1.1	2.07	0.12	23.0
1975	7.0	4.0	1.0	0.20	0.50	0.07	0.4	3.0	0.9	1.40	0.30	18.8
1976	9.0	4.5	1.1	0.22	0.60	0.07	0.5	4.3	1.0	2.30	0.50	23.5
1981	13.0 to 14.5	6.5 to 8.0	2.0	0.33	0.90	0.20	0.0	6.0	1.9	4.6	1.0	36.5 to 39.5
1986	15.0 to 18.5	8.0 to 10.0	3.0	0.45	1.20	0.30	0.0	8.0	2.5	9.0	2.0	49.5 to 55.0
Total (1965 - 1976)	87.5	22.0	12.9	4.33	3.70	0.53	2.2	27.8	4.7	18.81	1.08	185.5

Note: Bu IOMA = Butyltin isoctylmercaptoacetate plus blends
Me IOMA = Methyltin isooctylmercaptoacetate plus blends
Bu LM = Dibutyltin-bis(laurylmercaptide)
Bu Maleate = Dibutyltin alkylmaleate esters
Oct. IOMA = Di(n-octyl)tin-S,S'-bis(isooctylmercaptoacetate)
Oct. Maleate = Di(n-octyl)tin maleate polymers

DBTDL = Dibutyltin dilaurate
DBTH = Dibutyltin bis-(2 ethyl hexoate)
TBTO = Bis(tributyltin)oxide
TBTF = Tributyltin fluoride

taken from refs. 56 and 58.

involves exchange of allylic chloride atoms with the anionic portion of the organotin compound, and the absorption of liberated hydrogen chloride to release compounds which can add across the unsaturated centers.

Typical stabilizers are dialkyltin compounds containing thio or ester groups. The original patents issued to V. Yngve of Carbide and Carbon Chemicals Corporation in 1936 and based upon the discoveries of W.M. Quattlebaum, were for the application of dibutyl compounds, but dioctyltins are now in use as well. The addition of small amounts of monoalkyltins has a synergistic effect. The groups attached to the alkyltin moieties include the laurate and maleate, and several mercapto derivatives derived from octyl and isooctyl esters of thioglycolic acid. In the last decade there has been a shift of emphasis from flexible to rigid PVC products, the latter requiring much higher processing temperatures. The need for better stabilization has thus become more acute if PVC with the desired colorlessness and transparency for packaging films, piping, bottles and siding is to be produced. Dimethyltins, because of their extremely great thermal stability allow the use of high working temperatures and high working speeds, and their application may have economic advantages (80).

Organotin compounds are also used as catalysts in the production of rigid polyurethane foam and for the room temperature vulcanization of silicone elastomers. Biocidal and anthelmintic applications will be discussed separately, below.

Table II lists the estimated annual U.S. consumption of selected alkyltin compounds in the four use areas discussed above, plus miscellaneous uses and exports. The capital value of the organotin chemicals used in PVC heat stabilization was $50 million in 1976, with the total capital value for all uses estimated at $67.7 million.

Final Disposal. Consumption of commercial organotin chemicals is given by sector for 1976 in Figure 1. The route for each use area from introduction through consumption and release to the environment is given on a weight basis.

Industrial disposal options include evaporation, bacterial degradation settling ponds, sludge burial within property lines, use of contract disposal services, deep-well injection, hydrolysis and precipitation methods, discharge to municipal treatment plants, NPDES (National Pollution Discharge Elimination System) permits, and potential reclamation or recovery and recycling techniques. Midwest Research Institute estimates that only 0.5% of production, or *ca.* 0.12 million lbs. (*ca.* 0.054 million kg) are lost to the environment by these routes at the source of manufacture.

Consumer disposal options include municipal sewers, municipal waste collection which reaches landfill or incinerator, normal weathering of the consumer product, and

TABLE II. Estimated Annual U.S. Consumption of Selected Alkyltin Compounds By Use Area (Quantities in Million Pounds)

Year	PVC heat stabilizer	Catalysts	Biocidal	Anthelmintic	Miscellaneous excluding exports	Total
1965	3.5	0.5	0.50	0.15	0.36	5.0
1966	5.8	0.7	0.60	0.16	0.33	7.6
1967	6.3	1.0	0.70	0.17	0.50	8.7
1968	7.8	1.4	0.80	0.18	0.52	10.7
1969	8.8	1.8	0.90	0.19	0.60	12.3
1970	11.1	2.2	1.1	0.21	0.57	15.2
1971	11.8	2.6	1.3	0.22	0.67	16.6
1972	15.6	3.1	1.5	0.23	0.16	20.6
1973	17.1	3.7	1.7	0.24	0.26	23.0
1974	16.2	4.4	2.0	0.24	0.19	23.0
1975	13.2	3.7	1.5	0.20	0.20	18.8
1976	16.0	5.0	2.0	0.27	0.20	23.5
1981	23 to 26	7.5	5.0	0.35	0.60	36.5 to 39.5
1986	28 to 33.5	10.0	10.0	0.50	1.0	50 to 55
Total (1965-1976)	133.2	30.1	14.6	2.5	4.6	Grand total (1965-1976) 185.0

taken from refs. 56 and 58.

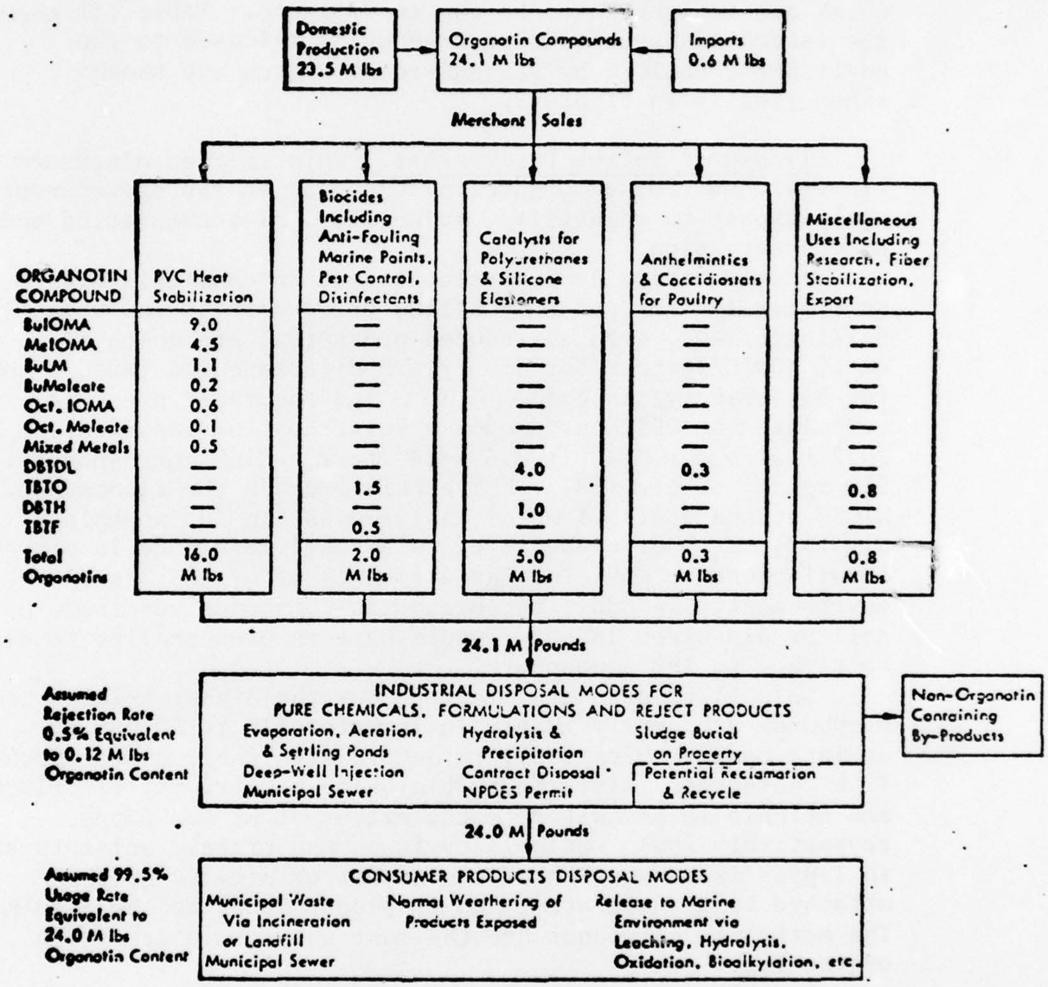


Figure 1. Organotin chemicals consumption in 1976 (58).

release to the marine environment through leaching. The 24 million lbs. (ca. 11 million kg) of organotin compounds annually manufactured in the U.S. will eventually reach the environment in some form. The 24 million lbs. of organotins are formulated or compounded into perhaps 2,400 million lbs. (ca. 1,100 million kg) of industrial and commercial products which are redistributed to the environment. Table III shows the estimated quantities of organotins released to the environment in 1976 by various routes which are shown schematically in Figure 2.

Transport in the Environment. This section discusses the transfer behavior of organotin compounds in the environment with respect to volatility, solubility, bioaccumulation and bioconcentration.

The industrially important organotin chemicals are generally liquids and waxy solids or powders of low volatility. Boiling points, even at reduced pressures, are quite high, e.g., 400°C/10 torr for dibutyltin dilaurate and 180°C/2 torr for bis(tributyltin)oxide (TBTO®), and the vapor pressure calculated at 25°C based upon a molar heat of vaporization of 20.2 Kcal/m for TBTO® is 1.6 x 10^{-3}torr, which corresponds to 510 mgm/m^3 of air (58). While this exceeds the recommended NIOSH standard of 0.1 mg/m^3 analyzed as tin for workplace air (57), a vapor pressure of this small magnitude is probably insufficient to mobilize large amounts of organotins in the environment. In addition, organotin compounds adsorbed in soil or dissolved in water would have an even smaller tendency to escape to the atmosphere.

Solubility data are limited, but the higher trialkyltin compounds are nearly insoluble in water [10 to 50 ppm at ambient temperatures (98)] in accord with their hydrocarbon-like character. Bis(tributyltin)oxide and tributyltin fluoride are soluble in sea water to the extent of 51 and 6 ppm, respectively (99). Solubility in common organic solvents and in lipids is a function of the number of organic groups attached to the tin atom, and is proportional to their bulk. The methyltin compounds are the most water soluble of the organotins.

Leaching from soils has been investigated using carbon-14 labeled compounds. Even hot methanol treatment fails to remove triphenyltin acetate completely, and neither this fungicide nor any of its abiotic transformation products are leached over a six-week period. Over 70% of the activity was found in the upper 4 cm of the packed soil column used (93).

Neutron activation analyses have been carried out on unspecified dried water plant material, sediments and fish samples taken from a Bavarian river both up- and downstream from a factory producing tin compounds and using a chlorine alkali-electrolysis process involving mercury. The results

TABLE III
Estimated Quantities of Organotins
Released to the Environment for 1976
Various Routes

Organotin bearing product	Organotin content (lb)	In use (lb)	Discarded (lb)	Environmental route and quantity (lb)	
Plastics, PVC, PU, silicones	21×10^6	16×10^6	5×10^6	0.5×10^6 4.5×10^6	incinerated landfill
Antifouling paints	0.8×10^6	0.4×10^6	0.4×10^6	0.4×10^6	ocean and estuarine water sediments
Industrial and consumer slimicides and other biocides	0.7×10^6	0.5×10^6	0.2×10^6	0.2×10^6	rivers and estuaries, sediments
Latex paints	0.5×10^6	0.475×10^6	0.025×10^6	2.5×10^3	dumped or leaked
All other applications including export	1.1×10^6	0.77×10^6	0.34×10^6	0.34×10^6	landfill

taken from ref. 58.

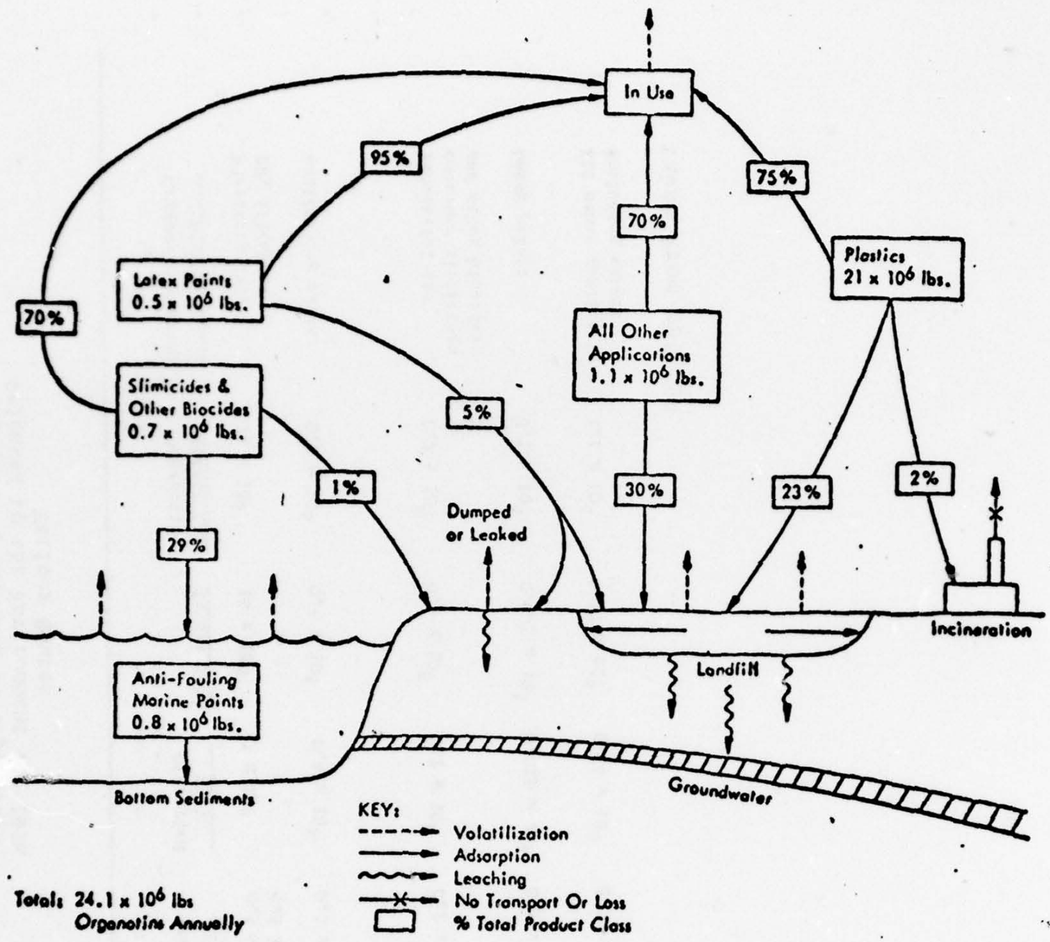


Figure 2. Organotin environmental exposure (58).

for the sediments were 0.9 and 112 ppm Hg and 16.6 and 69 ppm Sn up- and downstream, respectively, on a dry weight basis. The bioconcentration in the water plants is shown in Table IV.

TABLE IV

Element	Origin	Water plant samples (dry weight basis, ppm) Upstream	Downstream	Apparent magnification factor
Sn	Alz	13	3,100	240
Sn	Alzkanal	14	2,370	170
Hg	Alz	1.3	230	180
Hg	Alzkanal	0.6	295	500

Both tin and mercury were found in fish meat and livers at low (ca. 1 ppm) concentration. The species present were not identified (100).

Environmental Fate. Once in the environment the organotin compounds are leached from consumer products by environmental forces such as heat, light, and the action of water, oxygen, ozone, carbon dioxide and microorganisms. It has been estimated that ca. 5.0 million lbs. (ca. 2.3 million kg) of organotins in PVC are disposed of annually by landfill and incineration and that ca. 1.0 million lbs. (ca. 0.45 million kg) of biocides are released annually to the environment via municipal sewers, surface waterways, harbors and the oceans (58). The human and ecological significance of these inputs to the environment depend upon the persistence of the organotins, their mobility between media, and the available pathways to susceptible populations of the organotins themselves and their degradation products.

Organotin compounds are subject to both chemical and biological degradation.

Chemical Degradation. Carbon-tin bonds are thermally stable below 200°C, but are capable of polarization by attacking species in either direction. Organotin compounds are thus susceptible to attack at the carbon-tin bond by both nucleophilic and electrophilic reagents, leading to hydrolysis, solvolysis, acidic and basic reactions, halogenation, etc. (27-32). The results of scattered kinetic studies in the literature on the cleavage of alkyl-, unsaturated and aromatic groups from tin by hydrogen chloride and metal halides, CrO_3 in glacial acetic acid, alkali metal hydroxides in water and aqueous perchloric acid are displayed in Table V. Homolytic reactions involving organotin compounds with free radicals have been recently reviewed (81). All these studies were of course carried out in homogeneous media where it is found that the cleavage of the organic groups from tin is always first-order in each reactant. In polar solvents there is probably initial solvation of the tin compound, followed by electrophilic attack (S_E2) on a carbon atom adjacent to tin. With alkali there can be nucleophilic attack (S_N2) on the tin atom with expulsion of a carbanion. Although some organotin compounds will undergo unimolecular photolysis or thermolysis under mild conditions, free organotin radicals are usually formed by bimolecular reaction with some other radical. The attack can be at the tin-carbon bond, or elsewhere in the molecule (81). From these and other studies (90, 91) it can be generalized that the progressive cleavage of organic groups from tin is dependent upon the type of organotin compound, the number of organic substituents, and the solvolytic conditions. The relative ease of removal of aliphatic groups decreases with increasing size of the group, but unsaturated and aromatic groups are cleaved more rapidly. For the series:

$$R_4Sn \xrightarrow{k_4} R_3SnX \xrightarrow{k_3} R_2SnX_2 \xrightarrow{k_2} RSnX_3 \xrightarrow{k_1} SnX_4 \qquad (1)$$

the reaction rates are $k_4 >> k_3 >> k_2 \approx k_1$. Laboratory solvolytic reactions generally represent extreme pH conditions ($pH < 1$ or > 14). Half-lives range from one minute to 115 days, depending upon these conditions and specific organotin compounds studied. The solvolysis of tetraalkyltins carried out under less severe conditions (pH = 4 to 10), may be several orders of magnitude slower (10^{-4} to 10^{-6}), and these tetraalkyltins will react 10 to 100 times faster than trialkyltins. The solvolysis rates of dialkyltins again approach those of the tetraalkyltins.

The inorganic anionic groups in the organotin compounds react with moisture and air to cleave from tin in an hydrolysis-oxidation to give stannols and oxides. In this way successive reaction of both parts of the molecule leads eventually to completely inorganic hydrated tin oxides.

Biological Degradation. Microbial action is also significant. Rate constants and half-lives have been estimated from laboratory studies in water and are listed in Table VI (92). Other studies have utilized carbon-14 labeled triphenyltin acetate in which the release of $^{14}CO_2$ from soil samples was monitored in the dark, and a half-life of 140 days determined for concentrations of 5 and 10 ppm (93). Using UV irradiation for 10 minutes to one hour, degradation into di- and monophenyltin compounds was observed for the acetate (93, 94) and hydroxide (94). The degradation of the chloride on sugar beet leaves in a green house environment has been investigated using a tin-113

TABLE V (cont'd). Solvolysis of Organotins.

C. Alkyl-aryltins						
$(CH_3)_3Sn\text{-}\phi + HClO_4 \longrightarrow (CH_3)_3Sn\text{-}OH + C_6H_6$	0.77 and 0.86	50	H_2O/CH_3OH (40%/60%) $[O.T.] = 4.8 \times 10^{-4}$ M	$k_1 = 300 \times 10^{-3}\ min^{-1}$ $k_1 = 228 \times 10^{-3}\ min^{-1}$	2.3 min 3.0 min	86
$(CH_3)_3Sn\text{-}\phi + NaOH \longrightarrow (CH_3)_3SnOH + C_6H_6$	> 14	50	H_2O/CH_3OH (40%/60%) $[OH^-] = 1$ M $[O.T.] = 4.8 \times 10^{-4}$ M	$k_1 = 12.1 \times 10^{-3}\ min^{-1}$	57 min	87
$(CH_3)_3SnCH_2\phi + KOH \longrightarrow (CH_3)_3SnOH + CH_3\phi$	12	75	H_2O/DMSO (14%/86%) $[OH^-] = 10^{-2}$ M $[O.T.] = 1 \times 10^{-4}$ M	$k_1 = 566 \times 10^{-3}\ min^{-1}$	1.2 min	88

a/ [O.T.] = Organotin, moles/l.

TABLE V. Solvolysis of Organotins

Reaction	pH	Temperature (°C)	Reaction media	Reaction rate	Half-life	Ref
A. Alkyltin, saturated						
$(C_2H_5)_4Sn + HgCl_2 \xrightarrow[H_2O]{CH_3OH} (C_2H_5)_3Sn + C_2H_5HgCl$	-	25	H_2O/CH_3OH (30%/70%) $X_{CH_3OH} = 0.51$ [O.T.] = 1.25×10^{-3} M $[HgCl_2] = 1.00 \times 10^{-3}$ M	$k_2 = 5.59$ ℓ $mole^{-1}$ min^{-1}	143 min	81
$(C_2H_5)_4Sn + HCl \xrightarrow{C_6H_6} (C_2H_5)_3SnCl + C_2H_6$	2	20	HCl in C_6H_6 [O.T.] = 2.18×10^{-1} M	$k_2 = 7.5 \times 10^{-4}$ ℓ $mole^{-1}$ sec^{-1}	350 sec	82
$(C_4H_9)_4Sn + CrO_3 \xrightarrow{HOAc} (C_4H_9)_3SnOAc + C_4H_8$	<0	20	CrO_3 in glacial HOAc $[CrO_3] = 3 \times 10^{-4}$ M [O.T.] = 1×10^{-3} M	$k_2 = 2.84$ ℓ $mole^{-1}$ sec^{-1}	350 sec	82, 83
B. Alkyltin, unsaturated						
$(CH_3)_3SnCH_2CH{=}CH_2 + HCl \xrightarrow[96\%]{CH_3OH} (CH_3)_3SnCl + CH_2{=}CH{-}CH_3$	2-4	25	H_2O/CH_3OH (4%/96%) [HCl] = 10^{-2} - 10^{-4} M [O.T.] = 5×10^{-4} M	$k_2 = 0.475$ ℓ $mole^{-1}$ sec^{-1}	1.17 hr	84
$(CH_3)_3SnCH_2{-}C(CH_3){=}CH_2 + HCl \longrightarrow (CH_3)_3SnCl + CH_3{-}C(CH_3){=}CH_2$	2-4	25	H_2O/CH_3OH (4%/96%) [HCl] = 10^{-2} - 10^{-4} M [O.T.] = 5×10^{-4} M	$k_2 = 24.8$ ℓ $mole^{-1}$ sec^{-1}	80.7 sec	84
$(C_2H_5)_3SnCH_2CH{=}CH\phi + NaOH \longrightarrow (C_2H_5)_3SnOH + \phi CH_2CH{=}CH_2 + \phi CH{=}CH{-}CH_3$	12.7	25-40	H_2O/CH_3OH (40%/60%) [O.T.] = 1×10^{-4} M	k_2 varies from 9.2×10^{-6} (25°C) to 46.0×10^{-6} ℓ $mole^{-1}$ sec^{-1} (40°C)	23 to 115 days	85

Table continues on next page

TABLE VI

Rate Constants and Half-Lives at 20°C for Selected Organotin Compounds of Potential Commercial Interest in Distilled Water (92)

Compound	Concentration range (mg/ℓ)	Rate constants (day^{-1})	Half-life (days)
TBTO®	2-4	0.038	18.2
Tributyltin methacrylate	0.2-0.4	0.035	19.8
Bu IOMA	1.5-3	0.607	1.14
Diethyltin dicaprylate	1-2	0.311	2.22
Dioctyltin bis-(isobutylmaleate)	3-4	0.213	3.25

label. The pattern of conversion to inorganic tin can be seen in Table VII. No measurable amounts of acitivty were found in

TABLE VII

Degradation of Triphenyltin Chloride on Sugar Beet Leaves in a Greenhouse Environment (95)

		Percentage of total radioactivity applied				
Experiment No.	Days after application	ϕ_3Sn^+	ϕ_2Sn^{+2}	ϕSn^{+3}	Sn^{+4}	Not extracted[a/]
1	0	100	-	-	-	-
2	3	86	10	<1	3	1
3	7	67	13	1	16	3
4	14	47	9	1	38	5
5	21	33	7	1	55	4
6	28	26	4	1	60	9
7	35	22	2	1	65	10
8	42	19	<2	1	67	12

a/ Hydrolyzed and aged ϕSn^{+3} and Sn^{+4}.

the stems of the plants or in the sugar beets during the 42 days of the experiments. All the activity could be accounted for. The apparent half-life was initially two weeks, but the degradation rate slowed after this (95). Tributyltin fluoride, which is used as an antifouling agent, hydrolyzes very rapidly in low concentration in sea water to give the chloride and oxide. Carbon dioxide can react with the oxide to form the carbonate. Ultimately, through the action of sunlight and oxygen, hydrated inorganic tin oxide is formed in a stepwise degradation sequence (96). While the various results from separate studies disagree in their details, it is clear that the conversion to less alkylated and arylated tins proceeds sequentially to produce hydrated inorganic tin oxides with half-lives ranging from seconds to days, depending upon the conditions.

Tests on clay-based soils indicates that organotin compounds disposed of in landfills will be immobilized. Under simulated soil leaching conditions, using carbon-14 labeled compounds, high Freundlich isotherms were determined for different soil types suggesting retention of 94.9 to 99.2% of the organotin compounds at their original site of placement. No more than 0.2% of the test triorganotin compounds were found in the leachates (97).

Biomethylation of Inorganic Tin. Microbial aerobes can solubilize HgS (solubility product 10^{-53}*M*) in the form of Hg^{2+} by oxidizing the sulfide through sulfite to sulfate (101), whence Hg^{2+} can be reduced to mercury metal by bacterial enzymatic action and liberated to the atmosphere from the hydrosphere because of the considerable vapor pressure of Hg°. An alternative detoxification mechanism converts Hg^{2+} to methyl- and dimethylmercury (102, 103), the latter of which is volatile and lost to the atmosphere. The synthesis of dimethylmercury is *ca.* 6000 times slower than the synthesis of methylmercury (104).

The chemistry, biochemistry and toxicology of tin is somewhat different, however, beginning with the non-volatility of the metal itself. Microbial methylation of inorganic tin has been claimed for a *Pseudomonas* species isolated from Chesapeake Bay in a widely quoted conference report in 1974 (105). In the laboratory, tin(II) under nitrogen at pH 1 in 1.0 *M* aqueous salt solution in the presence of methylcobalamin at *ca.* 5 x 10^{-4}*M* with a single electron oxidizing agent such as iron(III) chloride or aquocobalamin is methylated during one day at 20°C. Carbon-14 labeled methylcobalamin showed no organic products resulting from the cleavage of the cobalt-carbon bond. Tin(IV) did not participate. The rate of the methylation reaction was measured in 10- to 100-fold excess of tin(II) as $1.4M^{-1}s^{-1}$ which is dependent upon the pH. In aqueous tartrate buffer at pH as high as 5, carbon-cobalt bond cleavage was found to occur (106). The mechanism for the methylation has been discussed in terms of the reduction potentials for the various species involved (76).

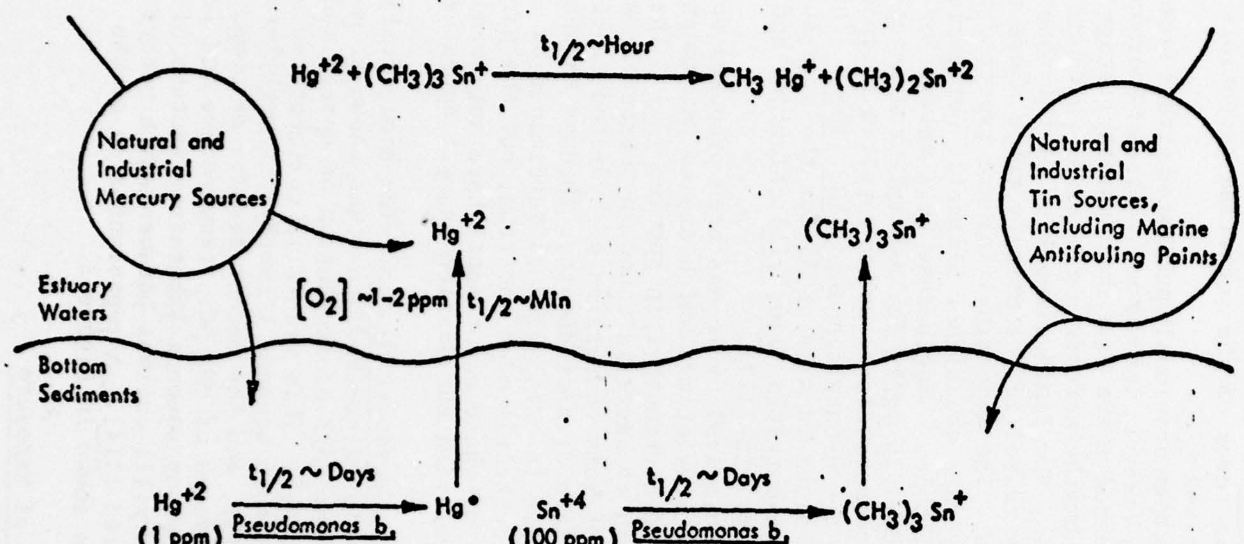
No evidence has been previously published either from the laboratory or Nature, however, for the methylation of inorganic tin by the species discussed above past the monomethyl stage (105, 106). Unlike the monomethylmercury derivatives which are deadly poisonous neurotoxins, the lipid solubility of the monomethyltins is too low, and they travel in the urinary tract where they can cause renal problems. The monomethyltins are expected to be more toxic generally than the higher aliphatic derivatives, but no data are yet available. Single-dose LD_{50} values for mice are in the range 1400-1520 mg/kg for n-butyl- and n-octyl tris(2-ethylhexylmercaptoacetate) and n-butyltin trichloride, and is >6,000 mg/kg for n-butyltin acid (107, 108). This compares with LD_{50} values in mice of 35 for the di-n-butyl-(109), and 117 for the tri-n-butyltin (110, 111) chlorides and 6,000 mg/kg for tetra-n-butyltin (117).

A complex biogeological cycle has been proposed for tin involving successive alkylations which are as yet undemonstrated to give di-, tri- and tetramethyltin species (76). The Pseudomonas b. strain of bacteria found in Chesapeake Bay gave evidence, however, of some conversion of hydrated tin(IV) chloride to dimethyltin dichloride after 10 days incubation at ambient temperature in >2% oxygen as determined by comparison with an authentic mass spectrum, but the parameters for reproducability of these experiments have not been worked out (105), and no refereed publication has yet appeared.

The Mercury-Tin Crossover System. The biologically produced methyltin species described above was shown to methylate Hg(II) ion after eight days of incubation as determined by mass spectrometry (105). This result is corroborated by an earlier observation that aqueous trimethyltin methylated mercury(II) ion (113), and the recent results of computer studies in which changes of pH, pCl, temperature and ionic strength were imposed on aqueous laboratory systems of pairs of tin(IV) and mercury(II) cations between which methyl groups were being transferred (114). A representation of the crossover scheme is shown in Figure 3.

Biological Effects of Exposure

Metabolism of Organotin Compounds. Tetraethyltin was shown to undergo destannylation in vivo by a rat liver microsomal enzyme system successively to the tri-(115), di-(116) and monoethyl (117) derivatives. Other trialkyltin compounds behave similarly (116, 118). The total metabolic yield was <10%, however. More recently, it was demonstrated that a



Adapted from: F.E. Brinckman and W.P. Iverson, 1975

Figure 3. Bimetallic mercury-tin "crossover" scheme (58).

cytochrome P-450 monooxygenase enzyme and not a lipid peroxidase system was responsible for metabolism, and that carbon hydroxylation occurred on the butyl groups of carbon-14 labeled tributyltin acetate at the α- to γ-positions (119, 120). The products were compared with authentic samples synthesized for the purpose, and similar *in vivo* reactions were shown to occur in mice (120). The primary hydroxylated metabolic products of tetrabutyltin-1-^{14}C were rapidly destannylated to the tributyltin derivatives (120). Successive *in vivo* destannylation of tricyclohexyltin hydroxide ultimately yields inorganic tin(IV) (118), but more recent findings reveal that a cytochrome P-450 dependent monooxygenase enzyme-induced hydroxylation is a major metabolic reaction yielding 2-, 3- and 4-hydroxycyclohexyltin derivatives as metabolites (121, 122). Tin-113 labeled triphenyltin acetate is apparently not hydroxylated *in vitro*, but rats can metabolize this organotin to give substantial amounts of di- and monophenyl-derivatives (120).

Exposure to Organotin Compounds. The toxic response of the common guppy, *Lebistes reticulatus*, to tributyltin compounds has been determined. Guppies appear to be fatally sensitive to less than 1 ppm of bis(tributyltin)oxide (123). Tests on *Lebistes* using triphenyltin hydroxide show that 0.1 ppm killed 43% after 19 hour exposure and 100% after 48 hours (124). Triphenyltin acetate used to control the operculate snail *Lanistes ovum* also had deleterious effects upon germinating swamp rice, and several other tributyltins have been tested for their phytotoxicities as well as their molluscicidal activity (125). Tributyl- and triphenyltins are also effective against algae and barnacles (126, 127, 128). Tripropyl-, butyl-, and triphenyltin derivatives are toxic to mollusks. Concentrations of trialkyltins of *ca.* 1.0 ppm are lethal to *Australorbis* (or *Biompharlaria*) *glabrata* (129). Values for bis(tributyltin) oxide range between 0.05 and 0.10 ppm (125). Maximum toxicity to all types of life occurs with the triorganotin derivatives, but there are important variations within this class of compounds. Mammaliam toxicity reaches a maximum with the ethyl group and falls off rapidly with increased chain length as shown in Table VIII. Insects, on the other hand, are most affected by the trimethyltins, and the tri-n-propyl and butyltins are most effective against fungi and bacteria (137, 137a, 138, 139). The tributyl and triphenyltin compounds, which are not particularly hazardous to mammals (LD_{50} 100-200 mg/kg), are very effective biocides against marine fouling organisms, for example, algae, barnacles, shrimp and tubeworms at levels of 0.1 to 1.0 ppm (125). The comparative bactericidal effects of the Group IV di- and tri-organo derivatives as shown in Table IX (140). Dibutyltin dilaurate controls the chicken parasite *Raillietina cesticillus* at dose

TABLE VIII. Oral LD_{50} Values for Organotin Compounds.

Compound	Species	LD_{50} (mg/kg)	References
Methyltin isooctylthioglycolate	Rat	1,261	Weisfeld (129a)
Butyltin trichloride	Mouse	1,400	Pelikan and Cerny (115, 116)
Butyltin isooctylmercaptoacetate	Mouse	1,520	Pelikan and Cerny (115, 116)
Dibutyltin bis(isooctylthioglycolate)	Rat	1,037	Weisfeld (129a)
Dibutyltin dichloride	Rat	100	Klimmer (130)
Dibutyltin dichloride	Rat, male	182	Mazaev, et al. (117)
Dibutyltin dichloride	Rat, female	112	Mazaev, et al. (117)
Dibutyltin dichloride	Mouse	35	Mazaev, et al. (117)
Dibutyltin dichloride	Guinea pig	190	Mazaev, et al. (117)
Dibutyltin oxide	Rat	520	Klimmer (130)
Dibutyltin bis(isooctyl)	Rat	200	Calley, et al. (120)
Dibutyltin dilaurate	Rat	175	Klimmer (130)
Dibutyltin bis(nonylmaleate)	Rat	120	Klimmer (130)
Dibutyltin bis(nonylmaleate)	Rat	170	Klimmer (130)
Dioctyltin oxide	Rat	2,500	Klimmer (130)
Dioctyltin maleate	Rat	4,500	Klimmer (130)
Dioctyltin maleate	Mouse	2,250	Pelikan, et al. (119)
Dioctyltin bis(butylmaleate)	Rat	2,030	Klimmer (130)
Dioctyltin bis(butylmaleate)	Mouse	3,750	Pelikan, et al. (110)
Dioctyltin bis(isooctylmaleate)	Rat	2,760	Klimmer (130)
Dioctyltin bis(isooctylmaleate)	Mouse	2,700	Pelikan, et al. (110)
Dimethyltin bis(isooctylthioglycolate)	Rat	1,380	Weisfeld (129a)

Table continues on next page.

TABLE VIII (cont'd). Oral LD_{50} Values for Organotin Compounds.

Trimethyltin acetate	Rat	9	Barnes and Stoner (131)
Triethyltin acetate	Rat	4	Barnes and Stoner (131)
Triethyltin sulfate	Rat	6	Stoner, *et al*. (132)
Triethyltin sulfate	Rabbit	10	Stoner, *et al*. (132)
Tripropyltin acetate	Rat	118	Barnes and Stoner (131)
Triisopropyltin acetate	Rat	44	Barnes and Stoner (131)
Tributyltin acetate	Rat	380	Barnes and Stoner (131)
Bis(tributyltin)oxide	Rat	132	Klimmer (130)
Bis(tributyltin)oxide	Rat	180	Truhaut, *et al*. (133)
Bis(tributyltin)oxide	Rat	234	Sheldon (134)
Trihexyltin acetate	Rat	1,000	Barnes and Stoner (131)
Triphenyltin acetate	Rat	136	Klimmer (130)
Triphenyltin acetate	Guinea pig	24	Kimbrough (135)
Triphenyltin acetate	Guinea pig	21	Klimmer (130)
Triphenyltin hydroxide	Rat, male	171	Marks, *et al*. (136)
Triphenyltin hydroxide	Rat, female	268	Marks, *et al*. (136)
Tetraethyltin	Rat, male	9	Mazaev, *et al*. (117)
Tetraethyltin	Rat, female	16	Mazaev, *et al*. (117)
Tetraethyltin	Mouse	40	Mazaev, *et al*. (117)
Tetraethyltin	Guinea pig	40	Mazaev, *et al*. (117)
Tetraethyltin	Rabbit	7	Mazaev, *et al*. (117)

levels of 75 mg/kg without harm to the chickens (141, 142), and the effect on egg production, fertility and hatchability was temporary (143). LD_{50} values for tricyclohexyltin hydroxide

TABLE IX

Comparative Bactericidal Effects of Group IVA Organometals

Figures represent the minimum concentration in g/ml needed to inhibit all growth on *Streptococcus lortis* (140).

	R_3MX			R_2MX_2		
	Ge	Sn	Pb	Ge	Sn	Pb
CH_3	>500	>500	200		200	1
C_2H_5	50	100	50	>500	50	5
n-C_3H_7	5	5	2		20	0.5
n-C_4H_9	1	5	1	>500	20	0.2
n-C_5H_{11}	2	10	5		50	0.2
n-C_6H_{13}	20	50	10		>500	1
C_6H_5	>500	5	1	>500	50	1

toward quail are in the range 255-390 mg/kg with no effect on egg production, fertility or hatching noted at the 20 ppm dietary level (144), and toward dogs, cats and monkeys at >800 mg/kg (145). Sheep receiving intrarumenal injections of tricyclohexyltin hydroxide in doses of 15 mg/kg experienced no ill effects; with 25 mg/kg a transitory anorexia set in; at 50 mg/kg reversible CNS depression and diarrhea, while four sheep dosed with 150 mg/kg died. Yearling cattle and goats can tolerate multiple treatments of up to 0.1% w/v of tricyclohexyltin hydroxide in a water spray on the hide with no behavioral effects, but one ewe aborted twin mid-term fetuses eight days after a single application of a 28% solution and died five days later (146).

Against the bollworm *Heliothis zea* and tobacco budworm *H. virescens* larvae, foliar spray of triorganotin compounds revealed LD_{50} values of 0.20 and 0.50 mg/kg, respectively (147). Bis(tributyltin)oxide at 1% w/v in wool killed 100% of clothes moths *Tineola bisselliell* larvae without injestion (148). Other triorganotin derivatives showed values of 0.25 to 0.30 ppm against the mosquito *Culex pipiens* larvae compared with 0.04 ppm for DDT (149, 150). Various triphenyltin derivatives act as

95% reproduction inhibitors on the housefly Musca domestica L. in as low as 62 ppm dietary dose levels, with LD_{50} values of 1,000 ppm (151), and act as chemosterilants toward the German cockroach Blattella germanica L. and the confused flour beetle Tribolium confusum at 0.1% by weight in the diet. Jacquelin du Val Antifeeding effects were also noted on various lepidoterous larvae including the cotton leafworm Prodenia litura F. and the Colorado beetle Leptinotarsa decemleneata Say and Agrotis ypsilon Rott (152). Sugar beet leaves treated with a 0.1% w/v solution of triphenyltin acetate and hydroxide stopped larvae feeding.

In 1973 the International Tin Research Institute organized a cooperative research project to investigate the environmental behavior of organotin compounds. The Organotin Environmental Project, or ORTEP, is funded by the prinicpal manufacturers of organotin chemicals in the U.S., U.K., Switzerland, Germany and Japan.

Human Exposure. Organotin compounds can be assimilated by inhalation, ingestion through food or water or by absorption through the skin. The lipid soluble derivatives will accumulate in fatty tissue. No data concerning the rates of metabolism degradation or excretion in humans or test animals are available. The total daily intake for tin in the diet has been estimated to be in the range 187 to 8,800 μg/day which corresponds to an average of 2.7 to 126 μg/kg for an adult (153). Tin, presumably as inorganic tin, has been shown to be an essential growth factor in the rat (154).

A harmful physiological effect was first noticed in 1858 for a diethyltin chloride which had a "powerfully pungent odor" and, when heated, produced a vapor that "painfully attacks the skin of the face" and caused fits of sneezing (155). Similar effects were experienced with triethyltin chloride and tetraethyltin (156). The vapors of triethyltin acetate were observed to cause nausea, headache, general weakness, diarrhea and albuminuria, and tetraethyltin caused headache (157). The sternutatory, irritative and lachrimatory properties of triethyltin iodide were studies for possible chemical warfare applications, but none of the effects were considered potent enough and the idea was, mercifully, abandoned (158, 159, 160). Widespread poisoning occurred, however, in France and Algeria in 1954 as a result of taking Stalinon capsules, each of which was stated to contain 15 mg of diethyltin diiodide, for the systematic treatment of staphylococal infections of the skin (161). The incident involved 210 known cases of harmful effects and one hundred deaths. It is estimated that the fatal doses of the organotin were in the range 380 to 750 mg (162-171). The preparation may have also contained tri-, mono- and tetraethyltin (172).

Adverse effects produced by occupational exposure to triphenyltin acetate used as an agricultural fungicide in Eastern Europe (172-176) include general malaise, headache, loss of conciousness, epigastric pain, vomiting, irritation of the skin, conjunctivae and mucosae, dyspepsia, diarrhea, foggy vision, dizziness, hyperglycemia, glycosuria and damage to the liver shown by increased collagen, some fibrosis and increased serum glutamic-pyruvic transmutase levels. All of these effects were reversible in a few week's time and complete recovery was effected. Organotins have been found to be highly irritating to the skin. Experiments with volunteers showed that undiluted butyltin derivatives produced follicular inflamation and pustulation. The lesions were most severe with tributyltin chloride which produced mild edema and itching (176, 177). In the most severe cases of organotin poisoning, involving peralkylated materials, bradycardia, hypotension and and abrupt variations in the sinus rhythm of the heart were noted (177). The illness lasted 4-10 weeks.

The one fatality in which occupational exposure to organotins has been implicated involved a 29 year old woman drenched with a slurry of tri- and diphenyltin chloride at 175°F (80°C) causing first-degree thermal burns over 90% of the body with erythema and second- and third-degree burns setting in with 85% desquamated skin. Death from renal failure set in 12 days later, but the agent responsible cannot be determined from the available data (179).

An analytical method based upon observation of SnH fluorescence in an H_2-air flame has been applied to organotin compounds present in human urine from males age 25-47. Reduction of the organotins to the corresponding hydrides allows speciation of the tin(IV), mono-, di- and trimethyltin derivatives. Averages of 11 determinations gave concentrations in the ppb range for tin(IV) (0.82 ppb; 82%), mono-(0.090 ppb; 9%), di-(0.073 ppb; 7.3%) and trimethyltin (0.042 ppb; 4.2%). Total tin constituted 1.0 ppb (180). The same techniques were applied to rain (25 pptr total tin, 44% tin(IV), 24% mono-, 30% di- and 0.88% trimethyltin) tap (9.2 pptr total tin, 24% tin(IV), 47% mono-, 14% di- and 16% trimethyltin), fresh ([average of 16 sites around Tampa Bay, Florida] 9.1 pptr total tin, 46% tin(IV), 22% mono-, 15% di- and 16% trimethyltin) estuarine ([average of a dozen sites around Tampa Bay, Florida] 12 pptr total tin, 63% tin(IV), 19% mono-, 14% di- and 3.7% trimethyltin) and saline ([average of a dozen Florida sites] 4.2 pptr total tin, 54% tin(IV), 15% mono-, 33% di- and 12% trimethyltin) waters.

Regulation of Organotins. The U.S. Occupational Safety and Health Act (OSHA) of 1970 requires standards for the protection of workers exposed to hazards at their workplace. The U.S. National Institutes for Occupational Safety and Health (NIOSH) has recommended a standard for occupational exposure to polymer compositions not to exceed 1 part of tin per hundred of polymer (196). A subsequent amendment to the act allowed the use of a di-n-octyltin S,S'-bis(isooctylmercaptoacetate) formulation of <15.1-16.1% by weight of tin in PVC. The starting materials for the synthesis of the mercaptoacetate derivative were controlled at not more than 5% of the trichloro- and not less than 95% of the dichlorotin. The Food and Agricultural Organization and the World Health Organization have jointly recommended residue limits of 2 ppm for apples and pears, 0.2 ppm for meat and 0.05 ppm for milk (197), and acceptable daily intake of less than 0.0075 mg/kg of body weight for the pesticide tricyclohexyltin hydroxide (198).

There are currently no specific federal restrictions on the transport or handling of organotin compounds. Some organotins are voluntarily labeled as Corrosive Materials in the U.S. Handling procedures for dealing with accidental spills are not legally specified. Neither the Hazardous Substances List of the Environmental Protection Agency (EPA) nor the Carcinogenic Suspect Agent list of the Occupational Safety and Health Administration (OSHA) contain any organotin compounds. The EPA Office of Pesticides has registered bis(tributyltin) oxide and tributyltin fluoride for use in antifouling paints. As for all pesticides, the labels of the containers of undiluted organotin as well as finished product must show analysis, contents, directions for use, accidental contact remedies and container disposal. Bis(tri-neophyl)tin oxide and tricyclohexyl- and triphenyltin hydroxides have been registered by the EPA as agricultural chemicals (199). The Food and Drug Administration code permits the use of organotin stabilizers in rigid PVC food containers, and in PVC for food wrap, including di-n-octyltin S,S'-bis(isooctylmercaptoacetate) and maleate polymer and butylthiostannoic acid (200). The EPA allows use in PVC pipe and conduit for potable water. Organotins have also been approved as catalysts and curing agents in the production of polyurethane resins, silicone polymers and PVC products for food packaging, and as adhesive preservatives for food use (200).

Water and Waste Treatment. A U.S. Patent has been issued for removal of inorganic and organolead compounds from the aqueous effluent from the manufacture of tetraalkyllead by treatment with an alkali metal borohydride to form insoluble lead products including hexaalkyldilead and lead metal which can be separated by settling (201). Russian authors have utilized absorption onto activated carbon, extraction into ether and electrochemical oxidation methods for the detoxification of waters polluted by organotin compounds (202, 203). Anodic stripping polarography has been used to determine organotin residues in surface waters (204).

organotin compounds. The recommended threshold limit value (TLV) of 0.1 mg/m^3 on a time-weighted average, calculated as elemental tin has not yet been adopted (57). This standard was itself based upon antecedent documents. The American Conference of Governmental Industrial Hygienists (ACGIH) established a TLV of 0.1 mg/m^3 measured as tin in 1965 for all organotin compounds in the occupational environment (186), and this standard was reaffirmed in 1971 by analogy with the standards for mercury, thallium and selenium because of a lack of pertinent data (187). A separate ACGIH standard was proposed for tricyclohexyltin hydroxide as 1.2 mg/m^3 measured as tin in 1973, and the standard was adopted in 1975 (188). In the German Democratic Republic the maximum allowable concentration of organotins is given as 0.1 mg/m^3 (189), and Romania and Yugoslavia use the same figure for a TLV based upon the 1966 ACGIH value (190). The current U.S. Federal standard, 29 CFR 1910.1000, is a time-weighted average concentration limit of 0.1 mg/m^3 measured as tin, and is based upon the 1965 ACGIH TLV (57). This value equates to an exposure of 0.02 mg/kg/day. The World Health Organization is currently drafting a review of the environmental health aspects of tin (191). The Midwest Research Institute report recommended a maximum daily dosage of 0.02 mg/kg which is the estimated dosage of a person exposed to 0.1 mg/m^3 over an eight-hour period for five days per week (58).

The Council of the European Communities listed organotin compounds as part of a group of substances selected on the basis of their toxicity, persistence and bioaccumulation to which states were directed to apply a system of zero-emission to discharges into ground water, and to require prior authorization by competent authority of the member states for all discharges into the aquatic environment of the Community (192). Russian authors have proposed standards of 20 mg/liter for dibutyltin sulfide (193), 2 mg/liter for dibutyltin dichloride (193), and 0.2 mg/liter for tetraethyltin (195) in resevoir water based upon no-effect doses found in chronic toxicity testing.

Both the NIOSH and Midwest Research Institute reports recognize the strong dependence of the toxicity of organotin compounds upon the number of organic substituents and their nature. The single standard that is recommended for airborne organotins does not reflect the varied toxicity and hazard of these compounds. However, there is lack of adequate data upon which to distinguish quantitatively between different compounds, and a lack of analytical techniques for the speciation of organotins in low environmental concentrations.

Another area for the regulation of organotins is in their use as additives in packaging materials for food and beverages. The Federal Food, Drug and Cosmetic Act was amended in 1963 to allow the introduction of dibutyltin dilaurate in silicone

1. E.S. Hedges, "Tin in Social and Economic History," Edward Arnold, London, 1964.
2. Grass, G. "The Tin Drum," transl. by R. Manheim, Pantheon Books, New York, 1962.
3. "The Apocrypha," Ecclesiasticus or the Wisdom of Sirach, 47: 18 (Said of Soloman) "Thou didst gather gold as tin, and multiply (accumulate) silver as lead."
4. Smith, P.J. and Smith, L., Inorg. Chim. Acta Rev. (1973), 7, 11.
5. Kennedy, J.D., and McFarlane, W., in "Reviews on Silicon, Germanium, Tin and Lead Compounds," ed. M. Gielen, Freund, Tel Aviv, Israel (1974), 1, 235.
6. Litzow, M.R. and Spalding, T.R., "Mass Spectrometry of Inorganic and Organometallic Compounds," Elsevier, Amsterdam, 1973.
7. Zuckerman, J.J., Advan. Organometal. Chem. (1970), 9, 21.
8. Tanaka, T., Organomet. Chem. Revs. (1970), A5, 1.
9. Limouzin, Y. and Maire, J.C., "Organotin Compounds: New Chemistry and Applications," J.J. Zuckerman, Ed., Advances in Chemistry Series, No. 157, p. 227, American Chemical Society, Washington, D.C.
10. Zubieta, J.A. and Zuckerman, J.J., Prog. Inorg. Chem. (1978), 24, 251.
11. Geller, S., Matthias, B.T. and Goldstein, R., J. Amer. Chem. Soc. (1955), 77, 1502.
12. Galasso, F.S., "Structure and Properties of Inorganic Solids," Pergamon Press, Oxford, 1970.
13. Vaipolin, A.A., Asmanov, E.O., and Tset'yakov, D.N., Izv. Akad. Nauk SSSR, Neorg. Mater. (1967), 3, 260.
14. Corbett, J.D. and Edwards, P.A., Chem. Commun. (1975), 984.
15. Einstein, F.W.B. and Penfold, B.R., J. Chem. Soc. (A), (1968), 3019.
16. Schlemper, E.O. and Britton, D., Inorg. Chem. (1966), 5, 507.
17. Rush, J.J. and Hamilton, W.C., Inorg. Chem. (1966), 5, 2238.
18. Schlemper, E.O. and Hamilton, W.C., Inorg. Chem. (1966), 5, 995.
19. Forder, R.A. and Sheldrick, G.M., J. Chem. Soc. (A) (1971), 1107.
20. Almenningen, A., Haaland, A., and Motzfeldt, T., J. Organomet. Chem. (1967), 7, 97.
21. Goldberg, D.E., Harris, D.H., Lappert, M.F., and Thomas, K.M., Chem. Commun. (1976), 261.
22. Hulme, R., J. Chem. Soc. (1963), 1524.
23. Nardelli, M., Pelizzi, C., Pelizzi, G., and Tarasconi, P., Z. Anorg. Chem. (1977), 431, 250.
24. Smart, L.E. and Webster, M., J. Chem. Soc. Dalton Trans., (1976), 1924.
25. Brownlee, G.S., Walker, A., Nyburg, S.C., and Szymanski, J.T., Chem. Commun. (1971), 1073.
26. Harrison, P.G., Coord. Chem. Rev. (1976), 20, 1.

27. Neumann, W.P., "The Organic Chemistry of Tin," Wiley-Interscience, New York, 1970.
28. Poller, R.C., "The Chemistry of Organotin Compounds," Academic Press, New York, 1970.
29. Sawyer, A.W., ed., "Organotin Compounds," 3 vols. M. Dekker, New York, 1971-1972.
30. Luijten, J.G.A. and van der Kerk, G.J.M., in "Organometallic Compounds of the Group IV Elements," ed. by A.G. MacDiarmid, vol. 1, part II, p. 91, M. Dekker, New York, 1968.
31. Clark, H.C. and Puddephatt, R.J., in "Organometallic Compounds of the Group IV Elements," ed. by A.G. McDiarmid, vol. 2, part II, p. 71, M. Dekker, New York, 1972.
32. Zuckerman, J.J., ed., "Organotin Compounds: New Chemistry and Applications," Advances in Chemistry Series, No. 157, American Chemical Society, Washington, D.C., 1976.
33. Schumann, H. and Schumann, I., "Gmelin Handbuch der Anorganischen Chemie," Zinn-Organische Verbindungen, Teil 1. Zinntetraorganyle, SnR_4, Springer-Verlag, Berlin, 1975.
34. Schumann, H. and Schumann, I., "Gmelin Handbuch der Anorganischen Chemie," Zinn-Organische Verbindungen, Teil 2, Zinntetraorganyle R_3SnR', Springer-Verlag, Berlin, 1975.
35. Schumann, H. and Schumann, I., "Gmelin Handbuch der Anorganischen Chemie," Zinn-Organische Verbindungen, Teil 3, Zinntetraorganyle R_2SnR_2', $R_2SnR'R''$, $RR'SnR''R'''$, Heterocyclen U. Spirane, Springer-Verlag, Berlin, 1976.
36. Schumann, H. and Schumann, I., "Gmelin Handbuch der Anorganischen Chemie," Zinn-Organische Verbindungen, Teil 4, Organozinnhydride, Springer-Verlag, Berlin, 1975.
37. Seyferth, D. and King, R.B., "Annual Survey of Organometallic Chemistry," covering the year 1964, vol. 1, p. 124, Elsevier, Amsterdam, 1976.
38. Seyferth, D. and King, R.B., "Annual Survey of Organometallic Chemistry," covering the year 1965, vol. 2, p. 161, Elsevier, Amsterdam, 1966.
39. Seyferth, D. and King, R.B., "Annual Survey of Organometallic Chemistry," covering the year 1966, vol. 3, p. 236, Elsevier, Amsterdam, 1967.
40. Luijten, J.G.A., "Tin, Annual Survey Covering the Year 1967," Organometal. Chem. Rev. (1968), B4, 359.
41. Luijten, J.G.A., "Tin, Annual Survey Covering the Year 1968," Organometal. Chem. Rev. (1969), B5, 687.
42. Luijten, J.G.A., "Tin, Annual Survey Covering the Year 1969," Organometal. Chem. Rev. (1970), B6, 486.
43. Bulten, E.J., "Tin, Annual Survey Covering the Year 1970," Organometal. Chem. Rev. (1972), B9, 248.
44. Bulten, E.J., "Tin, Annual Survey Covering the Year 1971,"

J. Organometal. Chem. (1973), 53, 1.
45. Harrison, P.G., "Tin, Annual Survey Covering the Year 1972," J. Organometal. Chem. (1973), 58, 49.
46. Harrison, P.G., "Tin, Annual Survey Covering the Year 1973," J. Organometal. Chem. (1974), 79, 17.
47. Harrison, P.G., "Tin, Annual Survey Covering the Year 1974," J. Organometal. Chem. (1976), 109, 241.
48. Harrison, P.G., "Tin, Annual Survey Covering the Year 1975," J. Organometal. Chem. Library (1977), 4,
49. Abel, E.W. and Stone, F.G.A., "Organometallic Chemistry, A Review of the Literature Published During 1970," Specialist Periodical Report, The Chemical Society, London, 1971.
50. Abel, E.W. and Stone, F.G.A., "Organometallic Chemistry, A Review of the Literature Published During 1971," Specialist Periodical Report, The Chemical Society, London, 1972.
51. Abel, E.W. and Stone, F.G.A., "Organometallic Chemistry, A Review of the Literature Published During 1972," Specialist Periodical Report, The Chemical Society, London, 1973.
52. Abel, E.W. and Stone, F.G.A., "Organometallic Chemistry, A Review of the Literature Published During 1973," Specialist Periodical Report, The Chemical Society, London, 1974.
53. Abel, E.W. and Stone, F.G.A., "Organometallic Chemistry, A Review of the Literature Published During 1974," Specialist Periodical Report, The Chemical Society, London, 1975.
54. Abel, E.W. and Stone, F.G.A., "Organometallic Chemistry, A Review of the Literature Published During 1975," Specialist Periodical Report, The Chemical Society, London, 1976.
55. Abel, E.W. and Stone, F.G.A., "Organometallic Chemistry, A Review of the Literature Published During 1976," Specialist Periodical Report, The Chemical Society, London, 1977.
56. T.W. Lapp, "Study on Chemical Substances from Information Governing the Manufacture, Distribution, Use, Disposal, Alternatives and Magnitude of Exposure to the Environment and Man," Task II - The Manufacture and Use of Selected Alkyltin Compounds, Environmental Protection Agency, Office of Toxic Substances, EPA. 560/6-76-011, PB-251819 (1976).
57. NIOSH Criteria Document No. 77-115, "Occupational Exposure to Organotin Compounds," U.S. Department of HEW, November, 1976.
58. EPA-OTS, Draft Report, "Assessment of the Need for, the Character of, and the Impact Resulting from Limitations on Selected Organotins," Phase I - Assessment of the Need for Limitations on Organotins, July, 1977.

59. Good, M.L., "Abstracts," Workshop on Organotins, New Orleans, 17-19 February, 1978.
60. Rochow, E.G., "Organometallic Chemistry," p. 98, Reinhold, New York, 1964.
61. Gmelin, L., "Karlesruher Zeitung," November, 1838.
62. Fleck, ., Z. Biol. (1872), 8, 444.
63. Gosio, B., Ber. (1897), 30, 1024.
64. Challenger, F., Chem. Ind. (London) 1935, 657.
65. Challenger, F., Chem. Rev. (1945), 36, 315.
66. Challenger, F., Quart. Rev. (1955), 9, 255.
67. Lenhert, P.G. and Crowfoot-Hodgkin, D., Nature (1961), 192, 937.
68. Thayer, J.S., J. Organometal. Chem. (1974), 76, 265; and references therein.
69. Jensen, S. and Jernelöv, A., Nature (1969), 223, 753.
70. Thayer, J.S., J. Chem. Educ. (1971), 48, 806.
71. Thayer, J.S., J. Chem. Educ. (1973), 50, 390.
72. Wood, J.M., Science (1974), 183, 1049.
73. Nriagu, J.O., ed., "Environmental Biogeochemistry," 2 vols., Ann Arbor Science, Ann Arbor, MI.
74. Hutchinson, E.C., ed., "Heavy Metals in the Environment," Univ. Toronto Press, Toronto, Ont., 1976.
75. Wood, J.M., in "Biochemical and Biophysical Perspectives in Marine Biology," ed. by D.C. Malins and J.R. Sargent, Vol. 3, p. 407, Academic Press, New York, 1976.
76. Ridley, W.P., Dizikes, L.J. and Wood, J.M., Science, (1977), 197, 329.
77. Thayer, J.S., J. Chem. Educ. (1977), 54, 604.
78. Thayer, J.S., J. Chem. Educ. (1977), 54, 662.
79. Ayrey, G., Head, B.C. and Poller, R.C., Macromol. Rev. (1974), 8, 1.
80. van der Kerk, G.J.M. in "Organotin Compounds: New Chemistry and Applications," ed. by J.J. Zuckerman, Advances in Chemistry Series No. 157, p. 1, American Chemical Society, Washington, D.C., 1976.
81. Davies, A.G. in "Organotin Compounds: New Chemistry and Applications, ed. by J.J. Zuckerman, Advances in Chemistry Series No. 157, p. 26, American Chemical Society, Washington, D.C.
82. Abraham, M.H. and Johnston, G.E., J. Chem. Soc. (A), 1970, 88.
83. Gielen, M., Accts. Chem. Res. (1973), 6, 198.
84. Deblandre, C., Gielen, M. and Nasielski, J., Bull. Soc. Chem. Belg. (1964), 73, 214.
85. Kuivila, H.G. and Verdone, J.A., Tetrahedron Lett., 1964, 119.
86. Roberts, R.M.G. and Kaissi, F.El., J. Organomet. Chem. (1968), 12, 79.
87. Eaborn, E., Trevorton, J.A. and Walton, D.R.M., J. Organomet. Chem. (1967), 9, 259.

88. Eaborn, C., Hornfield, H.L. and Walton, D.R.M., J. Chem. Soc. (B), 1967, 1036.
89. Bassingdale, A.R., Eaborn, C., Taylor, R., Thompson, A.R. and Walton, D.R.M., J. Chem. Soc. (B), 1971, 1155.
90. D.S. Matteson, "Organometallic Reaction Mechanisms of the Nontransition Elements," Academic Press, New York, 1974.
91. Gielen, M., Dehouck, C., Mokhtar-Jamai, H. and Topart, J., Rev. Silicon, Germanium, Tin, Lead Compd. (1974), 1, 9.
92. Mazaev, V.T., Golovanov, O.V., Igumnov, A.S. and Tsay, V.N., Gig. Sanit. (1976), 3, 17; Chem. Abstr. (1976), 85, 98903z.
93. Barnes, R.D., Bull, A.T. and Poller, R.C., Pestic. Sci. (1973), 4, 305.
94. Chapman, A.H. and Price, J.W., Int. Pest. Control (1972), 14, 11.
95. Freitag, K. and Bock, R., Pestic. Sci. (1974), 5, 731.
96. Engelhart, J.E. and Sheldon, A.W., "Abstr. 15th Marine Coatings Conf.," Point Clear, AL, Feb., 1975.
97. Slesinger, A.E., "Abstr.," Marine Coatings Seminar, National Paint and Coatings Association, Biloxi, MS., March, 1977.
98. Heron, P.N. and Sproule, J.S.G., Indian Pulp Pap. (1958), 12, 510.
99. Beiter, C.G., Engelhart, J.E., Freiman, A. and Sheldon, A., "Abstr. ACS National Meeting," Atlantic City, NJ, August, 1974.
100. Schramel, P.K. , Samsahl, K. and Pavlu, J., Int. J. Environ. Stud. (1973), 5, 37.
101. Jensen, S. and Jernelöv, A., Int. At. Energy Agency Tech. Rep. Ser. No. 137 (1972), p. 43.
102. Wood, J.M. and Brown, D.G., Struct. Bonding, (1972), 11, 47.
103. DeSimone, R.E., Penley, M.W., Charboneau, L., Smith, S., Wood, J.M., Hill, H.A.O., Ridsdale, P. and Williams, R.J.P., Biochim. Biophys. Acta (1973), 304, 851.
104. Jernelöv, A., Lien, E.L. and Wood, J.M. quoted in Wood, J.M., Science (1974), 183, 1049.
105. Huey, C., Brinckman, F.E., Grim, S. and Iverson, W.P., in "Proceedings of the International Conference on the Transport of Persistent Chemicals in Aquatic Ecosystems," Q.N. LeHam, ed., p. 73, National Research Council of Canada, Ottawa, Ontario, 1974.
106. Dizikes, L.J., Ridley, W.P. and Wood, J.M., J. Am. Chem. Soc. (1978), 100, 1010.
107. Pelikan, Z. and Cerny, E., Arch. Toxikol. (1970), 26, 196.
108. Pelikan, Z. and Cerny, E., Arch. Toxikol. (1970) 27, 79.
109. Mazaev, V.T., Korolev, A.A. and Skachkova, I.N., J. Hyg. Epidermiol. Microbiol. Immunol. (1971), 15, 115.

110. Pelikan, Z. and Cerny, E., Arch. Toxikol. (1968), 23, 283.
111. Pelikan, Z., Cerny, E. and Polster, M. Food Cosmet. Toxicol. (1970), 8, 655.
112. Calley, D.J., Guess, W.L. and Autian, J., J. Pharm. Sci. (1967), 56, 240.
113. Jewett, K.L., Brinckman, F.E., and Bellama, J.M., in "Marine Chemistry in the Coastal Environment," ed. by T.M. Church, ACS Symposium Series, No. 18, p. 304, American Chemical Society, Washington, DC, 1975.
114. Jewett, K.L., Brinckman, F.E. and Bellama, J.M., "Abstr. ACS National Meeting," Anaheim, California, March, 1978.
115. Cremer, J.E., Biochem. J. (1958), 68, 685.
116. Casida, J.E., Kimmel, E.C., Holm, B. and Widmark, G., Acta Chem. Scand. (1971), 25, 1497.
117. Bridges, J.W., Davies, D.S. and Williams, R.T., Biochem. J. (1967), 105, 1261.
118. Blair, E.H. Environ. Qual. Saf., Supplement (1975), 3, 406.
119. Fish, R.H., Kimmel, E.C. and Casida, J.E., J. Organomet. Chem. (1975), 93, C1.
120. Kimmel, E.C., Fish, R.H. and Casida, J.E., J. Agr. Food Chem. (1977), 25, 1201.
121. Fish, R.H., Kimmel, E.C. and Casida, J.E., in "Organotin Compounds: New Chemistry and Applications," ed. by J.J. Zuckerman, Advances in Chemistry Series No. 157, p. 197, American Chemical Society, Washington, D.C., 1976.
122. Fish, R.H., Casida, J.E. and Kimmel, "Chemical Problems in the Environment. Occurence and Fate of the Organoelements," ACS Symposium Series, American Chemical Society, Washington, D.C., 1978.
123. Weisfeld, L.B., J. Paint Technol. (1970), 42, 549.
124. Philips-Dulphar, N.V., as reported in Hopf, H.S., Dunean, J., Beesley, J.S.S., Webley, D.J. and Sturrock, R.F., Bull. WHO (1967), 36, 955.
125. Hopf, H.S., Duncan, J., Beesley, J.S.S., Webley, D.J. and Sturrock, R.F., Bull. WHO (1967), 36, 955.
126. Evans, C.J. and Smith, P.J., J. Oil Colour Chem. Assoc. (1975), 58, 160.
127. Englehart, J., Beiter, C. and Freiman, A., "Abstr. Controlled Release Pesticides Symposium," Akron, Ohio, Sept., 1974.
128. Phillip, A.T., Aust. Oil Colour Chem. Assoc. Proc. News (1975), 58, 160.
129. Frick, L.P. and DeJimenez, W.Q., Bull. WHO (1964), 31, 429.
129a. Weisfeld, Kunststoffe (1975), 65, 298.
130. Klimmer, O.R., Arzneimitt.-Forsch. (1969), 14, 934.
131. Barnes, J. and Stoner, H.B., Brit. J. Ind. Med. (1958), L5, 15.

132. Stoner, H.B., Barnes, J.M. and Duff, J.I., Brit. J. Pharmacol. (1955), 10, 16.
133. Truhaut, R., Chauvel, Y., Anger, J.P., Lieh, N.P., van den Driessche, J., Guesnier, L.R. and Morin, N., Eur. J. Toxicol. Environ. Hyg. (1976), 9, 31.
134. Sheldon, A., J. Paint Technol. (1975), 47, 54.
135. Kimbrough, R.D., Environ. Health Perspect. (1976), 14, 51.
136. Marks, M.J., Winek, C.L. and Shanor, S.P., Toxicol. Appl. Pharmacol. (1969), 14, 627.
137. van der Kerk, G.J.M. and Luyten, J.G.A., J. Appl. Chem. (1954), 4, 314.
137a. Bennett, R.F. and Zedler, R.J., J. Oil Colour Chem. Assoc. (1966), 49, 928.
138. Zedler, R.J. and Beiter, C.B., Soap Cosmet. Chem. Spec. (1962), 38, 75.
139. Hedges, E.S., Research (London) (1960), 13, 449.
140. Sijpesteyn, A.K., Luijten, J.G.A. and van der Kerk, G.J.M., in "Fungicides: An Advanced Treatise," ed. by D.C. Torgeson, p. 331, Academic Press, New York, 1969.
141. Kerr, K.G., Poult. Sci. (1952), 31, 328.
142. Peardon, D.L., Haberman, W.D., Marr, J.E., Garland, F.W., Jr., and Wilcke, H.L., Poult. Sci. (1964), 44, 413.
143. Wilson, H.R., Fry, J.L. and Jones, J.E., Poult. Sci. (1967), 46, 304.
144. McCollister, D.D. and Schober, A.E., Environ. Qual. Saf. (1975), 4.
145. Noel, P.R.B., Heywood, R. and Squires, P.F., quoted in ref. 58, p. 308.
146. Johnson, J.H., Younger, R.L., Witzel, D.A. and Radeleff, R.D., Toxicol. Appl. Pharmacol. (1975), 31, 66.
147. Wolfenberger, D.A., Guerra, A.A. and Loury, W.L., J. Econ. Entomol. (1968), 61, 78.
148. Pieper, G.R. and Casida, J.E., J. Econ. Entomol. (1965), 58, 392.
149. Castel, P., Gras, G., Rioux, J.A. and Vidal, A., Trav. Soc. Pharm. Montpellier (1963), 23, 45.
150. Baker, J.M. and Taylor, J.M., Ann. Appl. Biol. (1967), 60, 181.
151. Kenaga, E.E., J. Econ. Entomol. (1965), 58, 4.
152. Ascher, K.R.S. and Rones, G., Int. Pest Control. (1964), 6, 6.
152a. Anon., Chem. Eng. News, 13 March, 1978, p. 10.
153. Hamilton, E.I. and Minski, M.J., in "The Science of the Environment,"p. 375, (1972/1973).
154. Schwartz, K., in "Newer Trace Elements in Nutrition," ed. by W. Mertz and W.E. Cornatzar, Marcel Dekker, New York, 1971.
155. Buckton, G.B., Proc. R. Soc. London (1858), 9, 309.
156. Jolyet, F. and Cahours, A., C.R. Acad. Sci. (Paris) (1869), 68, 1276.
157. White, T.P., Arch. Exp. Pathol. Pharmakol. (1881), 13, 53.

158. McCombie, H. and Saunders, B.C., Nature (1947), 159, 491.
159. Gilman, H., Report No. 6004, National Defense Research Committee, Office of Scientific Research and Development, 1942, p. 1.
160. Glass, H.G., Coon, J.M., Lushbaugh, C.C. and Last, J., Univ. Chicago Toxicology Laboratory Report No. 15, 1942.
161. Anon., Brit. Med. J. (1958), 1, 515.
162. Rouzaud, M. and Lutier, J., Presse Med. (1954), 62, 1075.
163. Rondepierre, J., Truhaut, R., Guilly, P., Hivert, P.E. and Barande, I., Rev. Neurol. (1958), 98, 135.
164. Alajouanine, T.A., Derobert, L. and Thieffry, S., Rev. Neurol. (1958), 98, 85.
165. Gayral, L., Lozorthes, G. and Planques, J., Rev. Neurol. (1958), 98, 143.
166. Druault-Toufesco, M.N., Bull. Soc. Ophtalmol. Fr., 1955, 54.
167. Grossiord, A., Held, J.P., LeCoeur, P.Le., Verley, R. and Drosdowsky, M., Rev. Neurol. (1958), 98, 144.
168. Gruner, J.E., Rev. Neurol. (1958), 98, 109.
169. Pesme, P., Arch. Fr. Pediatr. (1955), 12, 327.
170. Rouzand, M., Rev. Neurol. (1958), 98, 140.
171. Derobert, L., J. Forensic Med. (1961), 7, 192.
172. Lecoq, R., C.R. Soc. Biol. Paris (1954), 239, 678.
173. Guardascione, V., DiBosco, M.N., Lav. Um. (1967), 19, 307.
174. Horacek, V. and Demcik, K., Prac. Lek. (1970), 22, 61.
175. Mijatovic, M., Jugosl. Inostrana Dokumentacija Zastite na Radu (1972), 8, 3.
176. Markicevic, A. and Turko, V., Arh. Hig. Rada. Toksikol. (1967), 18, 355.
177. Lyle, W.H., Br. J. Ind. Med. (1958), 15, 193.
178. Zeman, W., Gadermann, E. and Hardebeck, K., Dtsch. Arch. Klin. Med. (1951), 198, 713.
179. Ref. 57, p. 35.
180. Braman, R.S. and Tompkins, M.A., Anal. Chem. in press.
181. Barnes, J.M. and Magos, L., Organomet. Chem. Rev. (1968), 3, 137.
182. Luijten, J.G.A., in "Organotin Compounds," ed, by A.K. Sawyer, p. 931, Marcel Dekker, New York, 1971.
183. Ivanitskii, A.M., Farmakol. Toksikol. (1963), 26, 629.
184. Gerarde, H.W., Org. Ann. Rev. Pharmacol. (1964), 4, 223.
185. Piver, W.T., Environ. Health Perspect. Exper. Issue (1973), 61.
186. ACGIH, "Threshold Limit Values for 1965," adopted at the 27th ACGIH Annual Meeting, Houston, TX, 1965, p. 15.
187. ACGIH, Committee on Threshold Limit Values: Documentation of the Threshold Limit Values for Substances in Workroom Air, 3rd. ed., pp. 150-51, 224-25, 256, 258, 349-50, Cincinnati, OH, 1971.

188. ACGIH, "Threshold Limit Values for Chemical Substances in the Workroom Air," p. 32, Cincinnati, OH, 1975.
189. Landa, K., Fejfusova, J. and Nedomlelova, R., Prac. Lek. (1973), 25, 391.
190. International Labor Office, "Permissable Levels of Toxic Substances in the Working Environment," Occupational Safety and Health Series, Vol. 20, pp. 239, 353, ILO, Geneva, (1970).
191. Vouk, V.B., private communication, 1977, quoted in ref. 58, p. 344.
192. Off. J. Eur. Commun. (18 May, 1975), 19, 23.
193. Mazaev, V.T. and Shlepnina, T.G., Gig. Sanit. (1973), 38, 10.
194. Mazaev, V.T. and Korolev, A.A., Prom. Zagryaz. Vodoemov (1969), 15.
195. Skachkova, I.N., Gig. Sanit. (1967), 32, 11.
196. Federal Register (31 July, 1963), 28, 7777.
197. Tricyclohexyltin hydroxide, in Joint Meeting of the FAO Working Party of Experts on Pesticide Residues and the WHO Expert Committee on Pesticide Residues: 1973 Evaluations of Some Pesticide Residues in Food - the Monographs, WHO Pesticide Residues Series No. 3, pp.440-52, WHO, Geneva, 1974.
198. Tricyclohexyltin hydroxide, in Joint Meeting of the FAO Working Party of Experts and the WHO Expert Group on Pesticide Residues: 1970 Evaluation of Some Pesticide Residues in Food - The Monographs, pp. 521-42, The FAO of the UN and the WHO, Rome, 1971.
199. Code of Federal Regulations, Title No. 40, Protection of the Environment, SEctions 180.144 and 180.236 (1 July, 1976).
200. Code of Federal Regulations, Title No. 21, Food and Drugs, Sections 121.2514, 121.2520, 121.2522, 121.2566 and 121.2602 (1 April, 1976).
201 Lores, C. and Moore, R.B., U.S. Pat. 3,770,425 (6 Nov., 1973), Chem. Abstr. (1974), 80, 137055.
202. Chernega, L.G., Kozyura, A.S., Kazakova, A.A., Sirak, L.D., Kudenko, N.E. and Linchuk, K.F., Vodosnabzh. Kanaliz. Gidrotekh. Sooruzh. (1971), 13, 75; Chem. Abstr. (1972), 76, 158028.
203. Sirak, L.D., Lutsenko, F.A. and Shkorbatova, T.L., Vodosnabzh. Kanaliz. Gidrotekh. Sooruzh. (1974), 17, 72; Chem. Abstr. (1975), 82, 34748.
204. Woggon, H. and Jehle, D., Nahrung (1975), 19, 271.