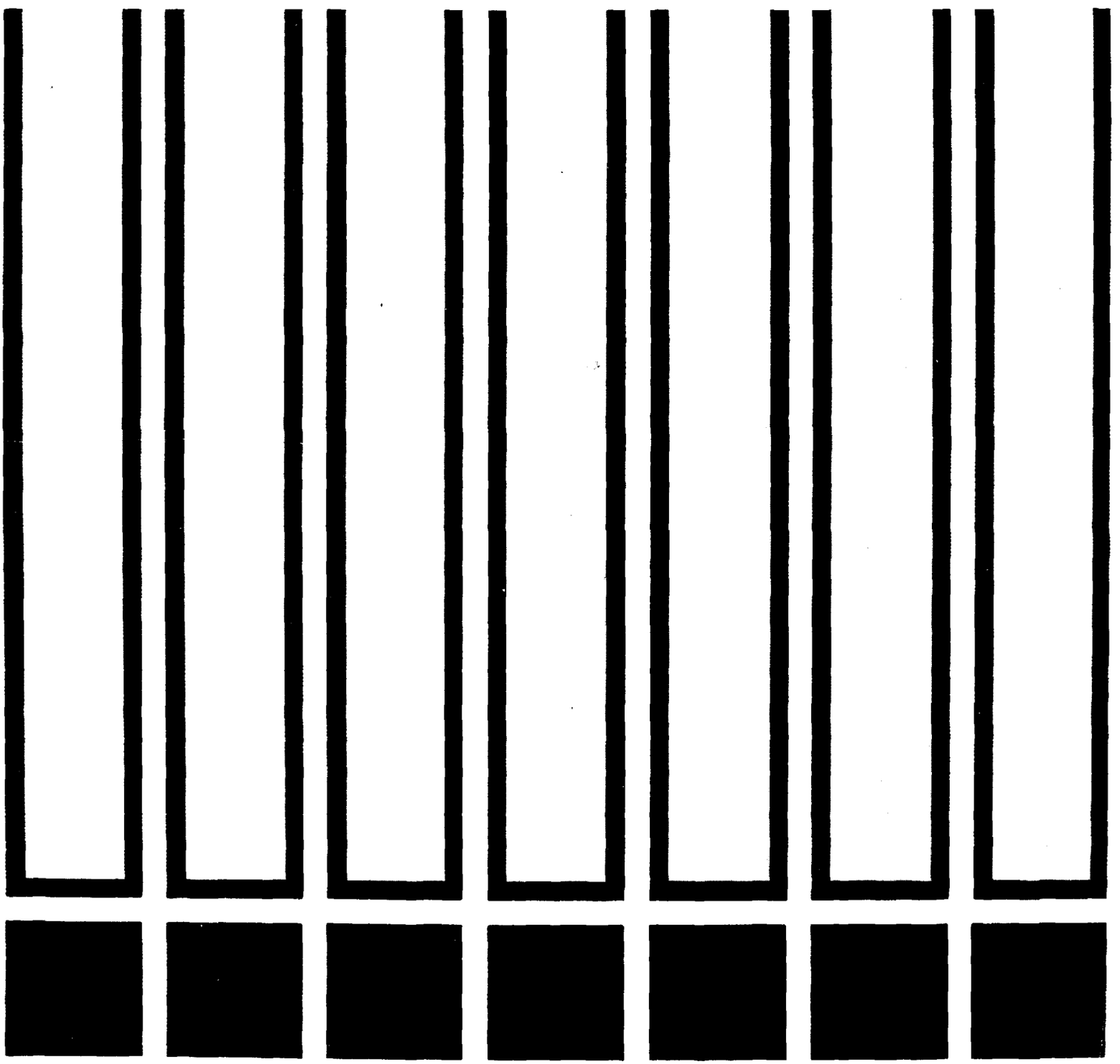
NIOSH

criteria for a recommended standard . . . .
occupational exposure to

ORGANOTIN COMPOUNDS



U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service Center for Disease Control
National Institute for Occupational Safety and Health

criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO ORGANOTIN COMPOUNDS

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health
NOVEMBER 1976

For sale by the Superintendent of Documents, U.S. Government
Printing Office, Washington, D.C. 20402

DHEW (NIOSH) Publication No. 77-115

PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

I am pleased to acknowledge the contributions to this report on the organotin compounds by members of the NIOSH staff and the valuable, constructive comments by the Review Consultants on organotins, by the ad hoc committees of the Society for Occupational and Environmental Health and the Society of Toxicology, and by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine. The NIOSH recommendations for

standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on organotins. A list of Review Consultants appears on page vi.

John F. Finklea, M.D.
Director, National Institute for
Occupational Safety and Health

The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for development of the criteria and the recommended standard for organotin compounds. The Division Review staff for this document consisted of J. Henry Wills, Ph.D., Frank L. Mitchell, D.O., and Douglas L. Smith, Ph.D., with Peter G. Rentos, Ph.D. (Division of Technical Services), and Herbert E. Stokinger, Ph.D. (Division of Biomedical and Behavioral Science). Hervey B. Elkins, Ph.D., and Clara H. Williams, Ph.D., served as special reviewers.

Stanford Research Institute developed the basic information for consideration by NIOSH staff and consultants under contract CDC-99-74-31. Earl S. Flowers, Ph.D., had NIOSH program responsibility and served as criteria manager.

NIOSH REVIEW CONSULTANTS ON ORGANOTIN COMPOUNDS

J. Bradford Block, M.D.
Medical Consultant
Kentucky Department of Labor
Frankfort, Kentucky 40601

Paul E. Morrow, Ph.D.
Professor of Pharmacology and Toxicology
School of Medicine and Dentistry
University of Rochester
Rochester, New York 14642

Rafael Moure
Industrial Hygienist
Oil, Chemical and Atomic Workers
International Union
Denver, Colorado 80201

Arthur W. Sheldon
Director of Safety and Environmental Affairs
M & T Chemicals Inc.
Rahway, New Jersey 07065

Lewis B. Weisfeld, Ph.D.
Director, Applied Sciences R&D Dept.
Cincinnati Milacron
Cincinnati, Ohio 45209

J. J. Zuckerman, Ph.D.
Professor of Chemistry
State University of New York at Albany
Albany, New York 12222

CRITERIA DOCUMENT:
RECOMMENDATIONS FOR AN OCCUPATIONAL
EXPOSURE STANDARD FOR ORGANOTIN COMPOUNDS

Table of Contents

Table of Contents (Continued)

I. RECOMMENDATIONS FOR AN ORGANOTIN STANDARD

The National Institute for Occupational Safety and Health (NIOSH) recommends that employee exposure to organotin compounds in the workplace be controlled by adherence to the following sections. The standard is designed to protect the health and provide for the safety of employees for up to a 10-hour work shift in a 40-hour workweek over a normal working life. Compliance with all sections of the standard should prevent adverse effects of organotin compounds on the health of employees and provide for their safety. Although NIOSH considers the workplace environmental limit to be a safe level based on current information, the employer should regard it as the upper boundary of exposure and make every effort to maintain the exposure as low as is technically feasible. The criteria and standard will be subject to review and revision as necessary.

Organotin is the common name assigned to the group of compounds having at least one covalent bond between carbon and tin. The term "organotin" will be used throughout the document to refer to such compounds. Major subgroups will be referred to as mono-, di-, tri-, and tetraorganotins. The "action level" is set at half the recommended time-weighted average (TWA) workplace concentration limit. An employee is exposed or potentially exposed to organotins if that employee is involved in the occupational handling of the compounds or works in a plant containing organotins. "Occupational exposure" occurs when exposure exceeds the action level or if skin or eye contact with organotins occurs.

"Overexposure" to organotins occurs if an employee is known to be exposed to the organotins at a concentration in excess of the TWA concentration limit, or is exposed at any concentration sufficient to produce irritation of eyes, skin, or upper or lower respiratory tract. If exposure to other chemicals occurs, the employer shall comply also with the provisions of applicable standards for these other chemicals. "Emergency" is defined as any disruption in work process or practice, such as, but not limited to, equipment failure, rupture of containers, or failure of control equipment, which is likely to result in unexpected exposure to organotin compounds in quantities which may cause physical harm.

Section 1 - Environmental (Workplace Air)

(a) Concentration

The employer shall control exposure to organotin compounds so that no employee is exposed at a concentration greater than 0.1 milligram, measured as tin, per cubic meter (mg/cu m) of air, determined as a TWA concentration for up to a 10-hour work shift in a 40-hour workweek.

(b) Sampling and Analysis

Environmental samples shall be collected and analyzed as described in Appendices I and II, or by any methods shown to be at least equivalent in accuracy, precision, and sensitivity to the methods specified.

Section 2- Medical

Medical surveillance shall be provided to employees or prospective employees who may be occupationally exposed to organotin compounds.

(a) Preplacement examinations shall include at least:

(1) Comprehensive medical and work histories.

(2) Comprehensive physical examination including the following tests and procedures:

(A) A 14- x 17-inch postero-anterior chest roentgenogram and determinations of the forced vital capacity (FVC) and the forced expiratory volume at 1 second (FEV 1).

(B) Determinations of activities in blood serum of glutamate-oxaloacetate transaminase (SGOT) and glutamate-pyruvate transaminase (SGPT) and other tests of hepatic function as desired by the attending physician.

(C) Eye examination including tests for visual acuity, color vision, pupillary reactions, and glaucoma. Particular attention should be given to the possible existence of choked disc.

(D) Electrocardiogram for workers over 40 years of age or where otherwise indicated.

(E) Neurologic examination to detect any prior history or evidence of increased intracranial pressure. If spinal fluid pressure is measured, the Queckenstedt maneuver should be performed.

(F) Urinalysis.

(3) An evaluation of the employee's ability to use positive or negative pressure respirators.

(4) Prospective employees or employees with evidence of a medical condition which could be directly or indirectly aggravated by exposure to organotin compounds should be counseled concerning the

advisability of their working with or continuing to work with these compounds.

(b) Periodic examination shall be made available on at least an annual basis or at some other interval determined by the responsible physician. These examinations shall include at least:

(1) Interim medical and work histories.

(2) Physical examination as outlined in paragraph (a)(2) of this section, except that the neurologic examination may be omitted at the discretion of the responsible physician.

(c) Initial medical examinations shall be made available to all employees within 6 months of the promulgation of a standard based on these recommendations. These examinations shall follow the requirements of the preplacement examination.

(d) If an emergency involving organotins arises, a qualified medical attendant designated by the employer shall examine all employees in the affected area, paying particular attention to the lungs and eyes, and determine the need for treatment. If contact with organotins occurs, any contaminated clothing and shoes shall be removed immediately and the eyes or skin shall be flushed immediately with water for at least 15 minutes.

(e) The employer shall provide appropriate medical services to any employee with adverse health effects reasonably assumed or shown to be due to exposure to organotin compounds in the workplace.

(f) The employer or successor thereto shall ensure that pertinent medical records are kept for all employees exposed to organotin compounds in the workplace for at least 5 years after termination of employment. These records shall be made available upon request to the designated

medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.

Section 3 - Labeling and Posting

(a) Containers of organotins shall carry a label which bears the trade name of the product, the chemical name of the organotin contained therein, and information on the effects of the particular compound on human health. The trade name and pertinent information shall be arranged as in the example below.

TRADE NAME
(CHEMICAL NAME)

HARMFUL IF INHALED, SWALLOWED,
OR ABSORBED THROUGH SKIN

IRRITATING TO SKIN AND EYES

Avoid contact with eyes, skin, and clothing.
Keep container closed.
Use only with adequate ventilation.

First aid: In case of skin or eye contact, flush thoroughly with water for at least 15 minutes; consult a physician. If ingested, consult a physician.

(b) In areas where organotins are used, a sign containing information on the effects of the specific compounds on human health shall be posted in readily visible locations. This information shall be arranged as in the example below.

TRADE NAME
(CHEMICAL NAME)

HARMFUL IF INHALED, SWALLOWED,
OR ABSORBED THROUGH SKIN

IRRITATING TO SKIN AND EYES

Avoid inhaling vapor, dust, or mist.
Avoid contact with skin, eyes, mouth, and clothing.
Provide adequate ventilation.

First Aid: In case of skin or eye contact, flush thoroughly with running water for at least 15 minutes; consult physician. If ingested, consult a physician.

(c) If respirators are required, the following statement shall be added in large letters to the sign required in Section 3(b):

RESPIRATORY PROTECTION REQUIRED IN THIS AREA

(d) In any workplace or area where there is a likelihood of emergency situations arising, signs required by Section 3(b) shall be supplemented by additional signs giving emergency and first-aid instructions and procedures, the locations of first-aid supplies and emergency equipment, and the locations of emergency showers and eyewash fountains.

(e) All warning signs and labels shall be printed in English and in the predominant language of non-English-reading employees, unless the employer uses equally effective means to ensure that non-English-reading employees know the hazards associated with organotin compounds and the areas in which there may be occupational exposure to organotins. Employers

shall ensure that employees unable to understand these signs and labels also know these hazards and the locations of these areas.

Section 4 - Personal Protective Equipment and Clothing

The employer shall use engineering controls and safe work practices to keep the concentration of airborne organotins at or below the limit specified in Section 1(a) and shall provide protective clothing impervious to organotins to prevent skin and eye contact. Emergency equipment shall be located at clearly identified stations within the work area and shall be adequate to permit all employees to escape safely from the area. Protective equipment suitable for emergency use shall be located at clearly identified stations outside the work area.

(a) Protective Clothing

(1) The employer shall provide chemical safety goggles or face shields and goggles and shall ensure that employees wear the protective equipment during any operation in which organotins may enter the eyes.

(2) The employer shall provide appropriate impervious clothing, including gloves, aprons, suits, boots, or face shields (8-inch minimum) and goggles and shall ensure that employees wear protective clothing where needed to prevent skin contact.

(b) Respiratory Protection

(1) Engineering controls shall be used whenever feasible to maintain organotin concentrations at or below the TWA concentration limit.

Respiratory protective equipment shall be used in the following circumstances:

(A) During the time necessary to install or test the required engineering controls.

(B) For operations such as maintenance and repair activities causing brief exposure at concentrations in excess of the TWA concentration limit.

(C) During emergencies when concentrations of airborne organotins might exceed the TWA concentration limit.

(D) When engineering controls are not feasible to maintain atmospheric concentrations below the TWA concentration limit.

(2) When a respirator is permitted by paragraph (b)(1) of this section, it shall be selected and used in accordance with the following requirements:

(A) The employer shall establish and enforce a respiratory protective program meeting the requirements of 29 CFR 1910.134.

(B) The employer shall provide respirators in accordance with Table I-1 and shall ensure that employees use the respirators provided. The respiratory protective devices provided in conformance with Table I-1 shall comply with the standards jointly approved by NIOSH and the Mining Enforcement and Safety Administration (formerly Bureau of Mines) as specified under the provisions of 30 CFR 11.

TABLE I-1

REQUIREMENTS FOR RESPIRATOR USAGE
AT TWA CONCENTRATIONS IN EXCESS OF
THE ENVIRONMENTAL LIMIT

Concentration Range (mg/cu m, as tin)	Respirator Type
Less than or equal to 2.5	(1) Full facepiece respirator with combination high efficiency filter and organic vapor canister (pesticide respirator) (2) Supplied-air respirator with full facepiece operated in demand (negative pressure) mode (3) Self-contained breathing apparatus with full facepiece operated in demand mode
Less than or equal to 50.0	(1) Supplied-air respirator with full facepiece operated in continuous-flow (positive pressure) mode, worn with impervious clothing (2) Supplied-air respirator with full facepiece operated in pressure-demand (positive pressure) mode, worn with impervious clothing (3) Powered air-purifying respirator with hood, helmet, or full facepiece and with combination high efficiency filter and organic vapor canister
Greater than 50.0	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand mode (2) Combination supplied-air respirator with full facepiece and auxillary self-contained air supply operated in the pressure-demand mode
Emergency (entry into area of unknown concentration for emergency purposes, such as firefighting)	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand mode, worn with impervious clothing (2) Combination supplied-air respirator with full facepiece and an auxiliary self-contained air supply operated in the pressure-demand mode, worn with impervious clothing
Escape (from area of unknown concentration)	(1) Self-contained breathing apparatus with full facepiece operated in pressure-demand mode (2) Gas mask with full facepiece and with combination high efficiency filter and either front- or back-mounted organic vapor canister

(C) Respirators specified for use in higher concentrations of organotins may be used in atmospheres of lower concentrations.

(D) When a self-contained breathing apparatus is permitted in accordance with Table I-1, it shall be used pursuant to the following requirements:

(i) The employer shall provide initial training and refresher courses on the use, maintenance, and function of self-contained breathing apparatus.

(ii) If the self-contained breathing apparatus is operated in the negative-demand mode, a supervisor shall check employees and ensure that the respirators have been properly adjusted prior to use.

(iii) Whenever a self-contained breathing apparatus is supplied for escape purposes, the respirator shall be operated in the pressure-demand mode.

Section 5 - Informing Employees of Hazards from Organotins

(a) The employer shall provide information at the beginning of employment and on a semiannual basis thereafter on the hazards, relevant symptoms, appropriate emergency procedures, and proper conditions and precautions for the safe handling or use of organotin compounds to employees working in areas where exposure to organotin compounds is likely to occur. Employees engaged in maintenance and repair shall be included in these training programs.

(b) The employer shall institute a continuing education program, conducted by persons qualified by experience or training, to ensure that

all employees have current knowledge of job hazards, proper maintenance and cleanup methods, and proper respirator usage. The instructional program shall include a description of the general nature of the medical surveillance procedures and of the advantages to the employee of undergoing these examinations. As a minimum, instruction shall include the information in Appendix III, which shall be kept on file, readily accessible to employees at all places of employment where exposure may occur.

(c) Required information shall be recorded on the "Material Safety Data Sheet" shown in Appendix III or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Emergency Procedures

Employers shall take all necessary steps to ensure that employees are instructed in and follow the procedures specified below and any others appropriate for the specific operation or process for all work areas where there is a potential for emergencies involving organotins.

(1) Instructions shall include prearranged plans for obtaining emergency medical care and for transportation of injured employees.

(2) Approved eye, skin, and respiratory protection as specified in Section 4 shall be used by personnel essential to emergency operations. Employees not essential to emergency operations shall be evacuated from hazardous areas where inhalation, ingestion, or direct skin or eye contact may occur. The perimeter of these areas shall be

delineated, posted, and secured.

(3) Only personnel properly trained in the procedures and adequately protected against the attendant hazards shall shut off sources of organotins, clean up spills, and repair leaks. Spills and leaks shall be attended to immediately to minimize the possibility of exposure.

(4) Any spills of organotins shall be cleaned up immediately.

(5) Eyewash fountains and emergency showers shall be provided in accordance with 29 CFR 1910.151.

(b) Control of Airborne Organotins

Engineering controls, such as process enclosure or local exhaust ventilation, shall be used whenever feasible, to keep organotin concentrations within the recommended environmental limit. Ventilation systems shall be designed to prevent the accumulation or recirculation of organotins in the workplace environment and to effectively remove organotins from the breathing zones of employees. Exhaust ventilation systems discharging to outside air must conform to applicable local, state, and federal air pollution regulations and must not constitute a hazard to employees. Ventilation systems shall be subject to regular preventive maintenance and cleaning to ensure effectiveness, which shall be verified by airflow measurements taken at least every 3 months.

(c) Storage

Containers of organotins shall be kept tightly closed at all times when not in use. Containers shall be stored in a safe manner to minimize accidental breakage or spillage and to prevent contact with strong oxidizers.

(d) Handling and General Work Practices

(1) Before maintenance work is undertaken, sources of organotins shall be shut off. If concentrations at or below the TWA environmental concentration limit cannot be assured, respiratory protective equipment, as described in Section 4 of this chapter, shall be used during such maintenance work.

(2) Employees who have skin contact with organotins shall immediately wash and shower, if necessary, for at least 15 minutes to remove all traces of organotins from the skin. Contaminated clothing shall be removed immediately and disposed of or cleaned before reuse. If contaminated clothing is to be reused, it shall be stored in a container, such as a plastic bag, which is impervious to the compound, prior to cleaning. Personnel involved in cleaning contaminated clothing shall be informed of the hazards involved and be provided with safety guidelines on the handling of these compounds.

Section 7 - Sanitation

(a) Eating and food preparation or dispensing (including vending machines) shall be prohibited in organotin work areas.

(b) Smoking shall not be permitted in areas where organotins are used, transfered, stored, or manufactured.

(c) Employees who handle organotins or equipment contaminated with organotins shall be instructed to wash their hands thoroughly with soap or mild detergent and water before eating or using toilet facilities.

(d) Waste material contaminated with organotins shall be disposed of in a manner not hazardous to employees. The disposal method must

conform with applicable local, state, and federal regulations and must not constitute a hazard to the surrounding population or environment.

Section 8 - Environmental Monitoring and Recordkeeping

Within 6 months of the promulgation of this standard, employers shall conduct an industrial hygiene survey at locations where organotins are released into workplace air to determine whether exposure to airborne concentrations of organotin is in excess of the action level. The employer shall keep records of these surveys. If the employer concludes that concentrations of airborne organotins are at or below the action level, the records must state the basis for this conclusion. Surveys shall be repeated at least annually and within 30 days of any process change likely to result in an increase of airborne organotin concentrations. If it has been determined that the environmental concentration of organotins might exceed the action level, then the employer shall fulfill the following requirements:

(a) Personal Monitoring

(1) A program of personal monitoring shall be instituted to identify and measure, or permit calculation of, the exposure of each employee occupationally exposed to organotins. Source and area monitoring may be used to supplement personal monitoring.

(2) Samples representative of the exposure in the breathing zone of the employee shall be collected in all personal monitoring. Procedures for the calibration of equipment, sampling, and analysis of organotin samples shall be as provided in Section 1(b).

(3) For each TWA concentration determination, a sufficient

number of samples shall be taken to characterize the employee's exposure. Variations in the employee's work schedule, location, and duties and changes in production schedules shall be considered when samples are collected.

(4) If an employee is found to be exposed above the action level, the exposure of that employee shall be monitored at least once every 3 months. If an employee is found to be overexposed, the exposure of that employee shall be measured at least once every week, control measures shall be initiated, and the employee shall be notified of the exposure and of the control measures being implemented. Such monitoring shall continue until two consecutive determinations, at least 1 week apart, indicate that the employee's exposure no longer exceeds the recommended environmental concentration limit; quarterly monitoring may then be resumed.

(b) Recordkeeping

Employers or their successors shall keep records of environmental monitoring for each employee for at least 5 years after the individual's employment has ended. These records shall include the name and social security number of the employee being monitored, duties and job locations within the work site, dates of measurements, sampling and analytical methods used and evidence for their accuracy, duration of sampling, number of samples taken, results of analyses, TWA concentrations based on these samples, and any personal protective equipment in use by the employee. Records for each employee, indicating date of employment with the company and changes in job assignment, shall be kept for the same 5-year duration. The employer shall make these records available upon request to authorized representatives of the Assistant Secretary of Labor for Occupational Safety

and Health or of the Director of the National Institute for Occupational Safety and Health. Employees or authorized representatives shall have access to information on their own exposures, and the employee or the employee's representative shall be given the opportunity to observe any measurement conducted in accordance with this section.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon that were prepared to meet the need for preventing occupational disease or injury arising from exposure to organotins. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria from which standards can be established to protect the health and to provide for the safety of employees from exposure to hazardous chemical and physical agents. Criteria for any recommended standard should enable management and labor to develop better engineering controls resulting in more healthful work practices and should not be used as a final goal.

These criteria for a recommended standard for organotins are developed as part of a continuing series of documents published by NIOSH. The proposed standard applies only to workplace exposure to organotins arising from the processing, manufacture, or use of the substances as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-large, and any

extrapolation beyond occupational environments is not warranted. It is intended to (1) protect against the development of systemic toxic effects and local effects on the eyes and skin, (2) be measurable by techniques that are valid, reproducible, and available to industry and government agencies, and (3) be attainable with existing technology.

The major concern in occupational exposure to organotins is the potential for liver, kidney, pulmonary, and central nervous system (CNS) damage at low concentrations. Dermatitis, irritation of the eyes, and irritation of the upper and lower respiratory tract have been associated with inhalation of, or skin or eye contact with, organotins and must be considered in any work practices program.

Very little information is now available on the toxic effects of the organotins on animals and on humans which is relevant to setting a standard for the working environment. Retrospective and prospective epidemiologic studies are needed to assess the potential occupational hazards from organotins. Both short-term and long-term inhalation studies on animals are necessary to assess the general toxic effects, particularly on the liver, kidneys, lungs, and CNS, of organotins which are used commercially or which may be used in the future. Chronic studies are also needed to investigate the carcinogenic, mutagenic, and teratogenic potentials of the organotin compounds.

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

(a) Physical and Chemical Properties

Organotins are defined as compounds having at least one covalent carbon-tin bond. Although tin may exist in either the (II) or the (IV) oxidation state, most organotins have a tetravalent structure which can be expressed by the general formula R(n)SnX(4-n), where R is an organic group, (n) is in the range of 1-4, and X is an anion [1]. The organotins are divided into four major groups, mono-, di-, tri-, and tetraorganotins, depending on the number and character of R groups attached to the tin by a C-Sn bond. Organotins as a class show widely varying chemical and physical properties. Table XII-1 [2,3] lists these properties for compounds of industrial importance.

The chemical names for the organotin compounds are often long and cumbersome. Common names are available for only a few compounds. Therefore, abbreviations for chemical names have been used in this document to refer to organotin compounds. Since isomers differ in their toxicity, different isomeric forms of the compounds have also been identified by specific abbreviations. The abbreviations used in this document are listed in Table III-1.

TABLE III-1

ABBREVIATIONS FOR ORGANOTIN COMPOUNDS

Monoalkyltins and Monoaryltins

MBTA	Mono-n-butyltin acid
MBTC	Mono-n-butyltin trichloride
MBTM	Mono-n-butyltin tris(2-ethylhexylmercaptoacetate)
MBTT	Mono-n-butylthiotin acid
METC	Monoethyltin trichloride
MOTM	Mono-n-octyltin tris(2-ethylhexylmercaptoacetate)

Dialkyltins and Diaryltins

DBDA	Dibutyltin diacetate
DBDC	Dibutyltin dichloride
DBDE	Dibutyltin di(2-ethylhexoate)
DBTB	Dibutyltin dibromide
DBTG	Dibenzyltin S,S'-bis(isooctylmercaptoacetate)
DBTM	Dibenzyltin bis(isooctylmercaptoacetate)
DBTO	Dibutyltin oxide
DCHO	Dicyclohexyltin oxide
DEDC	Diethyltin dichloride
DEDI	Diethyltin diiodide
DHDC	Dihexyltin dichloride
DiPDC	Diisopropyltin dichloride

TABLE III-1 (CONTINUED)

ABBREVIATIONS FOR ORGANOTIN COMPOUNDS

DMDC	Dimethyltin dichloride
DOBM	Di-n-octyltin bis(butylmaleate)
DOEH	Bis-2-ethylhexyltin dichloride
DOEM	Di-n-octyltin bis(2-ethylhexylmaleate)
DOTG	Dioctyltin bis(isooctylthioglycolate)
DOTM	Dioctyltin bis(isooctylmercaptoacetate)
DOTO	Di-n-octyltin oxide
DOTMa	Di-n-octyltin maleate
DPDC	Dipropyltin dichloride
DPeDC	Dipentyltin dichloride

Trialkyltins and Triaryltins

TBTA	Tributyltin acetate
TBTB	Tributyltin bromide
TBTBe	Tributyltin benzoate
TBTC	Tributyltin chloride
TBTF	Tributyltin fluoride
TBTH	Tributyltin hydride
TBTI	Tributyltin iodide
TBTL	Tributyltin laurate
TBTO	Bis(tributyltin) oxide
TBTOl	Tributyltin oleate

TABLE III-1 (CONTINUED)

ABBREVIATIONS FOR ORGANOTIN COMPOUNDS

TCHH	Tricyclohexyltin hydroxide
TETB	Triethyltin bromide
TETH	Triethyltin hydroxide
TETS	Triethyltin sulfate
TMTC	Trimethyltin chloride
TnBTF	Tri-n-butyltin fluoride
TPTA	Triphenyltin acetate
TPTB	Tripropyltin bromide
TPTC	Triphenyltin chloride
TPTF	Triphenyltin fluoride
TPTH	Triphenyltin hydroxide

Tetraalkyltins and Tetraaryltins

TeAT	Tetraamyltin
TeBT	Tetrabutyltin
TeET	Tetraethyltin
TeiAT	Tetraisoamyltin
TeiBT	Tetraisobutyltin
TeMT	Tetramethyltin

(b) Manufacture and Use

Until 1962, tetraalkyltin and tetraaryltin compounds had been prepared solely by various modifications of the Grignard reaction [1]. Since then, a number of other methods have been developed. Monomethyltin and dimethyltin salts are presently manufactured in the United States using a direct process involving the reaction of inorganic tin with methyl chloride. Other methods not currently in use in the United States involve the reaction of sodium with R(2)SnCl(2) and RCl to give R(4)Sn. Another method involves the alkylation of tin tetrahalide with organoaluminum, a process which achieves complete alkylation in one step and does not require the use of solvents. Tri-, di-, and monoorganotins are usually prepared by treating tetraorganotins with a tin halogen to form organotin halides, from which other derivatives are made.

Commercially, organotin compounds are used in three major types of applications: as stabilizers in polymers, as biocides, and as catalysts [4]. As stabilizers, organotin compounds, particularly the dialkyltins, prevent degradation of halogen-containing polymers and polyamides, and of such nonhalogenated products as lubricating oils, hydrogen peroxide, and polyolefins and other plastics. The largest use of organotin stabilizers is in polyvinyl chloride (PVC), where the dibutyltin and dioctyltin derivatives are the most important [5].

Diorganotin derivatives are used as heat stabilizers for plastics, as catalysts in the production of polyurethane foams, and in the cold curing of silicone rubber, while triorganotin derivatives are used mainly in biocidal applications [5]. As corrosion inhibitors in chlorinated heat-exchange fluids and as heat stabilizers in polyvinyl chloride, diorganotin

additives act by binding hydrochloric acid formed by thermal decomposition. Diorganotins containing mercaptide ligands stabilize polymers by reacting with organic radicals formed during decomposition. Other diorganotins combine with labile chloro-groups and reactive double bonds, which increases the stabilities of polymeric chains. Trialkyltin derivatives are used as preservatives for wood, textile, paper, leather, and glass, while both trialkyl- and triaryltins are used as rodent repellants, molluscicides, fungicides, and insecticides. In general, the triorganotins show greater toxicity than the diorganotins [6]. Table XII-1 lists industrial applications of selected organotin compounds.

World production of organotin compounds has shown a sustained increase since the 1940's: 1948, a few tons; 1956, hundreds of tons; 1962, 3,000 tons; 1965, 5,000 tons; 1967, 10,000 tons [7]; and 1975, 25,000 tons [8].

Individuals employed in manufacturing operations involving the various organotin formulations or as paint sprayers or PVC compounders represent occupational groups with the greatest potential for exposure. NIOSH estimates that 30,000 employees in the United States may be exposed to organotin compounds.

Historical Reports

The earliest known report of an organotin compound was made in 1849 by Frankland [9] describing the preparation of various ethylmetal compounds, including an unidentified ethyltin derivative. Frankland [10] was later able to characterize this compound as diethyltin diiodide, and he prepared, in addition, diethyltin oxide and dichloride and a compound he

believed to be tetraethyltin.

The first reference to biologic effects of organotin compounds was made in 1858 by Buckton [11], who noted that the chloride form of a class of compounds he called stannic bis-ethyls had a "powerfully pungent odour" and, when heated, produced a vapor that "painfully attacks the skin of the face" and caused fits of sneezing. Eleven years later, Jolyet and Cahours [12] experienced similar effects while conducting a comparative study of the toxic effects of diethyltin dichloride, trialkyltin chloride, and tetraethyltin on dogs. In the dogs, the diethyltin derivative had a strong purgative effect when administered by ingestion or by intravenous or subcutaneous injection. The latter two compounds were more noxious than was the diethyltin derivative. However, the diethyltin chloride, iodide, and sulfate were particularly distinguished, showing more powerful purgatory properties either by ingestion or injection (iv or subcutaneous). White [13], in 1881, noted that the vapor of triethyltin acetate produced headache, general weakness, nausea, diarrhea, and albuminuria, and that tetraethyltin caused severe headaches in the investigator. Chronic exposure studies on rabbits and dogs showed the presence of central nervous system (CNS) effects, motor disturbance, spasm of the gastrointestinal tract and, at high doses, death.

During the early 1940's, the sternutatory, irritative, and lachrimatory properties in humans and animals of triethyltin iodide were studied for possible war-related applications [14-16]. None of these effects were considered potent enough to warrant using the organotins as a war-related material.

In 1954, 102 people died and 100 others suffered permanent injury as a result of taking Stalinon, a French medication said to contain diethyltin diiodide and isolinoleic acid esters (vitamin F), in the treatment of staphylococcal skin infection [17].

Effects on Humans

Lyle [18] studied the qualitative effects of dermal application of some organotins by painting them on the back of the hands of an unstated number of volunteers. Tetrabutyltins and the diacetate, dilaurate, maleate, and oxide derivatives of dibutyltin produced no observable reactions after a single application. Dibutyltin dichloride and the chloride, acetate, laurate, and oxide derivatives of tributyltin produced follicular inflammation and pustulation of various intensities. The most severe lesions were produced by the application of tributyltin chloride (TBTC), while the least severe lesions occurred after the application of tributyltin laurate. Lesions produced by tributyltin acetate healed slowly compared with those produced by other compounds. Lyle [18] assessed the effects produced by single topical applications of TBTC on five volunteers. Skin irritation, characterized by mild edema and itching, developed 3-8 hours after application but was usually completely healed within 7 days.

In 1954, an oral medication containing diethyltin diiodide was marketed in France under the name of Stalinon for the systemic treatment of staphylococcal infections of the skin (eg, boils) [17]. Each capsule of Stalinon was stated to contain 15 mg of diethyltin diiodide (DEDI) and 100 mg of isolinoleic esters (vitamin F). It was responsible for widespread poisoning in France, Algiers, and the near East. A number of

investigations [17,19-29] were conducted on the incident, which involved 210 known cases of intoxication with 98 deaths [21,30]. Another report, in the British Medical Journal [17], placed the number of deaths from the use of Stalinon at 102 and of those permanently injured at 100. Very little information was provided on the precise amount of Stalinon taken by most persons and none on the number of people who took the medication without reported adverse effects. Of 400,000 capsules of Stalinon manufactured, only 7% [17] were taken by the 210 reportedly poisoned victims. The doses taken by patients for whom adequate data were available were calculated in terms of DEDI; this information is presented in Table XII-2. The data indicate that the fatal dose varied from 380 to 750 mg and nonfatal doses from 45 to 675 mg in people between 3.5 and 31 years.

Alajouanine et al [21] summarized the major clinical findings observed in 201 of the 210 known cases. The most characteristic complaint, reported by all but 3 of the 201 patients, was headache, generally diffuse but sometimes predominantly occipital. In some patients, the pain seemed to arise from the teeth and, in others, from the eardrums. Headaches began at various times after ingestion of Stalinon, ranging from 2 to 25 days in 11 of the 210 patients [22]. Nausea and vomiting were reported in 146 instances and "disturbances of consciousness and psychological disorders" in 140 [21]. Photophobia was noted in 67 cases. Other functional visual disorders, which were relatively rare, included double vision associated with oculomotor paralysis, dyschromatopsia (disturbance in color vision) associated with papilledema, acute glaucoma, and both transient and permanent blindness. Disorders of the urinary bladder (either temporary or permanent retention with, in some cases, overflow incontinence) were seen

in 46 patients. The authors considered these bladder function disturbances to be entirely neurologic in origin. Bradycardia or abnormal slowing of the heartbeat, observed in 44 individuals, was considered to be evidence of elevated intracranial pressure. Vertigo, or a feeling of physical instability or inebriation, was reported by 37 patients, and convulsions were observed in 23 persons. The pathologic process underlying all these manifestations of Stalinon poisoning, which was confirmed by autopsy in some cases [22,24] and by exploratory surgery in others [24], appeared to have been an acute cerebral, medullary, and meningeal edema [21].

However, despite the extensive listing of observed signs and symptoms, abnormal physical findings were not apparent in many victims [21]. Of the 98 patients who died, 51 had shown no prior clinical signs. Of the 103 patients who eventually recovered, 46 showed no neurologic signs or symptoms during the course of their illness, even when convalescence lasted several months [21].

Gruner [27] found that the lesions produced in the nervous system of humans by Stalinon intoxication were almost identical with those seen in the brains of monkeys and mice killed after the experimental administration of Stalinon (see Animal Toxicity for details). Macroscopically, the brain was swollen and heavy, but the meninges were dry and the ventricular system was collapsed. Microscopically, only minor lesions were detected in the cerebra. Myelin displacement and degeneration with degeneration of the supporting and glial tissues were also observed. The axons of the central regions were irregular, but fragmentation was a rarity. The macroglia were swollen and filled with granules, with a very pale cytoplasm. The cortex was not so severely affected, but had swollen myelin sheaths, tumefaction

of the oligoglia, and vasodilatation of the deep layer. No abnormalities were observed in the neurons. Peripheral nerves were not discussed.

Studies of the effects of pure DEDI in experimental animals have shown that this compound does not reproduce all the effects reported from the use of Stalinon. This preparation may, therefore, have been contaminated with triethyltin iodide [20,31], monoethyltin triiodide [20], tetraethyltin [20], diethyltin dibromide, or ethyltin tribromide [17]. DEDI may have reacted with the isolinoleic acid esters in the medication to form tetraethyltin [20], a reaction demonstrated to exist by Lecoq [32] in 1954.

Adverse effects produced by occupational exposure to triphenyltin acetate (TPTA) during its use as an agricultural fungicide have been reported by several investigators [33-36]. In 1967, Guardascione and Di Bosco [33] reported three cases involving exposure to TPTA. The first was that of a 68-year-old farmer who sprayed sugar-beet plants with an aqueous solution of TPTA for 2 hours. He developed general malaise and a violent headache, and then lost consciousness. He was hospitalized for 9 days, during which time clinical examinations of the heart function (pulse, blood pressure) and liver revealed no abnormalities, and he recovered completely. The second patient was a 27-year-old male agricultural employee who inhaled some TPTA powder while formulating a fungicidal spray solution. Within a few minutes, he experienced a sensation of facial flushing, then vomited, salivated excessively, and became short of breath. Tests during hospitalization of the patient showed glycosuria (reportedly 3,200 mg% of glucose) as the only clinical finding, and full recovery occurred in 16 days. The normal glucose level of the urine averages 130 mg/24 hr [37]

which is approximately 7.0 mg%. The third man, a 35-year-old farmer, inhaled TPTA dust during spray formulation, and a short time later complained of a violent headache, nausea, vomiting, and epigastric pains. He was hospitalized, but no abnormalities were observed on clinical examination. The epigastric pains and vomiting subsided in 1 day, headaches in 2 days, and he returned to work fully recovered on the 11th day following exposure to TPTA.

In 1967, Markicevic and Turko [36] reported their observations, made in 1963 and 1965, of two groups of Yugoslavian workers engaged in weighing and bagging a 20% triphenyltin acetate formulation known as Brestan. The first group of 13 employees was engaged in these activities 8 hours/day for up to 5 days, and the second group of 35 for 8 hours/day for 2-10 days. No personal protective devices were used, and personal hygiene was reportedly poor. Four of 13 employees in the first group and 9 of 35 in the second group developed signs of irritation of the skin and mucous membrane. A total of six cases from both groups had irritation of the conjunctivae and nasal mucosae. Eight employees suffered from skin irritation, which appeared 2-3 days after direct contact with TPTA-soiled clothing. When exposure ceased however, all such signs disappeared without therapy. No CNS effects were observed in any of the employees.

In 1970, Horacek and Demcik [34] described adverse effects of exposure to the fungicide Brestan-60 in two Czechoslovakian spray-plane pilots and their ground crews. These personnel had also been working with other pesticides during their exposure to Brestan-60. Brestan-60 is composed of 60% triphenyltin acetate, 15% manganese dithiocarbamate (Maneb), and 25% water. One pilot became sick with dyspepsia and severe

diarrhea after working with Brestan-60 for an unstated time. He continued to work for several days while experiencing severe heartburn and dryness of the mouth which was not relieved by drinking large amounts of fluid. After about a week, his vision was affected to the extent that he could only make out the outlines of nearby objects. About 2 weeks after the onset of the initial symptoms, he had an enlarged and very tender liver and, subsequent to hospitalization, hyperglycemia (382 mg%) and glycosuria (7.8 g%). The normal glucose level of whole blood in man is 60-100 mg% and of urine 7.0 mg% [37]. Although the results of other liver function tests were normal, the victim's serum glutamic-pyruvic transaminase (SGPT) was reported by the authors [34] to have increased slightly (2.45 μM/ml serum). However, the normal baseline SGPT value for the patient was not given. Levels continued to increase until the 6th day of illness. Liver damage was confirmed by biopsy and microscopic examination, which showed increased collagen, moderate round cell infiltration, and slight portal and periportal fibrosis in the edges of the affected portal biliary areas; also, there was evidence of hepatocyte regeneration. SGPT values returned to normal following dietary and insulin treatment for diabetes and vitamins and steroids to improve the liver condition. Eleven months later, biopsy revealed active regeneration of the damaged liver parenchyma, and, apart from a slight clinical enlargement of the liver, recovery was complete.

Another pilot was troubled with heartburn, foggy vision, diarrhea, general malaise, coughing, and burning sensations in the chest following exposure to Brestan-60 [34]. His liver was enlarged to two fingers' breadth below the costal margin. The only laboratory finding was moderate hyperglycemia (138 mg%). Liver function tests were normal, and no liver

biopsy was performed. He recovered within 4 days of the onset of symptoms, and, in 6 days, both the size of the liver and the concentration of glucose in the blood had returned to normal. One flight engineer and two ground crew members complained of transient symptoms: two of severe heartburn and unquenchable thirst, and one of diarrhea, postprandial epigastric pain, headache, eye pains, and foggy vision. However, all three were found normal after physical examination and laboratory tests (unspecified). The effects observed by Horacek and Demcik [34] may not have been due entirely to TPTA because other pesticidal agents handled by all affected employees may have influenced the findings.

Liver damage was also attributed to exposure to Brestan in a 1972 report [35] from Yugoslavia, where a fungicide formulator spilled Brestan solution on his hands and chest while loading a plane. Redness of the skin on his chest and abdomen appeared within 3 hours and was followed the next day by vesicles the size of wheat grains; he complained of dizziness, headache, epigastric pain, nausea, and fatigue. After he was hospitalized, most laboratory analyses were found to be within normal limits. At this time, his serum glutamic oxaloacetic transaminase (SGOT) value was 110 units (U) and his SGPT 134 units. The normal ranges for these values are 8-33 U/ml and 1-36 U/ml, respectively [37]. Within 1 month, his SGOT value had increased to 150 units and his SGPT to 575 units, respectively, and he complained of pain in the right hypochondrium (ie, over the liver) [35]. Two months after exposure, clinical examination revealed tenderness of the liver and enlargement to two fingers' breadth below the costal margin, resulting in a diagnosis of liver damage. SGOT and SGPT values were 94 units and 196 units, respectively. Continued deterioration over the next 2

years led to a diagnosis of chronic hepatitis.

A published paper [38] and a written communication (JM Peters, December 1975) described irritation of the eyes and of the respiratory tract in employees exposed to mixtures or products containing bis(tributyltin) oxide (TBTO). In 1973, Landa et al [38] studied women spraying latex paint containing Lastanox T20 (20% TBTO and an unspecified concentration of ethylene oxide condensate) in a ratio of 3 kg of Lastanox T20 to 1,000 kg of latex. After experimental spraying began, all the employees experienced tearing and burning of the eyes, as well as irritation of the nasal mucosa. Employees examined after 14 days of spray-painting exhibited nasal discharge and bleeding, moist and reddened nasal mucosa with purulent secretions, and small hemorrhages on the nasal septum. Signs and symptoms of nasal irritation always subsided on weekends and disappeared completely when the use of Lastanox was discontinued. There was a brief recurrence of the same signs and symptoms on one occasion when Lastanox was inadvertently added to the latex paint, suggesting that Lastanox was probably the cause of the observed signs and symptoms.

In a written communication to NIOSH, Peters (JM Peters, December 1975) reported using a questionnaire to determine the signs and symptoms in 43 employees making sonar domes from a special rubber material containing TBTO. Survey results showed that irritation of the upper respiratory tract and of the eyes occurred in more than 70% of the employees and possible effects on the lower respiratory tract (chest irritation, tightness, and pain) in 20-25% of the group. However, pulmonary function tests performed both before and after the work shift on 18 of the 43 employees failed to show any significant changes in either forced vital capacity (FVC) or

forced expiratory volume in the first second (FEV 1). Similar pulmonary function tests performed on 42 of the employees gave values within the normal range. Of the employees studied, 23% complained of some skin irritation and 23% complained of a loss of appetite.

Area measurements of TBTO were made at eight sites in the plant with a Greenberg-Smith impinger filled with 250 ml of methanol using sampling rates of 19.3-26 liters/minute and sampling times of 32-62 minutes (JM Peters, written communication, December 1975, WA Burgess, written communication, September 1976). Personal samples of two employees were taken using a lapel-mounted Millipore membrane filter and sampling 0.3 cu m of air at a rate of 1.9 liters/minute. All samples were ashed and analyzed for Sn(IV) by atomic absorption. Tin was not detected in the lapel samples of the two employees. Air concentrations of 0.19 and 0.29 mg/cu m of TBTO, measured as tin, were obtained at the two buffing operation sites. At five other locations, the authors reported that TBTO was not detected. However, the limits of sensitivity of the sampling and analytical methods were not given. At the "drop mill," the TBTO concentration was 0.104 mg/cu m, measured as tin. The authors were uncertain regarding the physical state of TBTO as measured in the working environment. Probably, the TBTO was an inseparable constituent of the rubber dust formed during buffing operations; therefore, the possible influence of other constituents of the dust cannot be ignored in considering the results of this study. The number of employees at each of the eight sampling locations and the occurrence of signs or symptoms by job assignment were not specified.

Johnson (written communication, June 1975) reported that irritation of both the upper and lower respiratory tracts was caused by TBTO at air

concentrations which the company measured as "approximately at the TLV." However, Johnson expressed doubt as to the chemical nature of the exposure, and speculated that the exposures might actually have been to an ester of TBTO. No details were given on the sampling and analytical methods employed.

In a butyltin-manufacturing plant, Lyle [18] found that, although there were no signs of systemic intoxication or skin sensitization in the employees, the chlorides of dibutyltin and tributyltin were highly irritating to the skin and eyes. Chemical burns commonly occurred in handlers of the chlorides of dibutyltin and tributyltin when the compounds were in contact with their skin for more than a few minutes. Although painful, these burns were never severe and healed in 7-10 days; itching was the principal complaint. Diffuse, slowly healing lesions were observed in all employees at the butyltin-manufacturing plant. The faint, erythematous eruptions occurred primarily on the lower abdomen, thighs, groin, and perineum of employees handling butyltins, probably resulting from prolonged contact with contaminated clothing. An accident involving the eyes of one employee was reported. Lacrimation and intense and sudden dilatation of the blood vessels of the conjunctivae appeared in minutes, despite immediate lavage, and persisted for 4 days. After 1 week, the employee's eyes were normal, but erythema of the surrounding skin persisted. The prevalence of skin lesions indicates the importance of a good program of work practices, with emphasis on personal hygiene to minimize skin and eye contact.

Only one report of a fatality through occupational exposure to an organotin compound has been found [39]. A 29-year-old woman was drenched

with a chemical slurry containing triphenyltin chloride, diphenyltin dichloride, hexane, and other unidentified compounds at a temperature of 175 F. She was wearing a hardhat, goggles, and coveralls; these articles of clothing were removed after the accident, and she was placed under a shower of water. However, her normal apparel was not removed until her arrival at a hospital. At that time, first-degree thermal burns over 10% of her body (neck, lower face, upper body) were diagnosed. Erythema was apparent 24-36 hours after exposure, followed by second- and third-degree burns with 80-85% desquamated skin 12 hours later. Within 48 hours of the accident, her blood urea nitrogen was 50 mg% and she was febrile. Death from renal failure occurred 12 days after exposure. The agent responsible for the observed effects and for the death of the patient cannot be determined from the available data.

Akatsuka et al [40] observed a marked decrease in the sense of smell of one employee engaged in the manufacture of butyltin compounds. First noted after 16 months of exposure, partial anosmia became almost complete after an additional 8 months of exposure. Nosebleed and occipital headaches were also reported. Two years later, there was no apparent recovery of the sense of smell.

Zeman et al [41], in 1951, reported four cases of employee exposure to unknown concentrations of tetramethyltin (TMT) and tetraethyltin (TET) in a laboratory. The routes and durations of their exposures were not specified. However, 2 days prior to his illness, one employee had cleaned up traces of TeMT with a wiping cloth. Initial symptoms in all four subjects included severe headaches and nausea, with vomiting in two instances. Illnesses lasted 4-10 weeks. In the most severe case of

organotin poisoning, bradycardia, hypotension, and abrupt variations in the sinus rhythm of the heart were observed. These findings suggest that these organotins tested are potent poisons of the circulatory system and may affect the autonomic nervous system.

Animal Toxicity

(a) Mice

(1) Inhalation

Several inhalation experiments have been performed using mice to assess the toxic effects of a number of organotin compounds [16,42].

Igarashi [42] exposed mice to a butyltin formulation composed of 81.2% tributyltin bromide (TBTB), 3.7% dibutyltin dibromide (DBTB), 8.5% of a material described as a hydrocarbon fraction, and 6.6% unspecified substances. Male mice averaging 10 g were divided into groups of 10 each and exposed to the butyltin formulation at concentrations of 5.65 and 2.12 mg/cu m, measured as tin, in an environment maintained at 20 C. Butyltin concentrations were determined by collecting the mixture in xylene and analyzing for tin with a quartz spectroscope. Two control groups of animals consisted of an unexposed group and a group placed in the exposure chamber but not exposed to butyltin. The surviving animals were monitored for at least 20 days.

Exposures to the butyltin mixture at a concentration of 5.65 mg/cu m, measured as tin, were carried out using varying exposure schedules [42]. During exposure to the butyltin mixture, all animals exhibited piloerection, reddening of the skin, and dilatation of the blood vessels of the nose, feet, and tail. Six to seven hours after exposure, the mice were

dyspneic, and some continued to have respiratory difficulty for several minutes after removal from the exposure chamber. Those mice exposed for longer periods of time had loss of fur, thin scabs on the ears and tail, and discharges from the eyes. Animals exposed for 8 hours had no fatalities. Those exposed for 8 hours on 1 day and 4 hours the next had 70% fatalities. Eight-hour exposures on 2 and 3 consecutive days produced 85 and 100% fatalities, respectively. All fatalities occurred within 5 days after exposure ended. All of the test animals lost weight. The skin, trachea, lungs, liver, kidneys, spleen, brain, and heart of three mice exposed to butyltin for 8 hours/day on 3 successive days were examined. Macroscopically, dilatation of all blood vessels was observed, and definite congestion was found in the lungs. Microscopically, edema in the skin and trachea, congestion in the liver and kidneys, and a large amount of bleeding and congestion in the lungs were observed. The other organs appeared normal.

Eight-hour/day exposures for 1-7 consecutive days at 2.12 mg/cu m of the butyltin mixture, measured as tin, were carried out on 11 groups of mice [42]. Control groups were monitored as in the study at 5.65 mg/cu m. Observations of the animals during exposure were similar to those described at 5.65 mg/cu m [42]. No fatalities occurred with exposures of 8 hours/day for 2 days, 10% died after 3 days of exposure, 55% after 4 days, 70% after 5 days, 90% after 6 days, and 100% after 7 days of exposure. All deaths occurred within 6 days after completion of exposure. All test animals lost body weight in proportion to the length of exposure.

Animals exposed to the butyltin mixture at 2.12 mg/cu m, 6 hours/day, 5 days/week, for 12 weeks had macroscopic findings similar to those in mice

subjected to exposures at 5.65 mg/cu m [42]. They included dilatation of the blood vessels. Microscopically, these mice had congestion and some edema of the cell nuclei and cytoplasm and thickening of the epidermis. All mice also had hemorrhages in their tracheas. Congestion was evident in the lungs and liver of all mice examined. Almost all mice had signs of edema of the glomerulus, and most had edema of the ureter, with edema and separation of the epithelium of the veins. No unusual effects were found in the myocardium, brain, or spleen. The examination 1 month after the termination of exposure showed no conspicuous macroscopic or microscopic changes, indicating that the conditions were reversible. Cellular edema and hemorrhaging in the trachea were absent in mice examined at 1 month but were present in two of three mice examined 2 months after the start of exposure.

The results obtained by Igarashi [42] indicate that the butyltin mixture containing 81.2% of tributyltin bromide is a potent poison affecting the respiratory tract, lungs, liver, and kidneys after single and repeated daily exposures. The lungs were found to be particularly sensitive in experiments involving repeated exposures. Lung damage persisted at least 1 month after exposure. Damage to the liver and kidneys sustained after 6 days of exposure at 2.12 mg/cu m was reversed within 1 month after termination of exposure.

Igarashi [42] evaluated the susceptibility of mice by sex to the tin formulation previously described. The mice were divided into 4 groups as follows: 1 group of 10 males, 2 groups of 10 females each, and 1 group of 5 males and 5 females. The mice in the first three groups weighed 9-11 g and those in the fourth group weighed 20-30 g each. The mice were exposed

for 6 successive days, 7 hours/day, at average concentrations of 2.12 mg/cu m of butyltin, and were monitored for 20 days from the start of the exposure. The females averaged 95% fatalities for mice weighing 10 g and 100% fatalities for mice weighing 20-30 g. For the males, the corresponding mortality figures were 70 and 80%.

Glass et al [16] examined the inhalation toxicity of triethyltin bromide (TETB), tripropyltin bromide (TPTB), tributyltin bromide (TBTB), tributyltin hydride (TBTH), tributyltin iodide (TBTI), and tetramethyltin (TMT) for white mice averaging 19-21 g in weight. The exposure chamber and methods of establishing desired vapor concentrations were similar to those described by Silver [43]. Nominal concentrations were estimated from the rates of air flow and the weights of the containers of organotins before and after each exposure [16]. Groups of 20 mice each were exposed for 10 minutes at the concentrations shown in Table XII-3 and were observed for up to 10 days. During exposure, all mice had intense lacrimation and gasping respiration. The numbers of deaths produced by the exposures to the six compounds are given in Table XII-3. All mice that died became prostrate and exhibited convulsions prior to death. An examination of those animals that died from exposure to TETB, TPTB, TBTB, or TeMT revealed marked edema of the lungs and of the perivascular connective tissue. At a TBTB concentration of 5.2 mg/liter (5,200 mg/cu m), all animals died of pulmonary edema with 50% dying on the 1st day. At other TBTB concentrations and with the other compounds, animals that survived for at least 2 days showed fatty changes in the liver and kidneys. No vesications were observed in these mice from any of these compounds at concentrations of 1.3-3.2 mg/liter (1,300-3,200 mg/cu m).

(2) Oral

Pelikan and Cerny [44,45] performed a series of experiments on mice to determine the single-dose oral LD50 and the toxic effects of monobutyltin and monooctyltin compounds. Strain H white mice, averaging 20 (±0.5) g were used in these experiments.

Single-dose, oral LD50's were determined for mono-n-butyltin trichloride (MBTC), mono-n-butyltin tris(2-ethylhexyl mercaptoacetate) (MBTM), mono-n-butyltin acid (MBTA), and mono-n-octyltin tris(2-ethylhexyl mercaptoacetate) (MOTM), using 36 experimental groups and 2 control groups of 5 male and 5 female mice each [44,45]. The experimental groups received by intubation doses of 200, 400, 800, 1,200, 1,600, 2,400, 3,200, 4,000, or 6,000 mg/kg body weight dissolved in 0.2 ml of sunflower seed oil and were observed for 48 hours. The control groups received 0.2 ml of sunflower seed oil or water. The results were evaluated using a modification of the probit method devised by Roth to obtain the following LD50 values: MBTC, 1,400 mg/kg; MOTM, 1,500 mg/kg; MBTM, 1,520 mg/kg; and MBTA, greater than 6,000 mg/kg [44].

Pelikan and Cerny [44,45] examined the toxic effects of MBTC, MBTM, MBTA, MOTM, and mono-n-butylthiotin acid (MBTT), using single doses of 4,000 mg/kg administered by intubation to five experimental groups composed of equal but unspecified numbers of male and female mice. Water or sunflower seed oil (0.2 ml) was administered to two control groups by the same route on the same day. Clinical observations were made during the 24-hour period immediately following the administration of the doses. During the first 4 hours, MBTC, MBTT, and MBTM had no effect, but they caused muscular weakness, reduced movement, lack of interest in the surroundings,

and loss of appetite by the end of 12 hours. After 24 hours, the mice did not respond to sound and light stimuli, and their reactions to mechanical stimuli had diminished. The authors observed similar but less severe effects with MOTM. With MBTA, clinical effects did not appear until 24 hours after administration and included general weakness, sporadic clonic convulsions, and, in most mice, a periodic respiration of the Cheyne-Stokes type. All mice were killed 24 hours after receiving the tin compounds. Macroscopic and microscopic examinations were performed on the liver, kidneys, adrenal glands, lungs, stomach, intestines, spleen, pancreas, and abdominal lymphatic tissues. These compounds induced enlargement of the liver, this effect being least severe with MBTA. All compounds except MOTM produced hyperemia of the kidneys, and all except MOTM produced hyperemia of the spleen in mice. Microscopically, fatty degeneration of the liver and kidneys was reported for all compounds except MBTC. This effect was most severe with MBtTA and least severe with MOTM. Hemorrhages of the stomach and intestinal walls were observed only with MBTC. No abnormalities were found in the controls.

In a continuation of their study of organotins, Pelikan et al [46] and Pelikan and Cerny [47] determined the oral LD50's and toxic effects in mice of di-n-octyltin bis(2-ethylhexylmaleate)(DOEM), di-n-octyltin bis(butylmaleate)(DOBM), di-n-octyltin maleate (DOTMa), tributyltin acetate (TBTA), tributyltin benzoate (TBTBe), tributyltin chloride (TBTC), tributyltin laurate (TBTL), and tributyltin oleate (TBTOl) [46,47]. They obtained the following single-dose LD50 values with a 48-hour observation period: DOBM, 3,750 mg/kg; DOEM, 2,700 mg/kg; DOTMa, 2, 250 mg/kg; TBTOl, 230 mg/kg; TBTL, 180 mg/kg; TBTC, 117 mg/kg; TBTBe, 108 mg/kg; and TBTA,

46 mg/kg.

Clinical signs at 4, 12, and 24 hours for the dioctyltins were similar to those observed with the monoalkyltins but were more severe [46]. Macroscopic and microscopic examinations for all compounds showed that damage to the liver, kidneys, and spleen produced by a single dose of 4,000 mg/kg was of the same nature as that from the monoalkyltins [46]. However, similar effects were obtained with doses of 500 mg/kg of the tributyltins [47], indicating that these compounds are more toxic than their monoalkyltin and dialkyltin counterparts.

Results from these studies [44-47] indicate that monoalkyltins are the least toxic and trialkyltins the most toxic of the compounds studied. The compounds are nonspecific in their toxic actions, but the liver, kidney, and spleen are the organs most susceptible to damage.

Calley et al [48] used albino mice to compare the toxic effects on the liver of some butyltin derivatives. To select the proper dosage for these experiments, the single-dose oral LD50 values for white mice of a uniform weight and age were determined for tetrabutyltin (TeBT), tributyltin acetate (TBTA), dibutyltin diacetate (DBDA), and dibutyltin di(2-ethylhexoate) (DBDE), with observation for 1 week after the dose was administered. The compounds were administered to mice in groups of 10 by intubation in doses increasing in a geometric progression by a factor of 2. The LD50 values obtained were 6,000.0, 99.1, 109.7, and 199.9 mg/kg for TeBT, TBTA, DBDA, and DBDE, respectively.

Torack et al [49] induced cerebral edema and swelling in mice by administering in the diet 12-32 ppm triethyltin sulfate or triethyltin hydroxide for an unspecified period. The authors examined brain tissues

microscopically to study the changes in fine structure associated with accumulation of cerebral fluid. Initially, the mice were irritable and showed prominent muscular weakness, especially of the hindlimbs. This was followed by increasing generalized rigidity of the body, with shallow respiration. Brain tissues from 25 mice were taken at varying stages of intoxication and clinical manifestations. Examination by light microscopy revealed evidences of edema in the myelinated areas of the brain, dilatation of the perivascular clear spaces, and swelling of the glial cell bodies. Electron microscope examination of brain tissues of 18 mice in the early stages of intoxication showed an enlargement of the glial cell processes, but, in the less severe lesions, the mitochondria, endoplasmic reticulum, and cell membranes appeared to be relatively normal. In the advanced stages, endothelial cells were swollen, mitochondria enlarged, and the number of microglia increased in the edematous areas. The clear glial cell membranes were ruptured, but there was no accumulation of fluid in the intracellular spaces.

Gruner [27] reported that mice and monkeys killed after the experimental administration of Stalinon had lesions of the CNS which were almost identical with those in humans suffering from Stalinon intoxication. Few procedural details were provided except that the Stalinon dose in monkeys was in the same range as that administered therapeutically to humans. Macroscopically, the brain was swollen and heavy, but the meninges were dry and the ventricular system was collapsed. Microscopically, only minor lesions were detected in the cerebra. Myelin displacement and degeneration, with degeneration of the supporting and glial tissues, were also observed. The axons of the central regions were irregular, but

fragmentation was rare. The macroglia were swollen and filled with granules, with a very pale cytoplasm. The cortex was not so severely affected but had swollen myelin sheaths, tumefaction of the oligoglia, and vasodilatation of the deep layer. No abnormalities were observed in the neurons. Peripheral nerves were not discussed. Examination of the organs of both species of experimental animals showed gross vasodilation, severe edema, small hemorrhages, and proliferation of the Kupffer cells in the liver. The study indicated that the organotins produced similar CNS changes in mice, monkeys, and humans.

The influence of aliphatic chain branching on the toxicity of tetrabutyltin and tetraamyltin was examined by Caujolle et al [50], using the normal and iso isomers of these compounds. Groups of 10-20 male and female mice weighing 18-20 g were observed for 30 days after the oral administration of the test compound at doses of 2-40 mM/kg for tetrabutyltin, 0.5-25 mM/kg for tetraisobutyltin, 1-40 mM/kg for tetraamyltin, and 0.25-20 mM/kg for tetraisoamyltin. The animals at all dose levels displayed a loss of muscle tone; those given the higher doses had paralysis of the hindquarters and superficial respiration. Mortality rates (Table XII-4 a-d) indicated that the iso derivatives were more toxic than the normal derivatives. The butyl derivatives were found to be more toxic than their amyl counterparts. Similar findings were reported by the authors with im, iv, and ip administration of these compounds at similar doses to mice [50].

The toxicities of dibutyltin dichloride (DBDC), tributyltin chloride (TBTC), and tetrabutyltin (TeBT) were compared by Yoshikawa and Ishii [51]. Single ip injections of 1-3.7 mg/kg were administered to groups of 10 male

mice. After 8 days, the surviving mice were killed and the weights of their organs, as fractions of the body weights, were compared with those of 20 untreated male mice. Mice given DBDC or TeBT had enlarged livers, but those given TBTC did not. All three compounds caused an increase in the weight of the spleen in the treated animals. Brain weight in animals treated with TBTC or TeBT was greater than that of the control mice, but this effect was not observed in DBDC-treated mice. All compounds produced increases in kidney weight. The results indicate that TeBT had some effects similar to those of both DBDC and TBTC, but DEDC and TBTC differed in their toxic actions.

(3) Intraperitoneal

Kolla and Zalesov [52] administered organotins by ip injection to study the influence of chemical structure on the toxicities of the compounds. Eight hundred white mice weighing 16-17 g were used for a series of experiments in which different groups were given one of 11 triaryl- or tetraryltin derivatives in progressive doses until 100% fatality was achieved. Animals were observed over a 10-day period or until 100% fatality, and LD50's were calculated using the Litchfield and Wilcoxon method. The LD50's obtained are listed in Table XII-5, along with results of a statistical analysis comparing the toxicities of these compounds. The results indicated that the toxicity of an organotin compound was dependent upon both the type of anion and the organic side group. The halide salts appeared to be more toxic than the corresponding alkylated compounds; the bromides were more toxic than the iodides. No chlorides were used. Toxicity decreased with an increase in methylation of the aromatic radical. The tetraaryl derivatives were less toxic than their triaryl counterparts.

Branching of the carbon chain in the alkyl group appeared to increase the toxicity of the compound.

(b) Rats

(1) Inhalation

Inhalation studies have been performed on rats under acute and chronic test conditions to evaluate the toxic properties of some triorganotins. Acute dust inhalation studies [53,54] were conducted for tri-n-butyltin fluoride (TnBTF) and triphenyltin fluoride (TPTF). For TnBTF studies, young adult albino rats with an average weight of 165 g were divided into five groups of five males and five females [53]. No control group was described in the studies. Animals were exposed to TnBTF in a test chamber for 4 hours, and mortality and behavioral reactions were noted. At the end of exposure, the animals were observed for an additional 14 days and then killed for gross pathologic examination. The concentration of TnBTF dust was determined from repeated samples from the breathing zone of the animals, using a glass-fiber filter. The average concentrations of TnBTF for the five groups were 1.1, 5.3, 23.0, 58.0, and 190.0 mg/cu m, which are equivalent to 0.4, 2.0, 8.8, 22.3, and 73.0 mg/cu m, measured as tin.

At 0.4 mg/cu m of TnBTF, as tin, the author reported that the only observed abnormality was a "less than normal" weight gain, which was also observed in the other four groups [53]. There were no deaths at 0.4 mg/cu m; 5 animals died at 2.0 mg/cu m; and all 10 died at the other three concentrations. At 2.0 mg/cu m, bloody lacrimation and weakness were apparent in all 10 animals, with prostration in 5 animals. At 8.8, 22.3, and 73.0 mg/cu m, sneezing, ptosis, lacrimation, clear nasal discharge,

bloody lacrimation, weakness, and prostration were observed in all animals. Salivation and bloody nasal discharge were seen in only three animals at 8.8 mg/cu m, but were present in all animals at 22.3 and 73.0 mg/cu m. An autopsy of animals from the five groups revealed no gross pathologic alterations; tissues and organs examined were not specified. From the mortality data, an LC50 of 2.0 mg/cu m, as tin, was determined.

Using the same acute inhalation procedures and protocol, the investigators exposed four groups of 10 young adult albino rats (5 males and 5 females), with an average weight of 214 g, to triphenyltin fluoride (TPTF) dust for 4 hours at a concentration of 130, 300, 510, or 930 mg/cu m [54]. These concentrations are equivalent to 41.9, 96.6, 164.2, and 299.5 mg/cu m, as tin. No control group was described. As with TnBTF, body weight gains in all four groups were reported to be "less than normal" by the authors. No abnormal reactions other than death were observed at 41.9 mg/cu m, as tin, while bloody nasal discharge and bloody ocular discharge were seen in eight rats at 96.6 mg/cu m and in all animals at 164.2 and 299.5 mg/cu m. There were 2 deaths at 41.9 mg/cu m, 3 at 96.6 mg/cu m, 8 at 164.2 mg/cu m, and 10 at 299.5 mg/cu m. From the mortality data, an LC50 of 93.4 mg/cu m, as tin, was determined. The only gross abnormalities observed in some of these animals at autopsy were mild to severe focal discoloration of the lungs and enlarged lungs.

The acute inhalation toxicity of dimethyltin dichloride (DMDC) vapor was evaluated in the presence of varying amounts of trimethyltin chloride (TMTC) contaminant, using young adult Charles River albino rats in groups of five males and five females [55]. Animals were exposed to DMDC for 1 hour, and mortality and behavioral reactions were observed for 21 days.

Nominal vapor concentrations were based on weight loss of the test material and total volume of air used. At the end of the 21-day period, animals were killed, and gross pathologic examination was conducted.

At DMDC concentrations of 1,910 mg/cu m (1,031 mg/cu m, as tin), 1,610 mg/cu m with 0.19% TMTC (870 mg/cu m, as tin), and 2,640 mg/cu m with 0.87% TMTC (1,428 mg/cu m, as tin), no deaths occurred [55]. Body weight gains were normal, and autopsy revealed no gross pathologic alterations. Hypoactivity and roughed fur were observed at these three concentrations; ptosis, enophthalmos, and salivation were present also at 2,640 mg/cu m with 0.87% TMTC. At a concentration of 2,110 mg/cu m with 2.09% TMTC (1,142 mg/cu m, as tin), all animals died within 11 days and hypoactivity, roughed fur, ptosis, enophthalmos, anesthesia, and tremors were observed in all animals. However, autopsy revealed no abnormalities attributable to DMDC toxicity. With DMDC at a concentration of 4,080 mg/cu m with 3.59% TMTC (2,205 mg/cu m, as tin), results were similar except that all animals died within 4 days.

Similar test procedures were used to study the effects of short-term inhalation of DBDC and TMTC vapors [55,56]. Rats exposed to DBDC for 1 hour at a concentration of 1,470 mg/cu m (575.0 mg/cu m, as tin) showed roughed fur, hypoactivity, ptosis, and salivation within the 14-day observation period [56]. There were no deaths. Body weight gains were normal and autopsy revealed no gross pathologic alterations. All rats exposed to TMTC at a concentration of 8,890 mg/cu m (5,334 mg/cu m, as tin) died on the 1st day; signs included hypoactivity, roughed fur, enophthalmos, ptosis, anesthesia, and dyspnea [55]. Autopsy revealed no abnormalities attributable to TMTC.

Two vapor inhalation studies were conducted to determine the toxic effects of tributyltin chloride (TBTC) and tributyltin bromide (TBTB) on rats [57,58]. Gohlke et al [57] exposed forty 4-month-old female albino rats to TBTC at concentrations of 4-6 mg/cu m for 6 hours/day, 5 days/week, during a 4-month period. A dynamic chamber with an airflow of 950 liters/hour was used. Appropriate TBTC concentrations were achieved by saturating dry air with TBTC in a bubbler and diluting the resulting saturated vapor with dry fresh air. Nominal exposure concentrations were calculated from the weight of TBTC evaporated and the airflow through the chamber. The controls consisted of 20 unexposed rats. Body weight and the threshold response of the hindlimbs to electric shock were determined every 2-3 weeks. Counts of red and white blood cells and hemoglobin determinations were made every 3-4 weeks. Eight experimental and four control animals were killed every 4-6 weeks, with the last rats killed 4 weeks after termination of exposure. There were no fatalities from TBTC inhalation. Inflamed eyes and nostrils were the only signs observed during the final month of exposure. Body weight, threshold response to electric shock, blood count, and hemoglobin concentration for the experimental group did not differ significantly from control values. The animals were weighed and their brains, lungs, hearts, spleens, kidneys, and adrenals were examined macroscopically. Microscopic examinations were performed on the brain, lungs, liver, and kidneys. The only significant difference from controls observed in these organs was in liver weight, which was higher than the control value after 2 months of exposure and lower 1 month after the end of exposure. Microscopically, the liver showed phagocytizing Kupffer cells, which were swollen, and proliferating, small areas of

necrosis, middle-grade fibrotic expansion of the periportal areas, and fine to medium droplets of fatty degeneration. Liver damage increased in severity with length of exposure and was not reversed after exposure ceased. Four months after exposure, the kidneys showed interstitial proliferation of inflammatory cells and an accumulation of cell detritus and eosinophils in the tubules. The brain contained massive arterial hyperemia, pronounced cerebral edema, and cellular necrosis. Brains of animals examined 1 month after the end of exposure showed signs of returning to normal. These results indicated that severe brain damage by TBTC may be asymptomatic.

Iwamoto [58] performed a series of inhalation experiments to study the effects of TBTB on the reproductive functions of rats. The material used was a mixture of 81.2% TBTB with small amounts of dibutyltin dibromide and hydrocarbons. Mature male and female rats weighing 200-320 and 150-180 g, respectively, were exposed to TBTB in a test chamber maintained at about 20 C at a concentration of 2 mg/cu m, measured as tin with a quartz spectrophotometer. The concentration of TBTB in the chamber was maintained by aeration of a TBTB mixture kept in the chamber. Five females exposed 5 hours/day for 38 days and mated to unexposed males during the hours of nonexposure in the last 28 days had a pregnancy rate of 60%, compared to 100% pregnancy in the controls. Ten females exposed 5 hours/day for 6 weeks, with mating occurring during hours of nonexposure for the last 4 weeks, had a pregnancy rate of 10%. A partial recovery of reproductive capabilities in the exposed rats occurred within 16 days after exposure ended. Three groups of five females exposed 2 hours/day for 2, 3, or 4 months, with mating occurring for the last 4 weeks, had pregnancy rates of

60%, 20%, and 0%. A partial recovery of reproductive capabilities was observed 1 week after the exposure ended in all females exposed for 3 months and 10 days after exposure ended in all females exposed for 4 months. Two groups of five males exposed 5 hours/day for 2 or 7 weeks, followed by a 5-hour/day exposure during a 4-week mating period, impregnated all unexposed females. When five males and five females were exposed 5 hours/day for 6 weeks, with mating during the last 4 weeks, no pregnancies occurred.

The sex organs of 3 males exposed 5 hours/day for 79-80 days, 3 females exposed for 42 days, 4 females exposed for 42 days and allowed to recover for 7-28 days, 5 females exposed for 7-14 days, and 10 females exposed for 14 days with a 7- to 28-day recovery period were examined microscopically [58]. No effects were observed in the male sex organs. However, a slight atrophy of the glandular tissues of the uterus could be seen after 14 days of exposure. After 42 days of exposure, a marked atrophic destruction of the glandular epithelium and a marked increase in interstitial connective tissues were seen in the uterus. No changes were observed in the ovaries.

The livers, kidneys, lungs, spleens, hearts, and adrenals of these animals also were examined microscopically [58]. All rats developed bronchitis, with one-half showing bronchogenic pneumonitis after 14 days of exposure. After 42 days, bronchitis was milder and pneumonitis was not observed. Mild atrophy was first observed in the liver 14 days after exposure, and was more severe after 42 days. After 14 days, the lymph nodes of the spleen were slightly atrophic and an increase in splenic cells was seen. After 42 days, thickening of the medullary sheaths was noted in

the spleen, with no changes in the condition of the lymph nodes. All effects were reversible, with time of recovery directly related to length of exposure. No effects were noted in the other organs examined.

(2) Oral

Stoner et al [59], Barnes and Stoner [60], and Barnes and Magee [61] used albino rats in a series of studies to compare the toxic effects of dialkyltin and trialkyltin salts administered orally in the animals' diet or by intubation. Groups of four male and four female rats were administered single doses of dibutyltin dichloride (DBDC) by intubation at concentrations of 10, 20, 50, 100, 200, and 400 mg/kg and observed for 10 days [60]. All rats survived except one female and one male at 200 mg/kg and two females and all males at 400 mg/kg. Rats receiving the 50-mg/kg dose were "ill" for 24-48 hours but recovered rapidly thereafter. At the end of the observation period, the survivors were killed and examined microscopically. The only tissue damage reported was an inflammatory bile-duct lesion at 20 mg/kg and at 50 mg/kg.

Three successive daily doses of DBDC at 50 mg/kg by intubation produced bile-duct damage in all rats; 9 of 18 males and 4 of 18 females died [61]. In a few of these cases, death was attributed to bile peritonitis or to severe liver damage produced by a rupture of the bile duct. All survivors 15 months after treatment showed a thickened and shortened, but functional, bile duct, indicating that the impairment of function was reversible. Four successive oral doses of 50 mg/kg of the dilaurate and diisooctylthioglycolate salts of dibutyltin given daily to groups of four rats produced no toxic effects significantly different from those due to DBDC. Mice given three consecutive daily doses of 50 mg/kg

DBDC sustained liver damage similar to that in rats, but effects were more severe. Guinea pigs were less susceptible, withstanding repeated daily doses of 50-100 mg/kg with no evidence of biliary tract damage.

Barnes and Magee [61] conducted a detailed study of DBDC-induced damage to the bile duct and surrounding tissues. A single dose of 50 mg/kg of DBDC was administered orally to an unspecified number of rats by intubation. The animals were killed and the bile duct and surrounding related tissues were examined. Inflammatory edema of the bile duct, spreading into the pancreas, could be seen 4 hours after the administration of DBDC. Fourteen hours after the dose, pancreatic edema became visible and definite breaks were identified in the epithelium of the intrapancreatic part of the bile duct. After 48 hours, damage to the extrahepatic bile duct was more extensive, and acute inflammation of the portal tract of the liver was present. At this stage, damage to the pancreas and bile duct was reversible. If another dose of 50 mg/kg was administered, the integrity of the wall of the duct was destroyed, with formation of a granulated tissue. Liver damage was not extensive, but the degree of damage was proportional to the severity of the bile-duct lesions.

Barnes and Magee [61] showed that bile-duct lesions did not develop in rats receiving 50 mg/kg DBDC orally if the flow of bile in the duct was stopped. The effects of pancreatic secretions on the development of bile-duct lesions were examined by iv administration of either a stimulant or an inhibitor of pancreatic secretions to rats after the administration of 50 mg/kg DBDC. No differences were found in the severity of lesions in the two groups.

The distribution of tin in the tissues of bile-cannulated rats was determined using a polarographic method [61]. Animals were administered DBDC at 50 mg/kg by intubation, and bile and pancreatic secretions were collected for a 24-hour period. The tin concentrations in the bile and the pancreatic juice were 1.8 μg/ml and 0.8 μg/ml, respectively, at 12 hours, when bile-duct lesions were first observed. After 16-24 hours, the concentration of tin increased to 9.8 μg/ml in the bile and 3.6 μg/ml in the pancreatic juice. During this period, the average concentration of tin was 5.0 μg/ml in the blood, 61.0 μg in the liver, and 19.0 μg in the kidneys. No tin was found in the pancreatic tissue. The authors concluded that the concentration of tin in the bile and the pancreatic juice was not high enough to be responsible for the observed bile-duct damage.

In another study, Barnes and Stoner [60] administered eight dialkyltin dichloride compounds by intubation at doses of 40, 80, and 160 mg/kg to pairs of female rats on the 1st and 4th days of the experiment. However, six of the compounds at 160 mg/kg and dihexyltin at 80 mg/kg were administered only on the 1st day. Some of these compounds produced bile-duct lesions similar to those induced by DBDC and of varying intensity (Table XII-6). When these eight compounds were administered to rats percutaneously (Table XII-7) or iv (Table XII-8), the same type of damage to the bile duct was observed.

Diets containing 20, 40, or 80 ppm of triethyltin hydroxide (TETH) were fed to groups of five rats for a 60-day period [59]. All rats had extensive CNS damage, including cerebral edema. Symptoms of intoxication appeared after 7 days of feeding and included slow breathing and hindleg paralysis. Muscular tremors were also observed at 40 ppm. These findings

suggest that TETH at concentrations as low as 20 ppm is toxic when administered in the diet for 2 months.

Barnes and Stoner [60] reported that oral doses of triethyltin acetate at 8 mg/kg given to five female rats at 2-day intervals significantly increased the water content of the brain and of the spinal cord. Similar effects were obtained when oral doses of 200 mg/kg tri-n-propyltin were administered to four female rats at 3-day intervals, when doses of 100 mg/kg tri-isopropyltin acetate were administered to five rats at 2-day intervals, or when doses of 300 mg/kg tri-n-butyltin acetate were given to four rats. No other procedures were given.

Gaunt et al [62] investigated the toxic effects of di-n-butyltin dichloride (DBDC) which was reported to contain 0.25% tri-n-butyltin chloride. Single doses of 50 mg/kg in arachis oil given by intubation to five male and five female rats produced edema in the pancreas around the lower bile duct, with varying degrees of hyperemia of the duct occurring after 24 hours. The fragmentation of the wall of the bile duct, reported by Barnes and Magee [61] to occur after three doses of 50 mg/kg of DBDC, was not reported by Gaunt et al [62] after a single dose.

Groups of 16 male and 16 female weanling rats were fed diets containing 0, 10, 20, 40, or 80 ppm DBDC for a 90-day period [62]. There were no fatalities at any of the levels tested. The only effects observed were a reduction in growth and a slight but statistically significant decrease in hemoglobin concentration in female rats after 6 weeks and in male rats after 13 weeks on a diet containing 80 ppm DBDC. Blood serum amylase activity in the 80-ppm group did not differ from that of the controls, suggesting that pancreatic damage was not present. Hematocrit

values and erythrocyte, reticulocyte, total and differential leukocyte counts, and liver function, as measured by SGOT and SGPT activities, were within the ranges of the control group. The urines of six rats of each sex at each dose level were examined for color, pH, microscopic constituents, protein, glucose, bile salts, and blood and were found to be normal in all tests. Tin was not found in the urine. The ability of the kidneys to concentrate solutes, as determined by measuring the volume and specific gravity of urine produced under varying conditions of hydration, did not differ from that of the control group. The weights of the brain, pituitary, heart, thyroid, liver, spleen, kidneys, adrenals, and gonads were comparable to those of the controls. Microscopic examinations revealed no abnormalities in these organs or in the bile duct, pancreas, duodenal loop, salivary gland, trachea, lungs, diaphragm, lymph nodes, thymus, stomach, ileum, colon, sacrum, rectum, urinary bladder, sternum, or uterus. The characteristic bile-duct lesions described by Barnes and Magee [61] were not observed by Gaunt et al [62].

Bartalini [63] administered to 10 rats a daily diet containing finely pulverized dibutyltin oxide (DBTO) at 100 mg/kg body weight for 5 days. Six of the rats died within 6 days after the final dose. Examination of these animals showed serious and widespread changes in the liver, including acute necrosis and cellular degeneration. The kidneys showed serious degenerative alterations of the epithelium, disintegration and fusion of the cytoplasm, and lysis of the nuclei. Similar effects were observed in six rats at a daily dose of 25 mg/kg body weight for 5 days.

In seven rats administered DBTO in the daily diet at 2.5 mg/kg body weight for 60 days, there were only slight alterations in the liver,

including nuclear hypertrophy, granular cytoplasm, and increased Kupffer cell count [63]. The kidneys contained desquamated cells in the lumina of the tubules and signs of nuclear regression, including pyknosis and occasionally lysis.

Characteristic bile-duct lesions reported for DBDC by Barnes and Magee [61] were not observed by Bartalini [63] for DBTO. Kidney damage occurred with DBTO but not with DBDC [61,62].

Calley et al [64] evaluated the hepatotoxicity of dibutyltin diacetate (DBDA) at the ultrastructural level in rats and mice. Ten young adult female Holtzman rats weighing 275-300 g were given DBDA daily by intubation over a 10-day period at a dose of 27.25 mg/kg, and a similar schedule was followed with 10 female Swiss-Webster white mice weighing 17-20 g. One rat was killed each day and liver tissues were removed for examination by light and electron microscopy. The development of visible liver damage was observed 2-3 days after exposure began. Maximum damage was seen on the 6th or 7th day. Light microscopy revealed cloudy swelling, fatty degeneration, necrosis, changes in nuclear size, nuclear dust, and chromatin condensation. Electron microscopy revealed a vacuolar degeneration of the mitochondria in the hepatic parenchyma cells. The rat-liver mitochondria were believed to exhibit a terminal recovery pattern. The granular endoplasmic reticulum showed progressive swelling but with no loss of ribosomes. The complexity of the agranular endoplasmic reticulum increased greatly after the first three doses. The bile canaliculi were completely closed by the third dose by swelling of the parenchyma cells and microvilli. Thickening of the Kupffer and endothelial lining cells was also observed. Rats recovered more rapidly from these effects after 7 days

of exposure than did the mice. The authors [64] have suggested that early mitochondrial injury in the parenchyma cells of the liver may be a result of an interference with ATP production by dithiol inhibition, and that inhibition of other cellular functions involving active transport would lead to the observed ultrastructural damage. Albino mice, also used in this study, were found to be more sensitive than rats to the toxic effects of DBDA.

The toxicities of the polyvinyl chloride stabilizers Advastab 17MO, composed of 75% dioctyltin bis(isooctylthioglycolate) (DOTG) and 25% epoxidized soybean oil, and Ergoterm TGO, composed of an unknown percentage of dibenzyltin bis(isooctylthioglycolate) (DBTG), were determined by Mazur [65]. Thin-layer chromatography revealed no trialkyltin derivatives in these products. Wistar strain rats weighing 80-100 g, in groups of 10 males and 10 females, were administered Advastab 17MO at 20 or 200 mg/kg/day or Ergoterm TGO at 18 or 180 mg/kg/day by intubation in an olive oil suspension over a 3-month period [65]. The control group received only olive oil. Behavior, general appearance, and mortality were noted and hemoglobin content and red and white blood cell counts were determined. At the end of 3 months, the animals were killed, and the livers, kidneys, and spleens were weighed and examined. At 200 mg/kg/day of Advastab 17MO, the rats were apathetic, drowsy, and exhibited an irregular gait during the course of the experiment. All died in 9-17 days. Autopsy revealed an acute inflammation of the alimentary canal and a hyperemic liver but no significant swelling of the lobes. At the lower dose of Advastab 17MO, three animals died within the 3-month period, but no macroscopic changes were seen. However, a significant increase in the average weight of the

liver for male rats was noted. Ergoterm TGO at a dose of 180 mg/kg/day killed three animals, but no macroscopic changes were observed except an increase in the liver weight of females. No effects were seen for Ergoterm TGO at 18 mg/kg/day.

Advastab 17MO and Ergoterm TGO were used in a 12-month study on groups of 20 male and 20 female rats [65]. The substances were fed daily at a dose of 200 mg/kg of food for Advastab or 180 mg/kg for Ergoterm. Behavior, general appearance, and mortality were observed. Hemoglobin concentration, and red and white blood cell counts, blood serum protein fractions, the levels of aspartate and alanine aminotransferases, and tin accumulation were determined. At the end of the study period, the animals were killed and examined macroscopically. The general appearance and behavior of the experimental groups did not differ from that of the untreated control group. Eight rats died in each of the two experimental groups, whereas only four died in the control group. Statistically significant increases in kidney weight were observed only in female rats receiving Advastab. Electrophoretic study of the blood serum protein fractions revealed a statistically significant decrease in the albumin content with a significant increase in alpha-2 globulin and gamma globulin in Advastab-fed rats. These changes generally indicate liver damage, but this was not confirmed by a microscopic examination. Examination of these animals and analysis for tin revealed no tin accumulations in the liver, kidneys, or spleen. No perceptible changes were observed in rats on an Ergoterm diet. Other chronic studies using similar doses for 7 or 18 months produced similar results. Mazur [65] indicated that the effects of DOTG and DBTG were similar and that both affected primarily the liver.

In a second report, apparently of the same basic experiment supplemented with a study of the effects of these compounds on reproduction and fetal development, Nikonorow et al [66] reported that the higher dose of Advastab 17MO had killed the rats, with purulent pneumonia, endometritis, and congestion of the small intestines. The high dose of Ergoterm TGO and the low one of Advastab 17MO produced significant increases in liver weight. The low dose of Ergoterm TGO had no observable deleterious effects. No microscopic changes were found in the liver, kidneys, and spleens of any of the experimental animals. Behavior, hemoglobin concentration, and red and white blood cell counts were normal.

Microscopic examinations of the livers, kidneys, and spleens of the rats fed Advastab 17MO or Ergoterm TGO for 12 months revealed no remarkable alterations even though 20% of the animals had died. At 0.02% DOTM, the albumin content of the blood decreased while gamma and alpha-2 globulin levels increased.

Reproduction and fetal development were studied using groups of 20 female rats [66]. Two groups of female rats were given by intubation either DOTM at 20 or 40 mg/kg/day or DBTM at 18 or 90 mg/kg/day in olive oil suspension. Another group receiving equal doses of oil served as the control. After 3 months of treatment with DOTM, the animals were mated, and 10 pregnant females, as determined by vaginal smear, were selected from each group. For these animals, exposures were stopped. After 21 days, the pregnant females were killed and the uteri and fetuses removed. The number of live and dead fetuses, number of fetal resorptions, fetal and placental weights, and bone development and rib fusion were recorded. No significant difference between the experimental groups and the control groups was

found. Other groups of 10 pregnant rats were administered by gavage DOTM at 20 or 40 mg/kg/day or DBTM at 18 or 90 mg/kg/day for 21 days immediately after conception. There were significant differences from the controls in the number of dead fetuses, the number of fetal resorptions, and fetal and placental weights. These differences were reported by the authors to be dose dependent. The results seem to indicate that reproduction and fetal development of rats were affected by the organotins only when exposure to these compounds occurred during gestation.

The effect of trialkyltins on the CNS has been investigated by Magee et al [67] using triethyltin hydroxide (TETH) in Porton-strain albino rats. TETH dissolved in arachis oil was added daily to the powdered diet of 18 rats at a concentration of 20 ppm for 2 weeks, followed by 10 ppm for 6 weeks. The animals were killed at the end of 8 weeks, and the brains and spinal cords were removed. Tissue samples were taken from the liver, kidneys, spleen, testes and adnexa, adrenals, pancreas, and heart of an unstated number of rats. The water content, total lipid, total phospholipid, total cholesterol, and total nucleic acids were determined for these tissues. These results were compared with those from the pair-fed controls.

The first neurologic symptoms appeared 7-9 days after ingestion of the TETH diet started and included difficulty in the manipulation of the hind limbs [67]. At this stage, an amount of food equivalent to 10 mg/kg body weight of TETH had been consumed. By 14 days, when the animals had consumed 12 mg/kg body weight, hindleg paralysis was apparent. During the 3rd week, 12 rats died. The general state of the surviving animals began to improve when TETH in the diet was reduced to 10 ppm. No further

clinical improvements occurred if the rats were restored to a normal diet at the end of 8 weeks. If the 10-ppm diet was continued, tremors of the skeletal muscles appeared after a few more weeks.

An examination of tissues showed damage to the CNS only [67]. Microscopic examination revealed small interstitial spaces only in the white matter of the brain after 3 days. Interstitial spacing increased by the end of 9 days and by the 14th day, when severe paralyses were observed, there were marked changes in the white matter. With a reduction in the dietary concentration of TETH to 10 ppm, no further deterioration occurred. At the end of 8 weeks, the white matter of the spinal cord and brain had a reticulated appearance. This was not found in the gray matter of the brain and cord or in the peripheral nerves but was well developed in the optic nerve. Lesions were reversed after 4 months on a normal diet. No abnormalities were found in the other organs examined.

Chemical investigations showed a significant increase in the water concentration in the brain and spinal cord of animals receiving 10 ppm TETH in the diet as compared to those of the pair-fed controls [67]. If animals were allowed a normal diet for 130 days after consuming a diet containing 20 ppm of TETH for 14 days and 10 ppm for a further 45 days, the water concentration of the CNS returned to normal. Rats fed a diet of 20 ppm TETH for 10 or 14 days had a significant increase in the sodium concentration of the brain and cord, but no changes were detected in potassium concentrations. The concentration of sodium and potassium in the plasma were not altered in rats killed after 11-16 days on a 20-ppm diet. Total nucleic acid, total lipid, total phospholipid, and total cholesterol in the brains and spinal cords of these animals did not differ

significantly from the control values.

The effect of TETH on the permeability of the blood-brain barrier was tested using dye-injection techniques [67]. Rats were fed a diet of 20 ppm TETH for 14 days followed by 10 ppm for either 2 or 42 days prior to injection of the dye. No abnormal staining of the CNS was observed, indicating that permeability of the barrier was not affected.

Findings by Magee et al [67] indicate that TETH produced a lesion of the white matter of the CNS, which was described as interstitial edema. There were no indications that the neurons of the CNS were affected. Magee et al [67] also reported that a single 10 mg/kg dose of triethyltin sulfate (TETS) injected intraperitoneally (ip) into rats significantly increased the water content of the brain and spinal cord. By contrast, even repeated oral or ip administration of diethyltin diiodide did not produce any of the neurologic effects which were observed after administration of triethyltin compounds.

Triethyltin-induced interstitial edema of the white matter of the CNS in rats has also been reported by a number of other investigators [68-73]. In addition to edema, splitting of the myelin sheath in the white matter has been reported from TETS [68,69,71,73], TETA [71], and TETH [70,72]. Graham and Gonatas [69] reported myelin splitting of the peripheral nerves (posterior lumbosacral nerves and sciatic nerves) in rats given TETS in drinking water at a concentration of 20 mg/liter during a 22-day period. Suzuki [73] gave eight newborn rats drinking water containing 5 mg TETS for 4 months and found that triethyltin-induced brain alterations were not accompanied by physical signs.

Investigations on rabbits [74,75], dogs [70], and mice [49] have shown that triethyltin-induced CNS damage was similar to that found in rats. Aleu et al [74] induced cerebral edema within 5-7 days in male albino rabbits given daily ip injections of TETS at 1 mg/kg. The authors [74] showed that there were no changes in the extracellular spacing of the white matter of the CNS, indicating that the edema fluid may be within the myelin. Cerebral edema was induced in 2 dogs, one receiving 2 iv injections of 1 mg/kg within 25 days, and the other 10 iv injections of 1 mg/kg within 30 days [70].

These studies [67,70,74] with triethyltin compounds described toxic effects which were similar in various animal species, but no indication of differences in severity among the animal species was provided.

Wakashin [76] also induced perivascular edema in the CNS in 12 male rats with single ip injections of tributyltin chloride (TBTC) at a dose of 2.2 mg/kg. The author also found extreme congestion of the lungs, atrophy of the parenchymal cells of the liver with slight fatty degeneration, swollen anemic kidneys with ultrastructural changes, and enlargement of the spleen. An ip injection of 5 mg/kg of dibutyltin dichloride produced effects similar to those of TBTC, including interstitial edema. Subcutaneous injection of 0.7 mg/kg daily for 6 days produced similar damage to the liver, kidneys, and spleen, but no CNS damage was apparent. Liver and kidney damage were reversible.

Verschuuren et al [77] compared the toxic effects of triphenyltin acetate (TPTA) and triphenyltin hydroxide (TPTH) with those of triethyltin hydroxide (TETH). Ninety-day oral studies were conducted on Wistar rats, using groups of 20 or more animals. The concentrations in the diet were 0,

5, 10, and 20 ppm of TETH, 0, 5, 10, 25, and 50 ppm of TPTA, and 0, 5, 10, 25, and 50 ppm of TPTH. Hemoglobin concentration and erythrocyte, leukocyte and differential blood cell counts were determined at the end of 90 days. At this time, the animals were killed; the liver, kidneys, heart, spleen, thymus, adrenals, thyroid, pituitary gland, uterus, ovaries, testes, prostate, pancreas, and brain were weighed and examined microscopically. The water content of the brain and spinal cord was also determined.

With TETH, seven rats died at 10 ppm, and all rats died at 20 ppm [77]. Male rats receiving TETH at concentrations of 5 and 10 ppm had a decrease in erythrocytes. At 10 ppm, neutrophils increased significantly. An examination showed decreases in organ weight compared to the controls in the thymus and spleen of both sexes at 5 and 10 ppm. The liver, thyroid, and pituitary glands of the males only and the ovaries, uterus, and prostate decreased in weight at 10 ppm. The weight of the brain in both sexes and of the adrenals in males increased at 10 ppm. Microscopically, interstitial edema of the CNS was present in all animals receiving TETH. There were significant increases in the water content of the brain and spinal cord in both sexes at 5 and 10 ppm TETH. Because of the fatalities which occurred at 20 ppm, water content of the brain and spinal cord of these rats could not be accurately determined.

Male rats on a diet containing TPTA showed decreases in leukocytes only at 10, 25, and 50 ppm [77]. Decreases in weight were observed for the pituitary glands of both sexes at 50 ppm and for the ovaries at 50 ppm. The uterus decreased in weight at 25 and 50 ppm. The thyroid decreased in weight at all concentrations in females but only at 25 and 50 ppm in males.

The possible existence of CNS edema was reported in one or two animals at 10, 25, and 50 ppm, while increased brain weights were found in only two animals at 50 ppm. The water content of the spinal cord increased only in female rats at 50 ppm, while the brain water content was unaffected. TPTH affected the blood picture only in female rats, producing decreases in the lymphocyte count at 5, 10, and 25 ppm. No effect was reported at 50 ppm. In females, the pancreas, uterus, and ovaries decreased in weight at 50 ppm. The prostate decreased in weight at 50 ppm. For both sexes, the adrenals increased in weight while the thyroids decreased in weight at 25 and 50 ppm.

Verschuuren et al [77] used the procedures outlined for rats to evaluate the effects in guinea pigs of TETH at doses of 5, 10, and 20 ppm, TPTA at 5, 10, 20, and 50 ppm, and TPTH at 2.5, 5, 10, 20, and 50 ppm. With TETH, the authors reported one death at each dose. Blood counts indicated no significant changes in any of the measured parameters. Organ weight decreases were reported for the liver and thymus in females and for the testes at 20 ppm of TETH. Increases in the weight of the pituitary gland at 10 and 20 ppm in females and of the brain in both sexes at 5, 10, and 20 ppm were observed. Significant increases in the water content of the brain and spinal cord were observed at 10 and 20 ppm.

One of 20 guinea pigs died on diets containing 5 or 10 ppm of TPTA, while 5 died at 20 ppm [77]. At 50 ppm, all guinea pigs died in the first 6 weeks. Blood counts revealed no changes except decreases in the percentages of lymphocytes and in the total leukocyte count at 5, 10, and 20 ppm in females and at 10 and 20 ppm in males. Weight decreases in the uterus and testes were observed at 20 ppm TPTA. Weight increases occurred

in the pituitary gland at 10 and 20 ppm and in the kidneys at 20 ppm in females, and in the liver at 20 ppm in males. The brain in both sexes increased in weight at 5, 10, and 20 ppm. However, increases in the water content of the brain and spinal cord were reported only at 20 and 50 ppm.

With TPTH, one guinea pig from each group died at 10 and 20 ppm while all died within 6 weeks at 50 ppm [77]. A decrease in hemoglobin content occurred in females at doses of 2.5, 5, 10, and 20 ppm and in males at 10 and 20 ppm. A corresponding decrease in leukocytes was reported for each of these groups except for males at 10 ppm. Decreases in the absolute lymphocyte counts were reported in females at 2.5, 5, 10, and 20 ppm and in males at 10 and 20 ppm. Decreased organ weights were reported for the spleen at 10 and 20 ppm in females, for the thymus of both sexes at 20 ppm, and for the uterus and testes at 20 ppm.

Results of the experiments on rats and guinea pigs indicate that the reaction of different species to the three compounds differed [77]. Rats were more susceptible to TETH than guinea pigs, but less so to TPTA and TPTH. Both species were more susceptible to TPTA than to TPTH.

In their investigation of TPTH, Gaines and Kimbrough [78] found no evidence of CNS damage in male rats after 99 days on diets containing 100, 200, and 400 ppm, with 10 rats on each concentration. A significantly lower leukocyte count occurred after 99 days at 200 ppm. All animals exposed to 400 ppm died in 7-34 days from extensive intraalveolar hemorrhage of the lungs or from loss of weight. No effect was detected at 100 ppm.

In his study of the fungicide, triphenyltin acetate (TPTA), Klimmer [79] administered single doses of 80-250 mg/kg of TPTA by intubation to

groups of 10 rats. Survivors had signs of general weakness and lack of mobility. From the mortality data, an oral LD50 of 136 mg/kg was obtained for a 2- to 3-week observation period. All animals had a decreased ventilatory rate, hypothermia, and coma prior to death. A macroscopic examination revealed stasis of the lung and liver and a slightly increased amount of water in the brain. A microscopic examination showed a focal liver cell necrosis with massive stasis of blood and a cloudy swelling of the tubular epithelia of the kidneys. Rabbits and guinea pigs underwent effects similar to those observed in the rats, but with no apparent increase in the proportion of water in the nerve tissues. These species were more susceptible to TPTA than rats. The LD50's were 21 mg/kg for the guinea pig and 30-50 mg/kg for the rabbit, for a 3-week observation period. Similar, but more severe, effects and peritonitis were reported when TPTA was administered by ip injection to rats, rabbits, and guinea pigs.

Klimmer [79] administered triphenyltin acetate (TPTA) in a 0.05-0.2% tylose (methylcellulose) suspension daily by stomach tube to four groups of Wistar rats weighing 160-180 g. Urine analyses (albumin, urobilinogen, sugar, and sediment), blood tests (hemoglobin, erythrocytes, leukocytes, and differential white blood count), and microscopic examinations of organs were performed. Twenty-five rats given TPTA at 25 ppm for 170 days had no abnormalities compared with the control group. However, the administration of 50 ppm TPTA for 105 days produced listlessness and weight gains lower than the controls in a group of 20 rats. Fourteen of these rats died within 7-49 days. Examination of these animals revealed bronchopneumonic foci in the lungs, stasis of the blood in the liver with epithelial atrophy, renal hyperemia, and an infectious swelling of the white pulp of

the spleen. Of the six survivors, two had bronchopneumonic foci. The brains of all animals had isolated shrunken cells and perivascular empty spaces. Other organs showed no abnormalities.

Two studies [80,81] reported on the effects of TPTA and triphenyltin chloride (TPTC) on the reproductive organs of rats. Pate and Hays [80] added doses of 20 mg/kg of TPTA or TPTC, dissolved in acetone, to the daily diets of groups of 20 sexually mature male Holtzman albino rats, weighing 95-130 g, for 19 days. The compounds were measured into the food according to the body weight of each animal. One rat served as the control for each group. Animals were killed on the 20th day, and body weights, appearance of organs, and relative size of the testes were determined. The testes were also examined micoscopically. The authors [80] reported an average weight loss in all animals of 12.4 g. Testes of TPTA-treated rats ranged from one-fourth to one-half the size of the testes in the control animals. A microscopic examination of the testes revealed degenerative changes, including a decreased number of layers in each tubule, a depletion of the more mature sperm cells in the tubules, 99% closing of the tubule lumina opening, and the presence of large, atypical, polynucleated cells. All animals were judged to have been rendered sterile by these comparatively large doses. However, there was insufficient evidence to determine whether the observed testicular changes were a direct effect of the compounds or were secondary to effects on body weight and on the blood-clotting mechanism. The authors suggested that the cumulative toxic effects of TPTA might involve an interference with the blood-clotting mechanism. The effect of TPTC was similar but less pronounced, with 60-70% sterility at the end of the experiment. However, TPTC appeared to have a more

pronounced effect on the blood-clotting mechanism, with 3 of 20 showing spontaneous bleeding.

Newton and Hays [81] investigated the effects of diets containing TPTA or TPTC dissolved in acetone at 20 mg/kg/day on the ovaries of 40 mature Holtzman rats. Rats on a normal diet served as controls. Three rats receiving each compound were killed after 4, 9, 14, 19, and 24 days of feeding. Three representative sections were taken from the ovaries of each animal and examined microscopically. The sections were evaluated for the numbers of secondary, tertiary, mature, atretic mature, atretic intermediate, and atretic immature follicles and corpora lutea. TPTA- and TPTC-treated animals differed from the controls in the numbers of mature, atretic intermediate, and atretic immature follicles and corpora lutea. Macroscopic examinations showed that the ovaries of TPTA- and TPTC-treated animals were half the size of those in the controls. The authors [81] concluded that TPTA and TPTC affected the reproductive organs of female rats, but they did not provide data to indicate whether this was a direct or a secondary effect of the intoxication.

Freitag and Bock [82] used thin-layer chromatography to identify the metabolites of TPTC in albino rats. A single 3-mg dose from an edible oil solution of 20 mg of radioactive TPTC and 370 mg of nonradioactive TPTC was administered by stomach intubation to 11 males and 11 females. The control rats received the oil solution containing nonradioactive material only. Urine and feces were collected daily and their mean radioactivities determined. Five males and five females were killed 7 days after exposure, and the organs were analyzed for radioactive tin. Within 7 days, 88% of the radioactive tin was excreted in the feces and 3% in the urine. Only a

total of 0.5% was detected in all the organs combined at the end of 7 days. There was no significant difference between the rates of excretion of tin by males and females. The concentration of triphenyltin in the urine and feces decreased while those of diphenyltin, monophenyltin, and inorganic tin increased during the 7-day period. The authors [82] suggested a degradation scheme of triphenyltin to diphenyltin to monophenyltin to inorganic tin.

Elsea and Paynter [83] reported no CNS damage in rats in their study of the effects of bis(tri-n-butyltin) oxide (TBTO). Single doses of TBTO were administered by intubation to groups of seven fasted male albino rats as a 10% v/v aqueous suspension (range, 91-251 mg/kg) or corn oil solution (range, 117-542 mg/kg). During the 7-day observation period, the animals had labored respiration, ataxia, decreased activity, diarrhea, and "squinting eyes." Most deaths occurred 2-4 days after administration and were preceded by bloody nasal discharge, bloating, and depression of reflexes. Gross autopsies of the animals that died revealed hyperemic lungs, congested kidneys and adrenals, and irritation of the gastrointestinal tract. Surviving animals had mottled and grainy livers and a thickening of the walls of the cardiac portion of the stomach. From this study, LD50's of 148 mg/kg for the corn oil solution and 194 mg/kg for the aqueous suspension were obtained.

In a second experiment, Elsea and Paynter [83] fed groups of 10 albino rats diets containing TBTO at concentrations of 32, 100, or 320 ppm for 30 days. A group receiving only the basal diet served as the control. Animals were observed for appearance and behavior. In animals receiving a diet of 100 ppm TBTO, food consumption was comparable to that of the

control group, but growth was markedly suppressed. At 320 ppm, food consumption was one-half that of the controls. A gross autopsy was performed on dead animals and on all surviving animals after 30 days of exposure. The only fatalities occurred in the group receiving a diet containing 320 ppm TBTO, where 6 of the 10 animals died. Prior to death, these animals lost weight and had bloody discharges from the eyes and nose and rapid and labored respiration. However, autopsy revealed only an almost complete lack of fat stores. No gross changes in the brain tissue were found. In addition, a single dermal application of 11.7 g/kg to the backs of rabbits produced a moderate degree of dermal irritation and signs of systemic poisoning. Five daily applications of a paper containing 8 ppm TBTO to the backs of rabbits produced no evidence of irritation or gross toxicity.

Banks et al [84] fed di-n-octyltin oxide (DOTO) to rats and dogs daily for 2 years and analyzed their tissues for tin content. Dietary DOTO concentrations were 9.6, 24, 39, 72, 98, and 215 ppm DOTO (3.2-71.0 ppm, as tin); no other details of the study were provided. Blood and the liver, kidneys, heart, lean muscle, and abdominal fat were taken from the controls and from the treated animals at the end of 2 years and analyzed for total tin. Dialkyltin levels were determined in individual liver samples of male dogs from several treatment groups and in female rats from the highest treatment group. In addition, brain samples from male dogs were analyzed for tin. For rats, paired composites were obtained from other tissues, including the testes. For the dogs, composite samples were taken only of the muscle and fat; pooled urine samples for the control and treatment groups were used. The dithiol method was used in analysis for total tin

and was reported to be reliable at tin concentrations as low as 5 μg. The dithizone method was used to determine the dialkyltins, but the sensitivity of the method was not given.

In male rats, the level of inorganic tin was highest in the liver and kidneys (Table XII-9) [84]. Female rats had similar levels in the liver and kidneys, the only tissues examined in these animals. For dogs, the highest levels were found in the liver, followed by the brain and kidneys (Table XII-10). Female dogs had comparable results.

Analyses of the liver of one dog from each of the six treatment groups showed that 10-13% of the total tin present in the liver was in the form of dialkyltin [84]. Approximately 50% was in the inorganic state, which the authors believed to be a stannous compound, and the remainder was present as tin oxide. In the rats, at least 50% of the total tin was present as a dialkyltin. The authors suggested that this figure may be lower than the actual dialkyltin concentration in the liver of the rats because of interference from the arsenic normally present in the rats' diet.

Cremer [85] used in vivo and in vitro experiments to study the conversion of tetraethyltin to triethyltin. In the in vivo experiments, albino rats weighing 200-230 g were administered a single iv dose of tetraethyltin at 20 mg/kg. Four animals were killed at 30, 60, and 120 minutes after experimental treatment, and samples of liver, kidney, brain, and whole blood were examined for triethyltin using the dithizone method. The conversion of tetraethyltin in all tissues examined proceeded slowly for the first 30 minutes, with triethyltin concentrations of 3.94 μg/g blood, 6.3 μg/g liver, 1.99 μg/g kidney, and 0.26 μg/g brain. After 60

minutes, concentrations were 31.9 μg/g blood, 18.1 μg/g liver, 5.6 μg/g kidney, and 0.66 μg/g brain. By the end of 120 minutes, concentrations were 34.3 μg/g blood, 18.0 μg/g liver, 6.9 μg/g kidney, and 2.14 μg/g brain. These findings suggest that tetraethyltin is degraded to triethyltin primarily in the liver and that the triethyltin formed is readily transported to other tissues. The concentration of triethyltin in the tissues appears to reach a steady state in 1-2 hours, with 4% of the total dose being converted to triethyltin in the first 1.5 hours and 25% within 2 hours.

In the in vitro tests, liver slices were most active in converting tetraethyltin, whereas conversion by kidney slices was very slow [85]. The brain and blood samples did not convert tetraethyltin to triethyltin. The liver was considered to be the main organ for the conversion of tetraethyltin to triethyltin.

The metabolism of monoethyltin and diethyltin has been studied by Bridges et al [86]. The authors administered monoethyltin trichloride (METC) orally at a dose of 25 mg/kg or ip at a dose of 12.7 mg/kg to groups of three rats. Animals were observed for a 3-day period. Feces and urine from all animals were analyzed colorimetrically for total tin using the dithiol method, which has a limit of sensitivity of 5 μg/ml of sample. Monoethyltin in the urine and bile was determined fluorometrically with a 98 ± 2% recovery rate. The monoethyltin content of fecal matter was determined using a radiochemical technique with an 89-95% recovery rate. When METC was administered orally at a dose of 25 mg/kg, 92% was excreted in the feces in 2 days, with 1-2% in the urine. By ip injection, 73% of the 12.7-mg/kg dose was excreted in the urine of uncannulated rats in 3

days. In rats whose bile ducts had been cannulated, 82% of an ip injection of 12.7 mg/kg was excreted in the urine, with less than 4% found in the bile. Dithiol tests for inorganic tin in the urines of normal and cannulated rats which had received doses of 12.7 mg/kg were negative.

Diethyltin dichloride (DEDC) was administered by ip injection to three normal rats and three with cannulae in their bile ducts, at doses of 10 mg/kg [86]. Urine and feces, as well as bile from the cannulated rats, were examined for tin by the dithiol method. Diethyltin in the bile was measured colorimetrically with a method having a recovery rate of 96 ± 5%. The diethyltin content of urine and fecal matter was analyzed using a radiochemical technique with a recovery rate of 89-95%. Following an ip injection of 10 mg/kg, 38% was excreted in the feces and 22% was excreted in the urine, while 5% was found in the carcass 6 days after exposure. Animals receiving 10 mg/kg ip of 14C-labeled DEDC had excreted an average of 79% of the dose (36% in urine and 43% in feces), calculated as tin, after 3 days. When measured as 14C, only 46% of the dose was accounted for. This discrepancy between the recoveries of tin and 14C suggested to the authors that diethyltin was being dealkylated. An examination of the urine and feces for monoethyltin and diethyltin in rats receiving 10 mg/kg of DEDC showed that, in the urine, 31% of the 14C occurred as monoethyltin and 5% as diethyltin, while in the feces, 32% occurred as monoethyltin and 10% as diethyltin. An examination of the bile from cannulated rats receiving DEDC at 10 mg/kg showed that only diethyltin was present.

Bridges et al [86] concluded that diethyltin was slowly dealkylated to monoethyltin. However, monoethyltin was not metabolized to inorganic tin. Upon ip injection of monoethyltin, monoethyltin did not enter the gut

via the bile or gut wall but was primarily excreted in the urine. Because diethyltin entered the bile after ip injections, the authors [86] suggested that dealkylation occurred in the gut and in the tissues.

Technical grade tricyclohexyltin hydroxide (TCHH), 95% pure, either labeled with 119Sn or unlabeled, was administered orally to rats and dogs to study its metabolism in animal tissues [87]. In the analysis of tissue and excreta for 119Sn-labeled TCHH, samples were combusted and the ash was analyzed for total radioactivity with a scintillation spectrometer. To identify TCHH and its possible metabolites, dicyclohexyltin oxide (DCHO) cyclohexylstannoic acid, and inorganic tin, the samples were homogenized and separated by extraction with solvents prior to ashing. Confirmation of separation and identification of the metabolites were by thin-layer chromatography. For samples containing unlabeled TCHH, the dithiol method was used to analyze for total tin, and a method developed by Getzendaner and Corbin [88] was used for total organotin. Inorganic tin was calculated as the difference between total tin and total organotin.

Two Wistar white rats (weight about 200 g) were given a single dose of 25 mg/kg body weight of 119Sn-labeled TCHH [87]. Approximately 99.9 and 100.07% of the total radioactivity was recovered in the urine and feces over a 9-day period, with 75 and 85% obtained in the first 4 days. The feces contained 97.5 and 98.1% of the total radioactivity and the urine 1.8 and 2.5%. The authors concluded that very small quantities of TCHH were absorbed from the gastrointestinal tract. To substantiate these conclusions, studies were carried out on two guinea pigs to determine the extent of excretion of the compound in the bile; each received a single oral dose of 2 mg of 119Sn-labeled TCHH. Bile collected over a period of 2

days showed only trace amounts of radioactivity.

In a 90-day study, 53 Wistar white rats of both sexes were provided rat laboratory chow containing 100 ppm of labeled TCHH [53]. At intervals of 0, 15, 60, and 90 days, three rats were killed. Tissue and organ samples were collected and analyzed for their tin content. At the end of 90 days, the remaining rats were placed on a diet free of TCHH and 1-3 were killed at intervals of 2, 10, and 40 days. Tin concentrations generally reached maximum levels in 15 days, with concentrations of 0.90 ppm in the kidneys, 0.67 ppm in the heart, 0.52 ppm in the liver, 0.31 ppm in the muscle, 0.29 ppm in the spleen, 0.26 ppm in the brain and fatty tissues, and 0.06 ppm in the blood. At the end of 90 days, the tin concentrations were 0.76 ppm in the kidneys, 0.67 ppm in the heart, 0.55 ppm in the muscle, 0.50 ppm in the liver, 0.45 ppm in the spleen, 0.44 ppm in the brain, 0.11 ppm in the fatty tissues, and 0.10 ppm in the blood.

Analyses of tissue samples 2, 10, and 40 days after the withdrawal of TCHH from the diet showed a decrease in total tin with time [53]. A detailed analysis of the muscle tissue for TCHH and its metabolites on the 2nd day showed that TCHH accounted for 61% of the total radioactivity, DCHO 18%, inorganic tin 16%, and cyclohexylstannoic acid 4.8%. These percentages decreased with time, except for that of DCHO, which increased with time.

In a 2-year feeding study, Long-Evans rats of both sexes, on daily diets containing 0, 0.73, 3, 6, and 12 mg TCHH/kg body weight, showed patterns of tin distribution in their tissues similar to those observed in the 90-day feeding study [53]. The organs and tissues of the rats in which tin was measured in order of decreasing concentration were kidneys, liver,

brain, muscle, and fat. For beagle dogs on similar diets, the distribution of tin was the same except for the kidneys and liver, where the order was reversed. The concentration of tin in the tissues of dogs and rats was proportional to the amount of TCHH ingested and increased with time during the study period. As in the 90-day study with rats, tin in the tissues was reduced when TCHH was removed from the diets of dogs and rats in the 2-year study.

Analysis of the kidney, liver, muscle, and brain from dogs and rats showed that 60-95% of the tin in these tissues was in the organotin form [53]. Analysis of liver samples from rats on a diet of 3 mg TCHH/kg for 90 days showed that TCHH accounted for 45% of the total tin, DCHO 40%, and inorganic tin 15%. Dogs on the 3-mg TCHH/kg diet for 180 days had 3.4 ppm of tin in the liver, of which 40% was inorganic tin, 45% DCHO, and 15% TCHH. In the kidneys, 1.3 ppm of tin was found, of which 50% was inorganic tin, 20% DCHO, and 30% TCHH. Brain tissues had 1.1 ppm tin, of which 30% was inorganic tin, 20% DCHO, and 50% TCHH.

Two dairy cows were given a ration containing 10 ppm TCHH for 2 weeks, followed by 100 ppm TCHH for 2 more weeks [53]. Samples of milk were collected morning and evening and combined to obtain a daily sample. Analyses showed only trace amounts (0.01 ppm or less) of TCHH in the milk.

(3) Dermal

The dermal effects of organotins in rats have been assessed by a number of investigators [60,83,89,90]. Pelikan and Cerny [89,90] studied the dermal effects of two commercial preparations: Lastanox T with 20% bis(tributyltin) oxide (TBTO) and Lastanox P containing 15% TBTO. Single doses of 0.1 ml of these products were applied to the shaved backs of

groups of five male and five female rats at concentrations of 0.25 and 0.5% [90] or 1, 10, 33, and 100% [89]. The control group received the undiluted commercial preparation without TBTO which had no dermal effects.

Four animals to which Lastanox T was applied in concentrations of 0.25 and 0.5% were killed after 7 days, as were four from a control group [90]. Observations continued for an additional 28 days for the remaining animals. A slight dermal edema appeared on the 1st day at 0.25 and 0.5% but was most pronounced at 0.5%. By the 8th day, hemorrhagic crusts appeared at the site of application. All signs disappeared by the 15th day at 0.25% and by the 18th-20th days at 0.5%. Autopsy after 7 days revealed hyperemic subcutaneous tissues with no other macroscopic changes. Microscopic examination confirmed these gross findings. With Lastanox P, the findings were very similar but less severe, with skin effects disappearing by the 12th-14th day at 0.25% and by the 15th-16th day at 0.5%.

Dermal exposure at concentrations of 1, 10, 33, and 100% of Lastanox T or P produced similar effects which differed only in severity [89]. Erythema and edema appeared on the 1st and 2nd days, followed by granulation tissue on the 9th-12th days. All signs disappeared in 35-38 days in the 1 and 10% groups and in 45-50 days in the 33 and 100% groups.

A second group of rats received single dermal applications of Lastanox T or P in concentrations of 1, 10, 33, and 100% [89]. All animals were killed and examined 10 days after treatment. Macroscopic examination of animals treated with Lastanox T revealed edematous and hyperemic subcutaneous tissues at all doses with no other changes. Microscopically, numerous large bullae filled with leukocytes were observed under the

stratum corneum in the epidermis at all doses. Well-marked acanthosis and vacuolization of epidermal cells were observed after exposure to the 33 and 10% concentrations and were less pronounced after exposure to the lower concentration. The liver had undergone parenchymatous dystrophy and the spleen had hyperplasia of the RES (reticuloendothelial system) cells. The effects of Lastanox P were similar but less severe. No changes were seen in the liver or spleen.

Kawai [91] applied tributyltin iodide (TBTI), tributyltin bromide (TBTB), or tributyltin chloride (TBTC) to the shaved backs of mature male rabbits, using a series of organotin concentrations and varying exposure schedules. For a single application of TBTI in doses of 0.2-1.0 cc/kg, using groups of three rabbits, the author reported a percutaneous minimum lethal dose for rabbits of about 0.2 cc/kg with a 14-day observation period. Blood analyses showed fluctuations in red blood cell count, hemoglobin, and hematocrit, with recovery in 7-10 days. Reticulocyte counts increased directly with the severity of the anemia and were highest during the recovery period. White blood cell counts decreased immediately after application of TBTI to the rabbits' skin. Urinalysis showed positive urobilinogen and porphyrin readings after the higher doses. Other tests were positive for glucose and negative for albumin, Rosin's test, and Millon's test. The latter two tests are blood serum analyses for protein and nitrogen. From single applications of TBTB at 0.5-1.0 cc/kg and TBTC at 0.5-1.0 cc/kg using groups of 2-3 rabbits, a percutaneous minimum lethal dose of 0.7 cc/kg with a 14-day observation period was obtained for both compounds. Results of blood and urine analyses for TBTB and TBTC were reported by the author to be similar to TBTI.

The application of TBTI at a dose of 0.02 cc/kg to the shaved backs of three rabbits, 6 days/week, for 4 weeks, resulted in severe weight loss, a loss of appetite, and asthenia [91]. Progressively severe anemia was observed throughout the course of the experiment, with decreases in red blood cells, hemoglobin, and hematocrit readings. Corresponding increases in reticulocytes were reported by the authors and were prevalent in animals with severe anemia. White blood cell counts fluctuated during the observation period in all animals. Urine tests were positive for urobilinogen and porphyrin. In a similar study using dermal applications of 0.02 cc/kg of TBTB, TBTC, and TBTI, TBTB and TBTC produced weight loss, loss of appetite, and asthenia in rabbits. These effects were similar to, but more severe than, those observed with TBTI. Anemia was also observed with TBTB and TBTC, TBTC having the greatest effect on the blood components followed by TBTI and TBTB. Urinalyses were positive for albumin and urobilinogen after TBTC and positive for urobilinogen and porphyrin after TBTB. The authors have suggested that these results may indicate severe damage to the liver and kidneys with TBTC and blood destruction with TBTB.

TBTB, TBTC, and TBTI had similar effects when applied to the backs of rabbits at a dose of 0.005 cc/kg, 6 days/week, for 12 weeks [91]. Each compound was administered to two animals. The test animals had gradual weight losses, loss of appetite, asthenia, and loss of fur. Blood analyses conducted 1, 2, 3, 5, 7, 9, and 12 weeks after the start of experimentation revealed a decrease in the number of red blood cells and in hemoglobin and hematocrit, and an increase in reticulocytes. Urinalyses were negative for albumin, sugar, urobilinogen, porphyrin, Rosin's test, and Millon's test. The cobalt test (turbidity test) results for liver function were abnormal

for all animals after 4 weeks of exposure.

Pelikan [92] reported the effects produced by the application of bis(tributyltin) oxide (TBTO) to the eyes of rabbits. Lastanox T (20% TBTO with nonionic surface-active substances) and Lastanox P (15% TBTO with nonionic surface-active substances) served as the source of TBTO. These commercial preparations were used in concentrations of 1 and 10% and a dose of 0.03 ml was introduced into the conjunctival sacs of the left eyes of rabbits (in groups of six). This was equivalent to doses of 0.46, 0.61, 4.6, and 6.1 mg/kg of TBTO. Control rabbits receiving the vehicle of Lastanox were not affected. At the two lesser doses, a marked hyperemia of the bulbar and palpebral conjunctivae, accompanied by violent watering, miosis, and blepharospasm were observed after 1-3 minutes. Within 3 hours, erythema and mild edema of the eyelids, numerous large necroses and petechial hemorrhages of the conjunctivae, and decreased corneal transparency were observed. Within 12 hours, corneal transparency had decreased further, irises were edematous and discolored, and the aqueous humor was opalescent. After 24 hours, tissue damage became progressively worse and the pupils became miotic and unresponsive to light. After 2-5 days, ulcerating surfaces appeared on the eyelid and cornea. The conjunctivae were necrotic and peeling. The condition of the pupils became worse, showing no reflex. After the larger doses, macroscopic examinations showed that the skin of the eyelids and surrounding area was necrotic. With the exception of one rabbit, total opacity of the cornea developed together with pronounced symblepharon (adherence of eyelids to eyeball) in most cases. An examination of the two rabbits that died showed that the brain, the medulla, and the abdominal organs were hyperemic.

Microscopically, the corneas were necrotic and the scleras edematous. The irises were congested, and the lenses dislocated. Retinas were unaffected. The spleen showed hyperplasia of the reticuloendothelial cells. Other organs were unaffected.

(4) In vitro

In 1955, Aldridge and Cremer [93] reported a series of experiments investigating the biochemical action of diethyltin dichloride (DEDC) on rat-brain brei, composed of the brain (weight 1.2 g) of one rat dispersed in 6 ml of sodium phosphate buffer, or on isolated rat-liver mitochondria equivalent to 167-333 mg wet-weight of original liver.

The reactivity of DEDC with SH (sulfhydryl) groups was assessed by studying its interactions with BAL (1,2-dimercaptopropanol) and glutathione [93]. After incubation of a mixture of a thiol compound and DEDC for 5 minutes in a water bath at 37 C, the oxidation-reduction indicator 2,6-dichlorophenolindophenol was added to the mixture. Decolorization of the dye was followed by measuring the absorbance at 620 nm. The results demonstrated that DEDC is capable of preventing reduction of the dye to its colorless form by either BAL or glutathione. The authors concluded that the affinity of DEDC for BAL was greater than that for glutathione.

Because DEDC decreases the activity of SH groups and the alpha-keto oxidases require the presence of SH groups for activation, Aldridge and Cremer [93] postulated that this tin compound might inhibit alpha-keto acid oxidases. The alpha-keto acids were determined colorimetrically by forming the 2,4-dinitrophenylhydrazone derivatives and measuring their absorbance at 520 nm. Rat-brain brei was used as the source of enzymes. DEDC increased the accumulation of pyruvate during oxidation of lactate, with a

decrease in the uptake of oxygen by the brei. The effect of DEDC on oxygen uptake was antagonized by either BAL or glutathione, BAL being several times more effective.

When aliquots of a preparation of mitochondria from rat liver were incubated with various substrates, the oxidations of pyruvate and L-malate were decreased particularly strongly, those of alpha-keto glutarate and L-glutamate less strongly, that of citrate still less strongly, and that of succinate only feebly [93]. DEDC was found to increase the accumulation of alpha-keto acids by inhibiting their further oxidation after their production during the metabolism of L-glutamate, L-malate, and citrate. The accumulation of alpha-keto acids during oxidation of citrate was prevented by BAL; glutathione had less than 1/10 the effectiveness of BAL in this regard.

From these studies, Aldridge and Cremer [93] concluded that DEDC inhibits alpha-keto acid oxidases, leading thereby to a reduced supply of energy to the cells that depend most heavily on the tricarboxylic acid cycle for their requirements.

Aldridge and Cremer [93] also studied the effects of triethyltin sulfate (TETS) on metabolic systems in brain and liver. TETS was found to have less affinity for either BAL or glutathione than DEDC and, unlike DEDC, to decrease the accumulation of pyruvate in a brei of rat brain metabolizing lactate, in rough proportion to the decrease in oxygen uptake that it induced. This effect by TETS was antagonized only slightly by glutathione and not at all by BAL; indeed, BAL may have enhanced the inhibition by decreasing oxygen uptake by the brei of rat brain. In addition, TETS reduced glycolysis by a brei of rat's brain under either

aerobic or anaerobic conditions.

TETS may have been somewhat more potent than DEDC in inhibiting oxidation by the rat hepatic mitochondria of citrate, L-malate, L-glutamate, and succinate and less effective in inhibiting those of pyruvate and alpha-ketoglutarate [93]. It was found to differ qualitatively from DEDC in that it decreased, rather than increased, the accumulation of alpha-keto acids by hepatic mitochondria metabolizing citrate, L-malate, or L-glutamate. The inhibition by TETS of accumulation of alpha-keto acids from oxidation of citrate was antagonized only slightly by BAL and glutathione.

The uptake of oxygen by rat-liver mitochondria oxidizing L-glutamate was reduced to zero by 0.99 mM TETS [93]. At the same time, the concentration of reduced cytochrome decreased to 5% of the control value, whereas the concentration of total cytochrome (reduced by K3Fe(CN)6 and measured at 540 nm) was equal to that of the control. These findings were taken to indicate that TETS does not inhibit cytochrome c oxidase.

A concentration of 0.26 mM TETS was found to decrease the ratio of μmoles of oxygen used to μmoles of succinate removed (from 7.05 to 1.14) [93]. This finding was considered to indicate that TETS depletes the substrate in some way rather than interfering with the respiratory chain.

The reduction of coenzyme A in an extract of a preparation of acetone-dried material from rat liver during oxidation of either lactate, L-glutamate, or L-malate was not altered by 0.40 mM TETS [93]. Mitochondria from rat liver suspended in either water or a potassium chloride solution underwent no striking changes in their concentrations of reduced coenzyme A during oxidations of L-malate and L-glutamate after

exposure to the same concentrations of TETS.

Oxidation of 3-hydroxybutanoate by rat-liver mitochondria was decreased by 0.02 mM TETS [93]. Coenzyme A was found to antagonize this action of TETS, whereas magnesium seemed to intensify it. Coenzyme A had a weaker antagonism to inhibition by this concentration of TETS in the oxidation of L-malate. This concentration of TETS decreased both oxygen uptake and uptake of inorganic phosphorus by rat-liver mitochondria during oxidation of such substrates as citrate, succinate, and 3-hydroxybutanoate. Phosphorylation was decreased more (67%) than oxygen uptake (45%). Aldridge and Cremer [93] concluded that TETS was a potent inhibitor of oxidative phosphorylation.

Aldridge [94,95], Rose [96], Aldridge and Street [97-99], Aldridge and Threlfall [100], and Aldridge and Rose [101] conducted in-depth in vitro studies of the effects of trialkyltins on oxidative phosphorylation. The biochemical procedures described by Aldridge and Cremer [93] were used. Aldridge [94] reported that the inhibitory effect of the trialkyltins generally decreased with an increase in the number of carbons in the alkyl group. In a later study, Aldridge [95] showed that the trialkyltins acted upon a component of the energy-transfer chain leading to the formation of ATP, but this compound has not been identified. However, in rat hemoglobin, which resembles rat-liver mitochondria in its affinity for triethyltin, binding sites situated between histidines have been identified [95]. Rose [96] reported that one molecule of rat hemoglobin combines with two molecules of triethyltin and that the binding site was situated between two histidine residues and that the site was on the globin. Aldridge and Street [99] showed that mitochondrial swelling may be due to the effects of

trialkyltins on oxidative phosphorylation in the mitochondria. However, they could not account for the diverse toxic effects observed under in vivo conditions. Aldridge and Threlfall [100] have shown that triethyltin and tri-n-butyltin inhibited the 32P-adenosine triphosphate exchange reaction in rat-liver mitochondria. Aspects of these in vitro findings were verified by Sone and Hagihara [102], Vardanis and Quastel [103], Wulf and Byington [104], Tyler [105], and Byington [106]. Cremer [107] used in vitro experiments to show that respiration was inhibited to a greater degree in the brain than in the liver or kidneys. Tissues from these three organs also concentrated triethyltin in vitro, so that concentrations were higher in the tissues than in the medium.

(5) Carcinogenic, Mutagenic, and Teratogenic Studies

Two studies [108,109] dealing with the carcinogenic potential of the organotins were found. Innes et al [108] screened triphenyltin acetate (TPTA) for its tumorigenic activities. Mice from two hybrid strains were segregated into groups of 18 males and 18 females. TPTA at a maximum tolerated dose (highest dose causing no mortality after 19 daily doses) of 0.464 mg/kg was administered by intubation at 7 days of age and continued daily until weaning at 4 weeks. After weaning, TPTA was administered in the diet at a concentration of 1,206 ppm, which was estimated to be equivalent to a daily dose of 0.464 mg/kg. When the mice were 18 months old, they were killed and an autopsy was performed. This included external examination, examination of the thoracic and abdominal cavities, and microscopic examination of unspecified major organs and all grossly visible lesions. Results were compared with those in four untreated groups and seven groups receiving known tumorigenic agents. The

numbers of tumors in the treated animals were not given. However, the authors [108] stated that the oral administration of TPTA caused no significant increase in tumors.

The carcinogenic potential of tributyltin fluoride (TBTF) was assessed in a 6-month dermal study on 200 male Swiss white mice, using a control, a positive control, and two test groups of 50 mice each [109]. Fifteen milligrams of a 10 or 30% solution of TBTF in propylene glycol was applied to the shaved back of each mouse in the two test groups three times weekly for 6 months. The positive control received a known carcinogen identified as R-911-10 in the same manner. The control animals were treated with 15 mg of propylene glycol. Animals were observed daily for 6 months for behavioral and skin changes. When any skin lesion reached 1 mm in diameter, it was measured and its size recorded weekly. At the end of 6 months, animals were killed, and all skin lesions were examined microscopically.

None of these animals showed signs of abnormal behavior or systemic intoxication [109]. There were no visible skin lesions in control animals, while 56% of the positive controls had such lesions. At 10% TBTF, no lesions were observed. However, at 30% TBTF, skin irritation occurred after 3 weeks, so the concentration was reduced to 5% TBTF for the remainder of the study. Under these circumstances, 10% of the mice developed skin lesions. The author attributed these lesions to irritation from the initial application of 30% TBTF. A microscopic examination of the positive controls showed a significant incidence of cancerous lesions while the lesions at 5% TBTF were described as hypertrophic changes and inflammation of the epithelium and were not neoplastic. A postmortem

examination of all animals revealed no gross pathologic changes, other than skin lesions, which could be related to TBTF or the test procedures. Mortality was 24% in the controls, 26% in the positive controls, 22% at 10% TBTF, and 28% at 5% TBTF. These results indicate that TBTF as a 10% dermal application was not carcinogenic. The reduction in the concentration of TBTF from 30 to 5% after 3 weeks of testing makes it difficult to assess the observed effects.

Epstein et al [110] included triphenyltin acetate (TPTA) and triphenyltin hydroxide (TPTH) in a screening study of many compounds for mutagenic potential by a modified dominant lethal assay. TPTA and TPTC were administered ip and by gavage to male ICR/Ha Swiss mice 8-10 weeks old [110]. For TPTA, single ip doses of 2.4 and 12 mg/kg and five consecutive daily oral doses of 6 mg/kg were used [110]. For TPTH, single ip doses of 1.3 and 8.5 mg/kg and five consecutive daily oral doses of 11 mg/kg were used. Seven male mice received the lower ip dose for the two compounds, 9 received the higher ip dose, and 10 received each of the oral doses. An analysis of the results showed that TPTA and TPTH at the doses used did not meet any of the criteria established by the authors [110] and were therefore not regarded as mutagenic within the selected dose range.

Correlation of Exposure and Effects

Organotins are compounds of diverse physical properties and toxicities. Tables III-2 and III-3 present data on toxic effects produced by exposure to organotin compounds. However, certain general characteristics common to organotin compounds may be useful in assessing

qualitatively the toxic effects where comprehensive toxicity data are lacking.

Organotin compounds differ in the severity of their toxic effects as well as in the organs they affect. The trialkyltins are apparently the most toxic group, followed by the dialkyltins and monoalkyltins. The tetraalkyltins are metabolized to their trialkyltin homologs [85], so that their effects are those of the trialkyltins, with severity dependent upon the rate of metabolic conversion. Animal species differ in their response to the dialkyltins, with mice affected most severely, followed by rats, guinea pigs, and rabbits [60,64,77,79]. However, no species differences were reported for CNS damage by the trialkyltins [67].

Barnes and Stoner [60] and Caujolle et al [50] showed that, for each major organotin group, the ethyltin derivative was the most toxic, and the methyltins were somewhat less toxic. The homologs above ethyltin tended to show decreasing toxicity with an increase in the number of carbon atoms in the organic group bonded through a C-Sn bond. These authors [50,60] also showed that the iso-isomers were more toxic than the normal isomers. The type of anionic group influences the severity of the toxic action [52,60]; however, no general pattern of effect could be discerned from the available data.

Interstitial edema of the white matter of the CNS (cerebral edema) and vacuolization of the nerve processes were observed in the brains of four people poisoned by Stalinon [27]. Stalinon administered to mice and monkeys at unspecified doses produced cerebral edema strikingly similar to that seen in the human victims [27]. Rabbits [74] and dogs [70] were similarly affected by trialkyltin intoxication.

Headaches and visual disturbances have been reported in occupational exposure incidents involving triorganotin compounds [33-36], but no incidents of CNS damage have been observed. However, in an inhalation experiment by Gohlke et al [57], female rats exposed to tributyltin chloride at a concentration of 4-6 mg/cu m, measured as tin, 6 hours/day, 5 days/week, for 4 months, developed pronounced cerebral edema and cellular necrosis, indicating that excessive exposure may lead to damage within the CNS. Damage was reversible, and its development was reported to be asymptomatic. Wakashin [76] used ip injections of tributyltin chloride at 2.2 mg/kg to produce cerebral edema in rats. At dietary levels of 5-50 ppm and at ip doses of 1-10 mg/kg [67,69,73,92], other trialkyltins also produced cerebral edema.

Liver damage has occurred in occupational exposure to triphenyltin acetate [34,35]. Of two spray-plane pilots exposed to a commercial formulation of triphenyltin acetate called Brestan-60, one developed an enlarged and tender liver with slightly increased SGPT and SGOT activity, indicating possible liver cell damage. This was confirmed by liver biopsy, which showed increased collagen and moderate round-cell infiltration with slight portal and periportal fibrosis. The other pilot had an enlarged liver, but no biopsy was performed since liver function tests were normal.

In animals, liver damage has been reported in mice, rabbits, rats, and guinea pigs from organotins at various concentrations [16,42,44,46,47,57]. A tributyltin mixture (81.2% tributyltin bromide) at an air concentration of 5.65 mg/cu m, measured as tin, caused congestion of the liver in mice after 3 consecutive days of 8-hour exposures [42]. At 2.12 mg/cu m, measured as tin, 3 consecutive days of exposure for 8

hours/day produced the same effect in mice [42]. A 10-day exposure to trialkyltin vapor at 900-3,200 mg/cu m, measured as tin, produced fatty changes in the liver of mice [16]. Tributyltin chloride at a concentration of 4-6 mg/cu m, measured as tin, for 6 hours/day, 5 days/week, for 4 months produced severe liver damage in mice [57]. Pelikan and Cerny [44-47] reported liver damage in mice 24 hours after single oral doses of 4,000 mg/kg of monoalkyltins and dialkyltins and 500 mg/kg of trialkyltins. Barnes and Stoner [60] reported that dibutyltin dichloride administered by intubation in three successive daily doses of 50 mg/kg produced severe liver damage in rats. Acute inflammation of the portal tracts of the liver occurred 48 hours after a single 50-mg/kg dose of dibutyltin dichloride but was reversible [61].

Inhalation studies using rats [53] showed that 4 hours of exposure to TnBTF at 0.4, 2.0, 8.8, 22.3, or 73.0 mg/cu m, calculated as tin, resulted in "less than normal" weight gain at 0.4 mg/cu m, death in 5 of 10 animals exposed at 2.0 mg/cu m, and death in all animals, exposed at 8.8, 22.3 or 73.0 mg/cu m. With similar inhalation conditions [54], exposure of 10 young adult rats (5 males and 5 females) for 4 hours to TPTF at 41.9, 96.6, 164.2, or 299.5 mg/cu m, calculated as tin, resulted in 2 deaths at 41.9 mg/cu m, 3 at 96.6 mg/cu m, 8 at 164.2 mg/cu m, and 10 at 299.5 mg/cu m. An LC50 of 93.4 mg/cu m for TPTF was derived from this information. Animal inhalation studies have shown that DMDC and DBDC are substantially less toxic than TMTC.

Bartalini [63] gave rats dibutyltin oxide at a dose of 100 mg/kg for a 5-day period and found severe and widespread alteration in the structure of the liver, including acute necrosis and cellular degeneration. Only a

slight alteration of the liver, including some nuclear hypertrophy and increased numbers of Kupffer cells, was observed after rats were given dibutyltin oxide at 25 mg/kg for 60 days [63]. Similar effects were found in rats given daily doses of 27.25 mg/kg of DBDA by gavage for 10 days [64], single subcutaneous or ip injections of 0.7 and 2.2 mg/kg, respectively, of TBTC [76], single oral doses of 80-250 mg/kg of TPTA, or a diet containing 50 ppm of TPTA (20 ppm, as tin) for more than 107 days [79].

Investigators have reported that bis(tributyltin) oxide (TBTO) is an irritant of the eyes and respiratory tract in humans. Peters (written communication, December 1975) reported irritation of the upper respiratory tract and eyes in employees by TBTO at concentrations reported to be below 0.1 mg/cu m, as tin. Landa et al [38] established a causal relationship between the use of a commercial preparation containing 20% bis(tributyltin) oxide and ethylene oxide condensate and irritation of the eyes and nasal mucosa.

In animals, damage to lung tissues, such as pulmonary edema, has been reported in a number of inhalation studies. Pulmonary edema was the cause of death in mice exposed for 10 days to triethyltin bromide at 1,600-3,400 mg/cu m, tripropyltin bromide at 1,700-3,200 mg/cu m, tributyltin bromide at 1,000-2,700 mg/cu m, or tetramethyltin at 2,500-10,800 mg/cu m [16]. Pulmonary edema, bleeding, and congestion were present in male mice exposed to a butyltin mixture (81.2% tributyltin bromide) at a concentration of 5.65 mg/cu m, measured as tin, 8 hours/day for 3 consecutive days [42]. At 2.12 mg/cu m, measured as tin, congestion of the lungs with bronchial pneumonia was observed in mice after an exposure of 7 hours/day for 3

consecutive days. Similar effects were observed in mice with triethyltin bromide at 2.12 mg/cu m, measured as tin, using a weekly exposure schedule of 4, 5, or 6 hours/day for 3 consecutive days, followed by 1 day of no exposure, 2 days of exposure, and 1 day of no exposure, over a 12-week period [42]. Male rats exposed 5 hours/day for 79-80 days and female rats exposed 5 hours/day for 42 days developed bronchitis with bronchogenic pneumonia from tributyltin bromide at a concentration of 2.12 mg/cu m, as tin [42]. Bronchitis was reversed within 42 days in female rats exposed for 5 hours/day, if exposure was terminated after 14 days [42].

Lyle [18] reported an incident of accidental exposure of humans to butyltin compounds which produced severe injuries to the eyes. Lacrimation and intense and sudden dilation of the blood vessels of the conjunctivae appeared in minutes, despite immediate lavage. Similar but more severe effects on the eyes were reported by Pelikan [92] and Scheinberg et al [111] in animals exposed to triethyltin and tributyltin analogs.

The organotins have been found to be highly irritating to the skin of humans [18,36] and of animals [61,89,90]. Experiments with volunteers showed that undiluted dibutyltin dichloride and the chloride, acetate, and oxide derivatives of tributyltin produced follicular inflammation and pustulation of various intensities [18]. The lesions were most severe with tributyltin chloride and least severe with tributyltin laurate. With tributyltin chloride, mild edema with itching appeared within 3-8 hours of application and was usually completely healed in 7 days. Occupational exposure to 20% triphenyltin acetate produced skin irritation 2-3 days after prolonged contact with contaminated clothing [36].

In animals, Pelikan and Cerny [89,90] reported mild edema with alterations in the subcutaneous tissues, including hyperemia, and a parenchymatous dystrophy of the liver of rats 60 days after a dermal application of a 1% solution of a commercial preparation containing 20% bis(tributyltin) oxide. A slight edema of the skin with hyperemic subcutaneous tissues was also reported in rats 35 days after the application of a 0.25% solution of the commercial preparation. Barnes and Magee [61] reported skin lesions with single and repeated applications (number unspecified) of undiluted dialkyltin and trialkyltin compounds. Dimethyltin and diethyltin dichlorides produced severe lesions, while dipropyltin dichloride and the higher homologs caused relatively little damage. Kawai [91] reported anemia and possible liver and kidney damage in rabbits with dermal applications of the iodide, chloride, or bromide analog of tributyltin at a dose of 0.005 cc/kg, 6 days/week for 12 weeks.

Ingestion studies [84] using DOTO showed that the organs with the highest level of tin were the liver and kidneys of the rat and the liver of the dog. Results were similar for both males and females. In the rat, at least 50% of the total tin was present as dialkyltin, while in the dog only 10-13% was found as a dialkyltin. Cremer [85] found that metabolic conversion of tetraethyltin to triethyltin occurred in the liver. A steady-state concentration was achieved in 1-2 hours after exposure, with about 25% conversion of tetraethyltin to triethyltin.

A single dose of 25 mg/cu m of TCHH labeled with 119Sn was excreted in the feces (98%) and urine (2%) by rats and guinea pigs within 9 days [53]. A 90-day study with Wistar rats of both sexes, using 119Sn-labeled TCHH in laboratory chow at a concentration of 100 ppm, showed that a

maximum concentration of tin was obtained after 15 days. The tin concentration was greatest in the kidneys, followed in order by the heart, liver, muscle, spleen, brain and fatty tissues, and blood. Analyses of tissues showed that 60-75% of the tin was in the organic form. Analysis of liver samples from rats on a diet of 3 mg TCHH/kg for 90 days showed 45% as TCHH, 40% as DCHO, and 15% as inorganic tin. Liver samples from dogs on a similar diet showed 15% as TCHH, 45% as TCHO, and 40% as inorganic tin. After withdrawal of TCHH from the diet, there was a decrease in total tin content of the organs with time.

Although not reported in human exposure incidents, effects on the kidneys have been observed in animal studies [44-47]. Pelikan and Cerny [44,45,47] and Pelikan et al [46] showed that fatty degeneration and hyperemia of the kidneys occurred within 24 hours after administration of oral doses of 4,000 mg/kg for the monoalkyltins and dialkyltins and of 500 mg/kg for the trialkyltins. Serious degenerative alterations of the epithelium, disintegration and fusion of the cytoplasm, and lyses of the nuclei occurred in the kidneys of rats ingesting dibutyltin oxide at 25 mg/kg for 5 days. Wakashin [76] injected mice ip with 2.2 mg/kg tributyltin chloride and produced swollen and anemic kidneys. Stasis and edema of the kidneys in rats were reported by Klimmer [79] after single oral doses of 80 to 250 mg/kg triphenyltin acetate.

The reproductive function of animals also was affected by exposure to organotin compounds. Iwamoto [58] exposed male and female rats to tributyltin bromide vapor at 2 mg/cu m, measured as tin, under subchronic and chronic exposure conditions and found that reproductive function was affected only in the females. This condition was reversible upon

termination of exposure. Triphenyltin acetate and triphenyltin chloride administered in the diet for 18 days at 20 mg/kg adversely affected the reproductive organs of male [80] and female [81] rats.

Carcinogenicity, Mutagenicity, and Teratogenicity

Carcinogenic effects were not evident in a screening study of triphenyltin acetate where mice received 19 daily oral doses of 0.464 mg/kg [108]. A 10% aqueous solution of tributyltin fluoride applied dermally to the backs of white mice 3 days/week produced no carcinogenic effects after 6 months. Triphenyltin acetate and triphenyltin hydroxide did not have any mutagenic properties in mice as determined by the dominant lethal mouse assay, using five daily oral doses of 6 mg/kg of TPTA or 11 mg/kg of TPTH [110]. Other studies have shown that animal species vary in their susceptibility to noncarcinogenic effects of the organotins [60,64,77,79]. Therefore, the possibility of carcinogenic or mutagenic effects in other animal species cannot be ignored. Studies on these and other compounds in different animal species are needed to assess more fully the carcinogenic, mutagenic, and teratogenic potentials of these compounds.

TABLE III-2

EFFECTS OF OCCUPATIONAL EXPOSURE TO ORGANOTIN COMPOUNDS

Compound	No. and Sex of Workers	Description of Exposure	Effects	Reference
TPTA	1 M	Spraying sugar beets with aqueous TPTA solution for 2 hr	Violent headache, unconsciousness	33
"	"	Formulating TPTA fungicidal spray solution	Vomiting, shortness of breath, glycosuria	33
"	"	"	Violent headache, nausea, vomiting, epigastric pain	33
"	48 M	Weighing and bagging TPTA formulation (Brestan) 8 hr/d for 2-10 d	Irritation of skin, mucous membranes, conjunctivae	36
"	1 M	Aerial spraying of Brestan	Dyspepsia, severe diarrhea, blurred vision, liver damage	34
"	"	"	Heartburn, blurred vision, diarrhea, coughing, hyperglycemia	34
"	"	Loading plane with Brestan	Skin irritation, dizziness, headache, nausea, fatigue, chronic hepatitis	37
TPTO	45 -	Construction of sonar domes using rubber containing TBTO; air concentrations 0.1-0.3 mg/cu m, as tin	Irritation of eyes and upper respiratory tract	*
"	- F	Spray-painting with latex paint containing TBTO	Irritation of eyes and nasal mucosae	38

TABLE III-2 (CONTINUED)

EFFECTS OF OCCUPATIONAL EXPOSURE TO ORGANOTIN COMPOUNDS

Compound	No. and Sex of Workers	Description of Exposure	Effects	Reference
TPTC	1 F	Drenched with hot slurry containing TPTC while working in organotin manufacturing plant	Severe burns, death	39
TBTC, DBTC	- -	Employed in organotin manufacturing plant	Dermatitis	46

*From written communications, JM Peters, December 1975, and MN Johnson, June 1975

TABLE III-3

EFFECTS OF EXPOSURE TO ORGANOTIN COMPOUNDS ON ANIMALS

Compound	Route of Exposure	Species	Largest Dose* With No Reported Effect	Smallest Fatal Dose	LD50	Largest Dose Not Killing All	Reference
MBTC	Oral	Mouse	-	-	1,400	>4,000	44
MBTA	"	"	-	-	>6,000	>6,000	44
MBTM	"	"	-	-	1,520	>4,000	44
MBTA	"	"	-	-	-	>4,000	44
MOTM	"	"	-	-	1,500	>4,000	45
DMDC	"	Rat	-	>80(x)	-	-	60
"	Inhalation	"	<1,030 (1 hr)	-	-	-	55
DEDC	Oral	"	40(x)	-	-	80(x)	60
DPDC	"	"	40(x)	-	-	80(x); 160	60
DiPDC	"	"	-	>80(x); 160	-	-	60
DBDC	ip	Mouse	<1(x)	-	-	-	51
"	Oral	Rat	<100(x)	200(x)	-	400(x)	60
"	ip	"	<5	-	-	-	76
"	Inhalation	"	<578	-	-	-	55
"	Dermal	"	<10	-	-	-	60
DBDA	Oral	Mouse	<25	-	109.7	-	48
"	"	Rat	<27	-	-	-	64

TABLE III-3 (CONTINUED)

EFFECTS OF EXPOSURE TO ORGANOTIN COMPOUNDS ON ANIMALS

Compound	Route of Exposure	Species	Largest Dose* With No Reported Effect	Smallest Fatal Dose	LD50	Largest Dose Not Killing All	Reference
DBDE	Oral	Mouse	<50	-	199.9	-	48
DBTG	"	Rat	>18(x)	<180(x)	-	-	66
DBTM	"	"	>18(x); <180 in diet	-	-	>180(x)	66
DBTO	"	"	<2.5	-	-	>100(x)	63
DHDC	"	"	<80	160; 40(x)	-	-	60
DOBM	"	Mouse	<4,000	-	3,750	-	46
DOEH	"	Rat	10; 40 in diet	>200; <75(x)	-	-	60, 62
DOEM	"	Mouse	>4,000	-	2,700	-	46
DOTM	"	Rat	<20(x); <200 in diet	<20(x)	-	<200(x)	66
DOTMa	"	Mouse	-	-	2,250	>4,000	46
DOTG	"	Rat	<20(x)	<20(x)	-	>200(x)	66
DPeDC	"	"	-	<80(x)	-	>160	60
TMTC	Inhalation	"	<5,245	-	-	<5,245	53
TETB	"	Mouse	<1,600(x)	<1,600(x)	-	>1,600(x); <3,400(x)	16

TABLE III-3 (CONTINUED)

EFFECTS OF EXPOSURE TO ORGANOTIN COMPOUNDS ON ANIMALS

Compound	Route of Exposure	Species	Largest Dose* With No Reported Effect	Smallest Fatal Dose	LD50	Largest Dose Not Killing All	Reference
TETS	Oral	Mouse	<12 in diet	>32 in diet	-	-	49
"	Oral	Rat	<20(x)	>20(x)	-	-	69
"	ip	"	<5	>10	-	-	60, 73
TETOl	Oral	Mouse	<500	-	230	-	47
TETH	"	Rat	<5 in diet	<20 in diet	-	>20 in diet	67
TPTC	"	"	<20(x)	>20(x)	-	-	80, 81
TPTB	Inhalation	Mouse	<1,700(x)	<1,700(x)	-	>3,200(x)	16
TPTF	"	Rat	<41.9	<41.9	-	>164.2; <299.5	54
TPTA	Oral	"	<20(x); <10 in diet	>80(x)	136	<250(x)	77, 79-81
"	"	Guinea pig	-	-	21	-	79
"	"	Rabbit	-	-	30-50	-	79
TPTH	"	Rat	100(x); <5 in diet	>200(x); <400(x)	-	<400(x)	77, 78

TABLE III-3 (CONTINUED)

EFFECTS OF EXPOSURE TO ORGANOTIN COMPOUNDS ON ANIMALS

Compound	Route of Exposure	Species	Largest Dose* With No Reported Effect	Smallest Fatal Dose	LD50	Largest Dose Not Killing All	Reference
TBTC	Oral	Mouse	-	-	117	>500	47
"	ip	Rat	<1.0	>3.7	-	-	51
"	Subcutaneous	"	<0.7	>0.7	-	-	76
TBTB	Inhalation	Mouse	<5.65; <2.12 (x)	-	-	>2,000; <2,700; <5.65 (x)	16, 42
"	"	"	<1,900(x)	<1,300(x)	-	>1,300(x)	16
"	"	Rat	<2.0 (x)	>6.0 (x)	-	-	57, 58
TnBTF	"	"	<0.4	>75.8	-	-	53
TBTA	Oral	Mouse	<50	-	46-99.1	-	47, 48
TBTH	Inhalation	"	<1,500(x)	>2,000(x)	-	-	16
TBTO	Oral	Rat	<91; 100 in diet	-	148-194	>320 in diet	83
"	Dermal	"	<0.0004%	>0.05%	-	-	90
TBTL	Oral	Mouse	<500	-	180	-	47
"	ip	Rat	<2.2	<2.2	-	-	76
"	"	Rabbit	<1.0	>1.0	-	-	74
"	"	Dog	<1.0	>1.0	-	-	70

TABLE III-3 (CONTINUED)

EFFECTS OF EXPOSURE TO ORGANOTIN COMPOUNDS ON ANIMALS

Compound	Route of Exposure	Species	Largest Dose* With No Reported Effect	Smallest Fatal Dose	LD50	Largest Dose Not Killing All	Reference
TBTBe	Oral	Mouse	<500	-	108	-	47
TeBT	"	"	<50; <694(x)	-	6,000	>13,880(x)	48, 50
"	ip	"	<1.0	>3.7	-	-	51
TeiBT	Oral	"	<174(x)	-	-	>6,940(x)	50
TeAT	"	"	<403(x)	-	-	>16,122(x)	50
TeiAT	"	"	<101(x)	-	-	>8,061(x)	50

*"Dose" means mg/kg for oral administration, ppm in the diet, mg/cu m for inhalation, mg/kg for all routes of injection. Doses are stated in terms of the entire molecule except in inhalation studies where concentration is in terms of tin in the molecule. When repeated doses were given, the symbol "(x)" follows the numerical dose.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION

Engineering Controls

Engineering controls must be instituted in areas where the airborne concentration of organotin dusts and vapors exceeds the TWA concentration limit, to decrease the concentration of organotins to or below the prescribed limit. Industrial experience indicates that closed-system operations are commonly used in manufacturing processes. Such systems must be used whenever feasible to control dust and vapor wherever organotin compounds are manufactured or used. Closed systems should operate under negative pressure whenever possible so that, if leaks develop, the flow will be inward. Closed-system operations are effective only when the integrity of the system is maintained. This requires frequent inspection for, and prompt repair of, any leaks.

A ventilation system may be required if a closed system proves to be impractical and is desirable as a standby if the closed system should fail. The principles set forth in Industrial Ventilation - A Manual of Recommended Practice [112], published by the American Conference of Governmental Industrial Hygienists, and Fundamentals Governing the Design and Operation of Local Exhaust Systems, Z9.2-1971 [113], published by the American National Standards Institute, should be applied to control workplace atmospheric concentrations of organotins. Ventilation systems of this type will require regular inspection and maintenance to ensure effective operation, and a program of scheduled inspection should be established in which the ventilation systems are checked routinely. These routine checks should include face velocity measurements of the collecting

hood, inspection of the air mover and collector, and measurements of workroom airborne concentrations. Any changes which may affect the ventilation system or the operations being ventilated must be assessed promptly to ensure that engineering controls provide adequate protection of employees.

Sampling and Analytical Methods

The few sampling methods described for collecting organotins in air [JM Peters, written communication, December 1975, 114-116] either are not generally suitable for collection of all the organotin compounds or are not suitable for personal monitoring. Most of the organotins are either solids or liquids. In general, techniques are well defined for sampling air for particulates [117,118] and for gases and vapors [119,120].

For collection of low-volatility solids, the membrane filter method described in NIOSH Method No. P & CAM 173 [116] will provide sufficient collection efficiency. Although no report describing a suitable collecting medium for personal monitoring of organotin vapor in air was found in the literature, activated charcoal tubes as described in NIOSH Method No. P & CAM 127 [121] would be expected to provide sufficient collection efficiency. The recommended sampling method for the determination of organotins in air consists of drawing a known volume of air through a membrane filter followed by an activated charcoal sampling tube, as described in Appendix I. Although this sampling method has not been evaluated by NIOSH, it is recommended as an interim method pending planned research by NIOSH. If this research results in the development of a better

method, the new method will be forwarded.

The analytical methods appropriate for the determination of the greatest number of organotin compounds generally do not distinguish between different organotins which may be present in the sample. Total tin in all the organotin compounds in the sample is usually determined, although certain classes of organotins may be determined by use of specific techniques such as chromatography or solvent extraction to separate compounds or types of compounds.

Where determination of a specific organotin compound is required, separation techniques which may be useful include thin-layer chromatography [122-124], column chromatography [125], and paper chromatography [126-130]. Sample preparation techniques which have been applied to the analysis of various organometallic compounds include oxygen-flask or wet combustion [131] and use of hydrogen peroxide to destroy organic matter [132]. After separation and sample preparation, a quantitative determination of the organotins or of tin is performed. Personal monitoring to evaluate concentrations of organotin in air, to determine compliance with this recommended standard, requires an analytical method which will quantitatively determine amounts of tin in the range of 1 μg or less in the total sample.

Colorimetric methods have been most generally applied to the determination of organotins or of tin following breakdown of the organotins. Reagents used for analysis of organotins or of tin include dithizone (1,5-diphenylthiocarbazone) [133-136], dithiol (toluene-3,4-dithiol) [137-140], phenylfluorone [114], and pyrocatechol violet (catechol violet) [141-144], as well as quercetin [145,146], oxine (8-quinolinol)

[147,148], 4-(2-pyridylazo)resorcinol (PAR) [149], and diphenylcarbazone [150]. A molybdenum blue method also has been described [151]. Since colorimetric reagents usually lack specificity [137], efficient separation of organotins may be required prior to measurement.

Use of dithizone for the colorimetric determination of organotins has been described by Chapman et al [133], Aldridge and Cremer [134], Hardon et al [135], and Chromy and Uhacz [136]. Chapman et al [133] applied the dithizone method to the determination of dibutyltin and dioctyltin compounds in polyvinyl chloride, as well as diethyltin dichloride, dibutyltin dilaurate, and diphenyltin dichloride. Aldridge and Cremer [134] described a method for the separation of mixtures of diethyltin dichloride and triethyltin sulfate, with subsequent colorimetric determination with dithizone. Hardon et al [135] presented a method for the determination of triphenyltin acetate residue on celery. Chromy and Uhacz [136] discussed the use of dithizone for the determination of microgram amounts of bis(tri-n-butyltin) oxide and tri-n-butyltin acetate in aqueous solutions. No report describing the use of dithizone for the analysis of air samples has been found. About 5 μg of tin in a sample is the minimum amount which may be quantitatively determined by the dithizone method.

The dithiol colorimetric reagent has been used by Corbin [137] and by Trombetti and Maini [138] for the determination of trace amounts of tin present as organotin residues on fruit sprayed with Plictran, a miticide containing tricyclohexyltin hydroxide. Farnsworth and Pekola [139,140] used dithiol for the determination of small amounts of tin in several materials, including various methyltins, butyltins, phenyltins, and

lauryltins. Tin in organotins can be determined to a lower limit of about 2 μg by methods using the dithiol reagent [137].

Two of the more sensitive colorimetric reagents are phenylfluorone (2,3,7-trihydroxy-g-phenylfluorone) [114] and pyrocatechol violet (cathechol violet) [141-145,152]. Selivokhin [114] reported the use of phenylfluorone for the determination of tetraethyltin and tetrabutyltin in factory air. The sensitivity was given as 0.1 μg of tin in the sample. Use of pyrocatechol violet for the determination of an organotin compound identified by the authors as dioctyltin S,S'-bis(isooctylmercaptoacetate), in the range of 0.2-1.6 μg of tin, was described by Adcock and Hope [141]. Thomas and Tann [142] described a method using pyrocatechol violet for the determination of triphenyltin hydroxide and triphenyltin acetate pesticide residues in potatoes. The limit of detection for tin as determined by this method was given as 0.5 μg. In a pyrocatechol violet method for the determination of tin presented by Corbin [143], a plot of absorbance against micrograms of tin was reported to deviate from linearity at quantities below 0.5 μg of tin in 50 ml of final solution.

In a report of work for the Metallic Impurities in Organic Matter Sub-Committee of the Analytical Methods Committee, Newman and Jones [153] presented a method for the selective extraction of tin(IV) iodide from a sulfuric acid solution into toluene. The tin(IV) was then determined by spectrophotometric measurement of the color of the complex formed between tin(IV) and pyrocatechol violet. No significant interference was found in tests made with a wide variety of anions and cations in which the ions under investigation were added to sulfuric acid solutions containing 20 μg of tin(IV). The ions which have shown no interference at the indicated

level are: Be, Ba, Cd, Hg(I), Hg(II), La(III), Ce(III), Ce(IV), Ti(IV), Th(IV), Ge(IV), Pb, As(III), As(V), Sb(III), Sb(V), Se(V), Bi, Cr(III), Cr(VI), Mo(VI), W(VI), U(VI), Mn(II), Co, Ni, Cu, Zn, and Fe(II) (100 μg); fluoride, chloride, nitrate, and pyrophosphate (1 mg); and Mg, Al, Fe(III), borate, orthophosphate, and citrate (5 mg). Since this method was found to be specific for tin in the presence of a wide variety of other metals and several anions, it should be applicable to the determination of tin in organic matter after wet decomposition in which a sulfate residue is produced. Recoveries of known amounts of tin analyzed by this procedure ranged from 96.0 to 101.0% with amounts of tin ranging from 5 to 30 μg. The calibration graph obtained by this pyrocatechol violet method was linear over the range of 0 to 1.2 μg of tin per ml.

The Metallic Impurities in Organic Matter Sub-Committee of the Analytical Methods Committee recommended the pyrocatechol violet colorimetric method for determination of amounts of tin up to 30 μg and suggested a dithiol colorimetric method for amounts of tin in the range of 30-150 μg [144]. No report on the use of pyrocatechol violet for the analysis of organotin compounds in air samples has been found. However, since quantities of tin collected in air samples may be in the vicinity of 1 μg or less, the pyrocatechol violet method offers sufficient sensitivity for evaluation of environmental samples to determine compliance with this standard. Although the color reaction between tin(IV) and pyrocatechol violet may not be completely selective [144], a separation of organotin compounds from interfering substances by chromatographic or solvent-extraction techniques would allow a specific determination.

Several analytical methods which have been used for the determination of tin do not possess the required sensitivity for the determination of organotins in the occupational environment, or the methods require tedious laboratory techniques or equipment not generally available. Chromatographic techniques used for separation of organotins have generally been followed by an appropriate sensitive colorimetric method such as pyrocatechol violet or phenylfluorone for quantitative determination of tin in the organotins identified.

Gas chromatography [115,126,145,154] has been used for the quantitative determination of various organotins. Only one report was found in which gas chromatography was applied to the analysis of air samples [115]. In this study, bis(tributyltin) oxide was collected on glass-fiber filters. A high-volume sampler was used to collect the tin compound from general workplace air. Following extraction with toluene, pyrolysis gas chromatography was used for analysis, since conventional gas chromatography of bis(tributyltin) oxide was unsuccessful. Gas chromatographic analysis has been applied to the determination of butyltin, octyltin, and phenyltin halides [154]. Under the analytical conditions used in this study, disproportionation did not occur, as shown by the absence of peaks associated with disproportionation products on the chromatogram. However, Franc et al [126] found that disproportionation was a problem which made gas chromatography unsuitable for the quantitative determination of some organotin mixtures.

Other chromatographic techniques have been used for the separation and identification of various organotins. Separation techniques have included thin-layer chromatography [122-124,145,155], paper chromatography

[126-130], and column chromatography [125].

Analytical methods, other than colorimetric or chromatographic techniques, which have been applied to the determination of tin include fluorimetric [156], polarographic [157,158], spectrographic [159,160], gravimetric [140,161], and atomic absorption [115,116,146,162,163] techniques. Generally, such techniques have not been applied to analysis of organotins in air; some have been applied predominantly to analysis of inorganic tin.

Vernon [156] presented a method for the determination of residues of triphenyltin compounds resulting from the treatment of potatoes with triphenyltin fungicides. The analytical method used the fluorimetric measurement of the triphenyltin moiety resulting from complex-formation with 3-hydroxyflavone. Recoveries averaging about 90% were obtained from potato samples to which 1 μg of tin as triphenyltin had been added. The limit of detection of this fluorimetric method was given as 0.16 μg of tin, with a standard deviation of $\pm$ 5.7%.

Atomic absorption spectrophotometric methods have been applied to the determination of tin in several types of samples. However, no study was found in which air samples obtained by personal monitoring were analyzed by atomic absorption. Jeltes [115] reported the determination of bis(tributyltin) oxide in high-volume air samples collected on glass-fiber filters. Following extraction of the filters with methylisobutyl ketone, the samples were analyzed by atomic absorption. To obtain a measure of filter efficiency for the collection of bis(tributyltin) oxide, sampling was done through two glass-fiber filters in series. More than 99% of the bis(tributyltin) oxide collected was obtained on the first filter. The

analytical sensitivity was not stated, but the determination of milligram quantities of bis(tributyltin) oxide was reported.

An atomic absorption analytical method for the determination of tin was applied to the analysis of several metallurgical samples by Capacho-Delgado and Manning [162]. The sensitivity for tin was about 1 ppm for 1% absorption, and the detection limit was about 0.1 ppm in a water solution.

Atomic absorption was found to be satisfactory for the determination of dibutyltin dilaurate in poultry feed formulations [163]. Essentially, theoretical recovery was obtained in formulations with dibutyltin dilaurate concentrations from 0.02 to 0.0375%. The authors stated that the method applies to feeds with dibutyltin dilaurate concentrations from 0.02 to 0.14%.

Engberg [146] reported that atomic absorption was satisfactory for the determination of tin in canned food, but the colorimetric method using quercetin (3,5,7,3',4'-pentahydroxyflavone) was preferred for very low tin concentrations, such as residues of organotin compounds. Amounts of tin as low as about 40 μg were quantitatively determined by atomic absorption.

In NIOSH Analytical Methods No. P & CAM 173 [116], a sensitivity of 5 μg/ml is given for the determination of tin. While this may be sufficient for some general workplace air samples, a more sensitive method is needed for personal monitoring.

Few of the methods described in the literature possess the required accuracy and sensitivity to quantitatively determine amounts of tin of less than 1 μg in an air sample as required to determine compliance with this standard. The two methods found which possess the required sensitivity were colorimetric methods using phenylfluorone [114] and pyrocatechol

violet [143,153]. Tin(IV) produces a colloidal system with phenylfluorone rather than a water-soluble type of complex such as that produced by tin(IV) with pyrocatechol violet. The water-soluble property allows the use of simpler manipulative techniques [153].

The pyrocatechol violet method is generally available to industry, requires no highly specialized laboratory equipment, and has been shown to provide sufficient accuracy, sensitivity, and precision within the range required to determine compliance with this standard for all organotins. For analysis of specific organotins, any method shown to be equivalent or superior in accuracy, sensitivity, and precision may be used.

Because of its high sensitivity and the general availability of the required analytical reagents and equipment, the pyrocatechol violet method described in Appendix II is the recommended analytical technique for determination of organotins, measured as tin. If the determination of a specific organotin compound is required, it will be necessary to separate that compound from other components prior to analysis. NIOSH has not evaluated this method for the analysis of samples of organotins collected from air but believes that it should be satisfactory on the basis of published reports of its use in the analysis of solutions. If research now underway by NIOSH determines that a better method can be devised, the improved methodology will be provided.

Biologic Evaluation

Experimental techniques for analysis of animal urine and feces have been developed [86] and may have potential use in monitoring employee

exposure to organotin compounds.

Bridges et al [86] described a spectrophotometric method for the determination of organotins as tin in biologic samples. Total tin was determined by treating urine or homogenized feces with concentrated sulfuric acid followed by an excess of nitric acid. The solution was heated until sulfur trioxide fumes appeared, then it was cooled and reheated. Dithiol was then added, and the resulting red color was measured at 530 nm with a spectrophotometer. The limit of sensitivity of the test was reported to be 5 μg of tin/ml of sample.

A colorimetric method has been described by Aldridge and Cremer [134] for the separation and determination of diethyltin and triethyltin compounds. The test involved the formation of a dithizone complex with diethyltin or triethyltin. The dithizone-diethyltin complex had an absorption maximum at 510 nm in the presence of borate buffer. With triethyltin, maximum absorption was at 440 nm in the presence of borate buffer at pH 8.4, whereas maximum absorption occurred at the same wavelength (510 nm) for both the triethyltin-dithizone complex and dithizone alone in the presence of trichloroacetic acid. This method has been used successfully in the analysis of bile samples from rats for diethyltin by Bridges et al [86], who reported recovery of 96 ± 5%. However, the method was found to be unreliable with urine samples. The applicability of this test to other organotin compounds needs to be determined.

The fluorimetric determination of monoethyltin in urine and bile samples has been used by Bridges et al [86]. The monoethyltin-(3-hydroxyflavone) complex is formed in the presence of sulfuric acid, and the

intensity of fluorescence at 445 nm is measured. The presence of phosphate ions interferes with the fluorescence, but this can be allowed for by the use of an internal standard.

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

Standards for organotin compounds have been established primarily to regulate the use of organotin additives in packaging materials for foods and beverages and to prevent occupational exposure of employees. As the first of many standards for the use of organotins in packaging materials, the Federal Food, Drug, and Cosmetic Act was amended in 1963 to allow the introduction of dibutyltin dilaurate in silicone polymer solids in amounts not to exceed 1 part of tin/100 parts of silicone polymer [Federal Register 28:7777, July 31, 1963]. Silicone polymers are used in the formulation of resinous and polymeric coatings in packaging materials which can be expected to come in contact with food products. A subsequent amendment to the Act allowed the use of di-n-octyltin S,S'-bis(isooctylmercaptoacetate) in vinyl chloride plastics. The amount of octyltin was limited to 15.1-16.4% by weight of tin and 8.1-8.9% by weight of mercapto sulfur. The amount of dioctyltin dichloride (if used in the synthesis of the mercaptoacetate derivative) was specified to be not less than 95% dichloride, not more than 5% trichloride derivative, not more than 0.2% isomers of dioctyltin, and not more than 0.1% for the higher and lower homologues of the octyltin. The Food and Agricultural Organization and 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 (fat bases) [164] and an acceptable daily intake for men of 0-0.0075 mg/kg body weight for the pesticide tricyclohexyltin hydroxide [165].

In 1965, the American Conference of Governmental Industrial

Hygienists (ACGIH) [166] established a threshold limit value (TLV) of 0.1 mg/cu m, measured as tin, for all organotin compounds in the occupational environment. The 1971 Documentation of the Threshold Limit Values for Substances in Workroom Air [167] by the ACGIH placed the TLV at 0.1 mg/cu m, measured as tin, by analogy with mercury, selenium, and thallium because of a lack of pertinent data. Only the TLV's for selenium and mercury were based on prolonged exposures of animals [167]. In 1973, the ACGIH [168] listed a proposed TLV for tricyclohexyltin hydroxide (Plictran) of 5 mg/cu m (1.2 mg/cu m, measured as tin). This standard was adopted in 1975.

The German Democratic Republic listed an NPK (maximum allowable concentration) for organotins of 0.1 mg/cu m [38]. No justification for this level was given. Rumania and Yugoslavia list maximum allowable concentrations of 0.1 mg/cu m, and these are based on the 1966 Documentation of TLV's of the ACGIH [169]. The level listed by Yugoslavia is measured as tin. Rumania does not state this qualification, but it is assumed that measurement is as tin.

The current federal standard, 29 CFR 1910.1000, is a TWA concentration limit of 0.1 mg/cu m, measured as tin. This is based on the ACGIH TLV established in 1965.

Basis for the Recommended Standard

Available reports on occupational exposure to the organotin compounds were descriptions of signs and symptoms of exposure. Only in the studies by Peters (written communication, December 1975) and Landa et al [38] were attempts made to relate the observed effects to the air concentration of

organotins. Landa et al [38] observed eye and upper respiratory tract irritation from bis(tributyltin) oxide (TBTO) at an average air concentration of 0.05 mg/cu m, measured as tin. However, since readings fluctuated at the limit of sensitivity of the analytical method (0.1 mg/cu m, as tin), the average concentration of 0.05 mg/cu m cannot be considered accurate. From data obtained by a questionnaire, Peters (written communication, December 1975) concluded that eye and upper respiratory tract irritation developed in employees exposed to TBTO at concentrations reported to be below the current TLV, but he did not provide any supportive information. Possible bias in the questionnaire was not accounted for in the report, nor was sufficient information on the sampling and analytical method provided to permit assessment of the accuracy of the reported air concentration. Because of its incompleteness, the report is of use only as an indicator of the irritative properties of the organotins at low concentrations.

Most of the animal data available was based on oral administration, and such studies are useful only in determining the type of effects that may occur from organotin exposure. Of the inhalation studies found, only one dealt with organotin air concentrations near the current TWA concentration limit of 0.1 mg/cu m, as tin; the only effect reported at this concentration was a "less than normal" weight gain in rats after a 4-hour exposure [53]. Other inhalation studies were performed at air concentrations well above the current standard and therefore do not provide information for assessing organotin toxicity at the current standard.

Human and animal toxicity data neither support nor negate the current federal standard, which was set by analogy with mercury, selenium, and

thallium. NIOSH therefore recommends that the current standard of 0.1 mg/cu m, as tin, as a TWA concentration limit be retained for all organotin compounds until more definitive information has been obtained. NIOSH recognizes that the organotins are of varied toxicity and hazard and that a single standard, as recommended, may be unnecessarily restrictive for many of the organotins. However, because of the lack of adequate data to evaluate the health hazard of the individual compounds to which employees may be exposed, and because of the absence of a sampling and analytical method which can quantitatively separate and identify the individual components of an organotin mixture in the working environments, there is no practical alternative.

Peters (written communication, December 1975) observed irritation of the eyes and of the respiratory tract in employees exposed to TBTO at concentrations reported to be at or near the recommended TWA concentration limit. Together with demonstrated systemic effects in humans with exposure to unknown concentrations of organotins [34-36], a need for a medical surveillance program is indicated. This program should include preemployment examinations and annual physical examinations to ensure adequate protection for the employee. An emergency medical examination should be required within 24 hours of overexposure to any organotin compound, with an appropriate followup examination. Personnel at risk must be warned of the adverse effects of overexposure and must be informed of the symptoms of these disorders. If eye contact occurs, the affected eye should be immediately flushed with water and examined by a physician.

Where triorganotins and tetraorganotins are present, a closed system of control must be used whenever feasible and should be used with

diorganotins and monoorganotins to control airborne concentrations of organotins within the TWA concentration limit. If a closed system is not feasible, other forms of engineering controls, such as local exhaust ventilation, must be used whenever feasible. Where engineering controls are not feasible, respirators and protective clothing must be used to prevent overexposure to organotins. During the time required to install adequate controls and equipment, to make process changes, to perform routine maintenance operations, or to make repairs, overexposure to organotins must be prevented by the use of respirators and protective clothing. Work practices must be designed to prevent skin and eye contact. Emergency showers and eyewash fountains must be available in case of accidental contact.

Because organotins are potent systemic poisons, it is recommended that medical records be maintained for the duration of employment plus a minimum of 5 years. Personnel records, which are of vital importance in assessing a worker's exposure, should be maintained for the same period.

Many employees handle only small amounts of the organotin compounds or work in situations where, regardless of the amount used, there is only negligible contact with these compounds. Under these conditions, it should not be necessary to conduct extensive monitoring and surveillance. However, because many of the organotins have proved to be highly irritating to the skin and eyes at low concentrations, care must be exercised to ensure adequate protection against these effects where the potential for exposure to organotin compounds exists. Concern for employee health requires that protective measures be instituted at concentrations at or below the workplace environmental limit to ensure that exposures stay below

that limit. For this reason, occupational environments with concentrations at or below the action level require environmental monitoring once every year. When concentrations are above the action level, more frequent environmental monitoring is required.

VI. WORK PRACTICES

Many organotins, especially the halogenated alkyltins and aryltins, produce toxic effects by contact with or absorption through the skin. Skin contact with organotin compounds has been reported to cause dermatitis including delayed local effects [18,35,36, JM Peters, written communication, December 1975], and systemic effects [34,35], as discussed in Chapter III. The halogenated alkyltins and aryltins have also been shown to be eye irritants [JM Peters, written communication, December 1975, 38]. Therefore, when employees are working with organotin compounds that are hazardous to the skin or eyes, they must use protective clothing and equipment to prevent skin contact and appropriate eye protective devices (goggles or face shields) to reduce the possibility of eye irritation or injury.

Good industrial hygiene practice requires that all reasonable efforts be used to limit the possibility of any organotin contacting the skin or eyes. Whenever skin contact with an organotin occurs, prompt washing of the affected area with soap and water is necessary. When an organotin compound contacts the eyes, immediate flushing with copious amounts of water is required and should be continued for at least 15 minutes, followed by prompt attention by a physician to determine the need for further treatment. Whenever there is a possibility for contamination of the clothing by an organotin compound, extra clothing must be available for the employee's use.

Certain organotin dusts, such as triphenyltin hydroxide, which is sold commercially as the miticide Du-Ter, have been found from industrial

experience [170 (pp 61-62)] to present special problems in formulation and application. These compounds are skin irritants, and contact should be avoided and prevented by full-body protective clothing, consisting of protection for head, neck, and face, coveralls or the equivalent, and impervious gloves with gauntlets. An alternative method of preventing employee exposure to irritating organotin dusts that has been found practical in the user industries [170 (pp 61-62)] is to purchase the dust premeasured and packaged in soluble plastic bags, and to adjust batch sizes so that the soluble plastic bag and its contents can be added to the chosen liquid vehicle without exposing employees to the hazardous dust.

In the manufacture of various organotin stabilizers, catalysts, fungicides, miticides, molluscicides, and other products, the appropriate aryltin and alkyltin halides are used as intermediates [6]. These compounds are, in general, quite irritating to the skin.

In emergency operations or in operations in which the concentration of organotin compounds cannot easily be reduced below the TWA concentration limit, respiratory protection based upon the expected or estimated airborne concentration must be provided for use by employees. Respiratory protective devices must be maintained in good working condition and must be cleaned and routinely inspected after each use.

Gloves, aprons, goggles, face shields, and other personal protective devices must be clean and maintained in good condition. All personal protective equipment should be cleaned frequently, with inspection and replacement as necessary on a regular schedule. Employers are responsible for assuring that such equipment is stored in suitable, designated containers or locations when the equipment is not in use. The proper use

of protective clothing requires that all openings be closed and that garments fit snugly about the neck, wrists, and ankles whenever the wearer is in an exposure area. Clean work clothing should be put on before each work shift. At the end of the work shift, the employee should remove the soiled clothing and shower before putting on street clothing. Soiled clothing should be deposited in a designated container and appropriately laundered before reuse.

A supply of potable water must be available near all places where there is potential contact with organotins. A water supply may be provided by a free-running hose at low pressure, or by emergency showers. Soap should be available at emergency showers. Where contact with the eyes is likely, eyewash fountains or bottles should be provided.

In all industries which must handle organotins or organotin-containing substances, written instructions informing employees of the particular hazards of the organotins, the method of handling, procedures for cleaning up spilled material, personal protective equipment to be worn, and procedures for emergencies must be on file and available to employees. The employer must establish a program of instruction which will ensure that all potentially exposed employees are familiar with the procedures. The Material Safety Data Sheet described in Appendix III may be used as a guide for employers in providing the necessary information. The duties of employees involved in maintenance and repair activities pose special problems of potential contact and exposure, especially in work on enclosed systems or in operations involving ventilation-system repair and maintenance. The nature of this type of work increases the potential for exposure. Maintenance employees may not be sufficiently familiar with the

hazardous materials with which they are involved. Therefore, special supervisory control and work-practice precautions are required to prevent exposure of these employees.

VII. RESEARCH NEEDS FOR ORGANOTIN COMPOUNDS

Proper assessment of the toxicity of the organotins and evaluation of their potential hazard to the working population requires extensive animal and human studies. The following are aspects of epidemiologic and toxicologic research which are especially important.

Epidemiologic Studies

No published epidemiologic study on the organotin industry has been found. Retrospective and prospective studies are needed to supply information on the effects of occupational exposure by inhalation and by skin or eye contact.

Acute Animal Studies

No basic acute inhalation studies have been found for many of the organotin compounds currently in use. Acute dermal and eye irritation studies would also aid in evaluating the toxic effects of organotin compounds. Such investigations require only a short time to produce data and permit a rapid preliminary assessment of the local toxicity of the organotin compounds.

Chronic Animal Experiments

Chronic experiments have been performed with several organotin compounds. Additional studies in this area are needed to assess the toxic

effects of other organotin compounds, especially on the liver, kidneys, lungs, and CNS of various species. Studies should use an exposure schedule simulating occupational exposure and should involve routes of exposure which are likely to occur in occupational contact with the compounds (inhalation and percutaneous absorption). These results may provide an insight into human susceptibility to the organotins.

Studies of Carcinogenic, Mutagenic, and Teratogenic Effects

Preliminary screening tests have been performed to assess the carcinogenicity of triphenyltin hydroxide and the mutagenicity of triphenyltin acetate [108,110]. Screening tests should be extended to all compounds which are currently in use or may be used in the future. These tests should be considered as only a preliminary survey and should be followed by extensive chronic and multigeneration experiments to evaluate the carcinogenic and syngenetic actions of these compounds. Multigeneration studies are particularly important because, when properly designed and performed, they furnish information on all three types of nucleidophilic activities.

Biochemical Experiments on Animals

Cremer [85] and Bridges et al [86] have examined the metabolism of a few organotin compounds in rats. Tests should be extended to other organotin compounds to see whether the metabolic pathway is the same. The rates of degradation of the organotins in both the occupational environment and the human body should be established. An understanding of the

mechanisms underlying the metabolic degradation of the organotins could lead to identification of the site of action and of the mechanism of toxic effects. This might allow development of a definitive medical treatment for organotin intoxication.

Sampling and Analysis

Studies are needed to improve the accuracy, sensitivity, and precision of the recommended methods. Investigations of other sampling and analytical techniques are encouraged, especially with regard to development of an analytical approach which can identify individual compounds at the proposed action level.

VIII. REFERENCES

1. Banks CK: Tin compounds, in Kirk-Othmer Encyclopedia of Chemical Technology, ed rev 2. New York, Interscience Publishers, 1968, vol 20, pp 304-27

2. Weast RC (ed): Handbook of Chemistry and Physics--A Ready-Reference Book of Chemical and Physical Data, ed 55. Cleveland, Chemical Rubber Co, 1974, pp C-707-14

3. Weiss RW: Tin, in Dub M (ed): Organometallic Compounds--Methods of Synthesis Physical Constants and Chemical Reactions--Compounds of Germanium, Tin and Lead Including Biological Activity and Commercial Application, ed 2. New York, Springer-Verlag, 1973, vol 2, pp 301-899

4. Ross A: Industrial applications of organotin compounds. Ann NY Acad Sci 125:107-23, 1965

5. Piver WT: Organotin compounds--Industrial applications and biological investigation. Environ Health Perspect 4:61-79, 1973

6. Neumann WP: The Organic Chemistry of Tin. London, Interscience Publishers, 1970, pp 1-282

7. Luijten JGA: Applications and biological effects of organotin compounds, in Sawyer AK (ed): Organotin Compounds. New York, Marcel Dekker Inc, 1971, pp 931-74

8. Van der Kerk GJM: Organotin chemistry--Past, present and future. Read before the American Chemical Society, New York. 1976

9. Frankland E: [On the isolation of organic radicals.] Annalen Chem 71:171-216, 1849 (Ger)

10. Frankland E: [Concerning a new class of organic substances which contain metals.] Annalen Chem 85:329-73, 1853 (Ger)

11. Buckton GB: XII. Further remarks on the organo-metallic radicals, and observations more particularly directed to the isolation of mercuric, plumbic, and stannic ethyl. Proc R Soc Lond 9:309-16, 1858

12. Jolyet F, Cahours A: [Investigations on the physiological effect of methyl and ethyl tins.] CR Acad Sci (Paris) 68:1276-80, 1869 (Fre)

13. White TP: [IV. The effects of tin on the animal organism.] Arch Exp Pathol Pharmakol 13:53-69, 1881 (Ger)

14. McCombie H, Saunders BC: Toxic organo-lead compounds. Nature 159:491-94, 1947

15. Gilman H: Organo-Tin Compounds, report No. 6004 (Contract-B-128, OEMsr 97). National Defense Research Committee, Office of Scientific Research and Development, 1942, pp 1-25

16. Glass HG, Coon JM, Lushbaugh CC, Last J: Toxicity and Vesicant Action of Various Organic Tin Compounds, University of Chicago Toxicity Laboratory report No. 15. Chicago, University of Chicago, Toxicity Laboratory, 1942, 11 pp

17. HP: "Stalinon"--A therapeutic disaster. Br Med J 1:515, 1958

18. Lyle WH: Lesions of the skin in process workers caused by contact with butyl tin compounds. Br J Ind Med 15:193-96, 1958

19. Rouzaud M, Lutier J: [Subacute cerebromeningeal edema due to an intoxication of current interest.] Presse Med 62:1075, 1954 (Fre)

20. Rondepierre J, Truhaut R, Guilly P, Hivert PE, Barande I: [An acute intoxication caused by an organotin derivative.] Rev Neurol 98:135-40, 1958 (Fre)

21. Alajouanine T, Derobert L, Thieffry S: [Clinical study of 210 cases of poisoning with organic tin salts.] Rev Neurol (Paris) 98:85-96, 1958 (Fre)

22. Cossa P, Duplay, Fischgold, Arfel-Capdevielle, Passouant, Lafon, Minvielle, Radermecker J: [Toxic encephalopathies after Stalinon.] Rev Neurol 98:97-108, 1958 (Fre)

23. Druault-Toufesco MN: [Two cases of severe poisoning with Stalinon.] Bull Soc Ophtalmol Fr, 54-58, 1955 (Fre)

24. Fontan, Verger, Pery, Loiseau, Mulon: [Four cases of "Stalinon" poisoning in children, including two fatal instances.] J Med Bordeaux Sud-Ouest 132:399-405, 1955 (Fre)

25. Gayral L, Lozorthes G, Planques J: [Hypertensive meningoencephalitis induced by Stalinon toxicity--Clinical recovery.] Rev Neurol 98:143-44, 1958 (Fre)

26. Grossiord A, Held JP, LeCoeur P, Verley R, Drosdowsky M: [Stalinon and damage to the medulla oblongata.] Rev Neurol 98:144-47, 1958 (Fre)

27. Gruner JE: [Damage to the central nervous system after ingestion of an ethyltin compound (Stalinon).] Rev Neurol 98:109-16, 1958 (Fre)

28. Pesme P: [Ocular complications in four children poisoned with "Stalinon."] Arch Fr Pediatr 12:327-29, 1955 (Fre)

29. Rouzaud M: [Stalinon poisoning, course of a case subjected to premature surgery.] Rev Neurol 98:140-42, 1958 (Fre)

30. Derobert L: Poisoning by an organic tin compound (di-iodoethyl tin or Stalinon). J Forensic Med 7:192, 1961

31. Barnes JM, Magos L: The toxicology of organometallic compounds. Organomet Chem Rev 3:137-50, 1968

32. Lecoq R: [Contribution to the study of the toxic effect of tetraethyl tin.] CR Soc Biol (Paris) 239:678-80, 1954 (Fre)

33. Guardascione V, Di Bosco MM: [Contribution to the study of occupational pathology caused by pesticides--Three cases of triphenyltin acetate fungicide poisoning.] Lav Um 19:307-13, 1967 (Ita)

34. Horacek V, Demcik K: [Collective poisoning during crop treatment with Brestan-60 (triphenyl tin acetate).] Prac Lek 22:61-66, 1970 (Cze)

35. Mijatovic M: [Chronic hepatitis due to Brestan exposure.] Jugosl Inostrana Dokumentacija Zastite na Radu 8:3-9, 1972 (Ser)

36. Markicevic A, Turko V: [Lesions caused by triphenyltin acetate (Brestan).] Arh Hig Rada Toksikol 18:355-58, 1967 (Ser)

37. Tables of normal values, in Davidsohn I, Henry JB (eds): Todd-Sanford Clinical Diagnosis by Laboratory Methods, ed 15. Philadelphia, WB Saunders Co, 1974, pp 1376-92

38. Landa K, Fejfusova J, Nedomlelova R: [Hazards of organic tin compounds used as fungicidal agents in some industrial applications.] Prac Lek 25:391-94, 1973 (Cze)

39. Information Concerning the Development of the Criteria Document and Recommended Health Standard for Organotin Compounds. Unpublished report submitted to NIOSH by M and T Chemicals Inc, Rahway, NJ, 1976

40. Akatsuka K, Miyazawa J, Igarashi I, Morishita M, Handa A, Kawame N, Iwamoto I, Morito F, Murayama K, Nakano S, Yanagibayashi H, Nagasaki T, Kotani Y, Matsutani W, Fukuda I, Iyo T: [Experimental studies on disturbance of sense of smell due to butyltin compounds.] J Tokyo Med Coll 17:1393-1402, 1959 (Jap)

41. Zeman W, Gadermann E, Hardebeck K: [Genesis of disturbances in circulatory regulation--Intoxication with peralkylated tin compounds.] Dtsch Arch Klin Med 198:713-21, 1951 (Ger)

42. Igarashi I: [Experimental studies on butyl-tin poisoning through respiratory tract and its prevention and treatment.] J Tokyo Med Coll 17:1603-32, 1959 (Jap)

43. Silver SD: The Relation of Time to the Dose Required to Produce a Given Physiological Effect, medical division report No. 22. Edgewood

Arsenal, Md, Army Service Forces, Chemical Warfare Service, Office of the Chief, 1945, 21 pp

44. Pelikan Z, Cerny E: The toxic effects of some di- and mono-n-octyl-tin compounds on white mice. Arch Toxikol 26:196-202, 1970

45. Pelikan Z, Cerny E: Toxic effects of some "mono-n-butyl-tin compounds" on white mice. Arch Toxikol 27:79-84, 1970

46. Pelikan Z, Cerny E, Polster M: Toxic effects of some di-n-octyltin compounds in white mice. Food Cosmet Toxicol 8:655-58, 1970

47. Pelikan Z, Cerny E: [The toxic effects of tri-n-butyltin compounds on white mice.] Arch Toxikol (Berl) 23:283-92, 1968 (Ger)

48. Calley DJ, Guess WL, Autian J: Hepatotoxicity of a series of organotin esters. J Pharm Sci 56:240-43, 1967

49. Torack RM, Terry RD, Zimmerman HM: The fine structure of cerebral fluid accumulation--II. Swelling produced by triethyl tin poisoning and its comparison with that in the human brain. Am J Pathol 36:273-87, 1960

50. Caujolle F, Lesbre M, Meynier D: [The effect of aliphatic chains branching on the toxicity of tetra alkyl tin compounds.] Ann Pharm Fr 14:88-97, 1956 (Fre)

51. Yoshikawa H, Ishii M: Experimental studies on the toxicity of alkyl-tin compounds--Report I. Changes of organ weight in mice treated with di-, tri-, and tetra-butyltin salts. Bull Natl Inst Ind Health (Japan) 5:25-31, 1961

52. Kolla VE, Zalesov VS: [The relationship between chemical structure and toxicity in a series of organotin compounds.] Uch Zap Permsk Gos Univ 111:196-202, 1964 (Rus)

53. Schadeberg KJ: Acute Dust Inhalation Toxicity Study with Biomet (tri-N-butyltin flouride) in Albino Rats, IBT No. N1368. Unpublished report submitted to NIOSH by M and T Chemicals Inc, Rahway, NJ, 1976

54. Elliott CB: Acute Dust Inhalation Toxicity Study with Triphenyltin Fluoride in Albino Rats, IBT No. N1632. Unpublished report submitted to NIOSH by M and T Chemicals Inc, Rahway, NJ, 1976

55. Myers TW: Acute Vapor Inhalation Toxicity Study in Rats, IBT No. 8562-08285. Unpublished report submitted to NIOSH by M and T Chemicals Inc, Rahway, NJ, 1976

56. Myers TW: Acute Vapor Inhalation Toxicity Study in Rats, IBT No. 663-07183. Unpublished report submitted to NIOSH by M and T Chemicals Inc, Rahway, NJ, 1976

57. Gohlke R, Lewa W, Strachovsky A, Kohler R: [Animal experimental studies on the inhalatory effect of tributyltin chloride in a subchronic test.] Z Gesamte Hyg 15:97-104, 1969 (Ger)

58. Iwamoto I: [Experimental studies on the influence of butyltin poisoning through the respiratory tract upon the reproductive function.] J Tokyo Med Coll 18:1351-76, 1960 (Jap)

59. Stoner HB, Barnes JM, Duff JI: Studies on the toxicity of alkyl tin compounds. Br J Pharmacol 10:16-25, 1954

60. Barnes JM, Stoner HB: Toxic properties of some dialkyl and trialkyl tin salts. Br J Ind Med 15:15-22, 1958

61. Barnes JM, Magee PN: The biliary and hepatic lesions produced experimentally by dibutyltin salts. J Pathol 75:267-79, 1958

62. Gaunt IF, Colley J, Grasso P, Creasey M, Gangolli SD: Acute and short-term toxicity studies on di-n-butyltin dichloride in rats. Food Cosmet Toxicol 6:599-608, 1968

63. Bartalini E: [Experimental study on the toxicity of an organostannous compound used as plasticiser (sic).] Med Lav 50:338-50, 1950 (Ita)

64. Calley D, Guess WL, Autian J: Ultrastructural hepatotoxicity induced by an organotin ester. J Pharm Sci 56:1267-72, 1967

65. Mazur H: [Effect of dioctyl tin and dibenzyl tin bis-isooctylthioglycolates on the rat organism when administered per os--I. Study of subacute and chronic toxicity--II. Effect on fertility and fetal development.] Rocz Panstw Zakl Hig 22:39-54, 509-18, 1971 (Pol)

66. Nikonorow M, Mazur H, Piekacz H: Effect of orally administered plasticizers and polyvinyl chloride stabilizers in the rat. Toxicol Appl Pharmacol 26:253-59, 1973

67. Magee PN, Stoner HB, Barnes JM: The experimental production of oedema in the central nervous system of the rat by triethyltin compounds. J Pathol 73:107-24, 1957

68. Dieckmann W, Butler WH: Histopathological studies and chronic toxic effects. Proc Eur Soc Study Drug Toxic 12:247-52, 1971

69. Graham DI, Gonatas NK: Triethyltin sulfate-induced splitting of peripheral myelin in rats. Lab Invest 29:628-32, 1973

70. Smith JF, McLaurin RL, Nichols JB, Asbury A: Studies in cerebral oedema and cerebral swelling--I. The changes in lead encephalopathy in children compared with those in alkyl tin poisoning in animals. Brain 83:411-24, 1960

71. Hirano A, Zimmerman HM, Levine S: Intramyelinic and extracellular spaces in triethyltin intoxication. J Neuropathol Exp Neurol 27:571-80, 1968

72. Lee JC, Bakay L: Ultrastructural changes in the edematous central nervous system--1. Triethyltin edema. Arch Neurol 13:48-57, 1965

73. Suzuki K: Some new observations in triethyl-tin intoxication of rats. Exp Neurol 31:207-13, 1971

74. Aleu FP, Katzman R, Terry RD: Fine structure and electrolyte analyses of cerebral edema induced by alkyl tin intoxication. J Neuropathol Exp Neurol 22:403-13, 1963

75. Katzmann R, Aleu F, Wilson C: Further observations on triethyltin edema. Arch Neurol 9:178-87, 1963

76. Wakashin K: [Experiments on the toxicity of organic tin compounds-- The morphology of experimental butyltin poisoning.] J Tokyo Med Coll 33:573-96, 1975 (Jap)

77. Verschuuren HG, Kroes R, Vink HH, Van Esch GJ: Short-term toxicity studies with triphenyltin compounds in rats and guinea-pigs. Food Cosmet Toxicol 4:35-45, 1966

78. Gaines TB, Kimbrough RD: Toxicity of fentin hydroxide to rats. Toxicol Appl Pharmacol 12:397-403, 1968

79. Klimmer OR: [Nutritional physiology, analytical and toxicological studies with the fungicide triphenyltin acetate.] Zentralbl Veterinaermed Reihe C 11:29-37, 1964 (Ger)

80. Pate BD, Hays RL: Histological studies of testes in rats treated with certain insect chemosterilants. J Econ Entomol 61:32-34, 1968

81. Newton DW, Hays RL: Histological studies of ovaries in rats treated with hydroxyurea, triphenyltin acetate, and triphenyltin chloride. J Econ Entomol 61:1668-69, 1968

82. Freitag KD, Bock R: Degradation of triphenyltin chloride on sugar beet plants and in rats. Pestic Sci 5:731-39, 1974

83. Elsea JR, Paynter OE: Toxicological studies on bis(tri-n-butyltin)oxide. Arch Ind Health 18:214-17, 1958

84. Banks CK, Putnam R, Pekola J, Corbin H, Hoffman J: Part V--Tissue Storage Study. Unpublished report submitted to NIOSH by M and T Chemicals Inc, Rahway, NJ, 1976

85. Cremer JE: The biochemistry of organotin compounds-- The conversion of tetraethyltin into triethyltin in mammals. Biochem J 68:685-92, 1958

86. Bridges JW, Davies DS, Williams RT: The fate of ethyltin and diethyltin derivatives in the rat. Biochem J 105:1261-67, 1967

87. Hoerger FD, Sheldon AW, Corbin HB, Getzendaner ME, Smith GN: Metabolism of Tricyclohexyltin Hydroxide in Animals--Observations on Absorption, Distribution, and Excretion in Rats, Dogs, Cattle and Sheep. Unpublished report submitted to NIOSH by M and T Chemicals Inc, Rahway, NJ, 1976

88. Getzendaner ME, Corbin HB: Residues on apples and pears from use of Plictran miticide. J Agric Food Chem 20:881-85, 1972

89. Pelikan Z, Cerny E: Toxic effects of "Bis (Tri-n-Butyltin) Oxide" (TBTO) on the skin of rats. Berufsdermatosen 17:305-16, 1969

90. Pelikan Z, Cerny E: The effect of low doses of bis(tri-n-butyltin) oxide on the skin of rats. Berufsdermatosen 16:340-47, 1968

91. Kawai T: [Experimental studies on toxicity of tributyl tin monohalides.] J Tokyo Med Coll 20:291-333, 1962 (Jap)

92. Pelikan Z: Effects of bis (tri-n-butyltin) oxide on the eyes of rabbits. Br J Ind Med 26:165-68, 1969

93. Aldridge WN, Cremer JE: The biochemistry of organo-tin compounds--Diethyltin dichloride and triethyltin sulphate. Biochem J 61:406-18, 1955

94. Aldridge WN: The biochemistry of organotin compounds--Trialkyltins and oxidative phosphorylation. Biochem J 69:367-76, 1958

95. Aldridge WN: The interaction of trialkyltin compounds with the oxidative phosphorylation system in mitochondria, in Effects of Metals on Cells, Subcellular Elements, and Macromolecules. Proceedings of the Second International Conference on Environmental Toxicity, Rochester, New York, 1969, pp 255-74

96. Rose MS: Evidence for histidine in the triethyltin-binding site of rat haemoglobin. Biochem J 111:129-37, 1969

97. Aldridge WN, Street BW: Oxidative phosphorylation--The specific binding of trimethyltin and triethyltin to rat liver mitochondria. Biochem J 118:171-79, 1970

98. Aldridge WN, Street BW: Oxidative phosphorylation--The relation between the specific binding of trimethyltin and triethyltin to mitochondria and their effects on various mitochondrial functions. Biochem J 124:221-34, 1971

99. Aldridge WN, Street BW: Oxidative phosphorylation--Biochemical effects and properties of trialkyltins. Biochem J 91:287-97, 1964

100. Aldridge WN, Threlfall CJ: Trialkyltins and oxidative phosphorylation--The [32P]phosphate-adenosine triphosphate-exchange reaction. Biochem J 79:214-19, 1961

101. Aldridge WN, Rose MS: The mechanism of oxidative phosphorylation--A hypothesis derived from studies of trimethyltin and triethyltin compounds. FEBS Let 4:61-68, 1969

102. Sone N, Hagihara B: Inhibitory action of trialkyltin compounds on oxidative phosphorylation in mitochondria. J Biochem 56:151-56, 1964

103. Vardanis A, Quastel JH: The effects of lead and tin organometallic compounds on the metabolism of rat brain cortex slices. Can J Biochem 39:1811-27, 1961

104. Wulf RG, Byington KH: On the structure-activity relationships and mechanism of organotin induced, nonenergy dependent swelling of liver mitochondria. Arch Biochem Biophys 167:176-85, 1975

105. Tyler DD: Evidence of a phosphate-transporter system in the inner membrane of isolated mitochondria. Biochem J 111:665-78, 1969

106. Byington KH: Effects of triphenyltin compounds on the adenosine triphophatase (sic) activity of beef heart submitochondrial particles. Biochem Biophys Res Commun 42:16-22, 1971

107. Cremer JE: The metabolism in vitro of tissue slices from rats given triethyltin compounds. Biochem J 67:87-96, 1957

108. Innes JRM, Ulland BM, Valerio MG, Petrucelli L, Fishbein L, Hart ER, Pallotta AJ, Bates RR, Falk HL, Gart JJ, Klein M, Mitchell I, Peters J: Bioassay of pesticides and industrial chemicals for tumorigenicity in mice--A preliminary note. J Natl Cancer Inst 42:1101-14, 1969

109. Ladd R: Six-Month Study of the Carcinogenic Potential of Tributyl Tin Fluoride (TBTF) in Male Swiss White Mice, IBT No. J8996. Unpublished report submitted to NIOSH by M and T Chemicals Inc, Rahway, NJ, 1976

110. Epstein SS, Arnold E, Andrea J, Bass W, Bishop Y: Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol Appl Pharmacol 23:288-325, 1972

111. Scheinberg LC, Taylor JM, Herzog I, Mandell S: Optic and peripheral nerve response to triethyltin intoxication in the rabbit and ultrastructural studies. J Neuropathol Exp Neurol 25:202-13, 1966

112. American Conference of Governmental Industrial Hygienists, Committee on Industrial Ventilation: Industrial Ventilation--A Manual of Recommended Practice, ed 13. Lansing, Mich, ACGIH, 1974

113. American National Standards Institute: Fundamentals Governing the Design and Operation of Local Exhaust Systems, Z9.2-1971. New York, American National Standards Institute Inc, 1971

114. Selivokhin PI: Determination of tin tetrabutyl and tin tetraethyl in factory air and in sewage (condensate). Hyg Sanit 31:270-72, 1966

115. Jeltes R: Determination of bis(tributyltin)oxide in air by atomic absorption spectroscopy or pyrolysis gas chromatography. Ann Occup Hyg 12:203-07, 1969

116. Crable JV, Taylor DG: General Procedure for Metals, in NIOSH Manual of Analytical Methods, HEW publication No. (NIOSH) 75-121. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Laboratories and Criteria Development, 1974, pp 173(1-8)

117. Lippmann M: Filter media for air sampling, in Air Sampling Instruments for Evaluation of Atmospheric Contaminants, ed 4. Cincinnati, American Conference of Governmental Industrial Hygienists, 1972, pp N(1-7)

118. Roach SA: Sampling air for particulates, in The Industrial Environment--Its Evaluation and Control. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1973, pp 139-53

119. Vance GH: Gas and vapor sample collectors, in Air Sampling Instruments for Evaluation of Atmospheric Contaminants, ed 4. Cincinnati, American Conference of Governmental Industrial Hygienists, 1972, pp R(1-6)

120. Pagnotto LD, Keenan RG: Sampling and analysis of gases and vapors, in The Industrial Environmental--Its Evaluation and Control. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, 1973, pp 167-79

121. Crable JV, Taylor DG: Organic Solvents in Air, in NIOSH Manual of Analytical Methods, HEW publication No. (NIOSH) 75-121. Cincinnati, US Dept of Health, Education, and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Division of Laboratories and Criteria Development, 1974, pp 127(1-11)

122. Neubert G: The analysis of organic tin stabilizers. Z Anal Chem 203:265-72, 1964

123. Akagi H, Takeshita R, Sakagami Y: Separation and detection of inorganotin and organotin compounds by thin layer chromatography. Koshu Eiseiin Kenkyu Hokoku 19:185-92, 1970

124. Tinner A: Detection and determination of tributyltin compounds in treated wood. British Wood Preservative Association, Annual Convention, 1971, pp 55-59

125. Figge K, Bieber WD: [Column-chromatographic separation of methyl and n-octyl tin chlorides.] J Chromatogr 109:418-21, 1975 (Ger)

126. Franc J, Wurst M, Moudry V: [Chromatography of organic compounds-- IX. Separation of organic tin compounds by paper and gas chromatography.] Collect Czech Chem Commun 26:1313-19, 1961 (Cze)

127. Gasparic J, Cee A: [Identification of organic compounds-- XLV. Separation and identification of organic tin compounds by paper chromatography.] J Chromatogr 8:393-98, 1962 (Cze)

128. Reutov OA, Ptitsyna OA, Turchinskii MF: [A method for the paper chromatography of diaryl organo stannous compounds and its application to the study of products resulting from the reaction of unsymmetrical diaryl iodine salts with stannous chloride.] Dokl Akad Nauk SSSR 139:146-49, 1961 (Rus)

129. Williams DJ, Price JW: The paper chromatography of some organo-tin compounds--Part II. Reversed-phase systems. Analyst 89:220-22, 1964

130. Williams DJ, Price JW: Paper chromatography of some organo-tin compounds. Analyst 85:579-82, 1960

131. Macdonald AMG, Sirichanya P: The determination of metals in organic compounds by oxygen-flask combustion or wet combustion. Microchem J 14:199-206, 1969

132. Metallic Impurities in Organic Matter Sub-Committee: The use of 50 per cent hydrogen peroxide for the destruction of organic matter. Analyst 92:403-07, 1967

133. Chapman AH, Duckworth MW, Price JW: The determination of dialkyltin compounds in polyvinylchloride. Br Plast pp 78,87, 1959

134. Aldridge WN, Cremer JE: Organo-tin-dithizone complexes--The colorimetric determination of diethyltin and triethyltin compounds. Analyst 82:37-43, 1957

135. Hardon HJ, Brunink H, van der Pol EW: Colorimetric determination of triphenyltin residues. Analyst 85:847-49, 1960

136. Chromy L, Uhacz K: Antifouling paints based on organotin compounds-- Part I. Colorimetric determination of microgram amounts of organotin

compounds in aqueous solutions. J Oil Colour Chem Assoc 51:494-98, 1968

137. Corbin HB: Separation and determination of trace amounts of tin present as organotin residues on fruits. J Assoc Off Anal Chem 53:140-46, 1970

138. Trombetti G, Maini P: Determination of tricyclohexyltin hydroxide residues in apples and pears. Pestic Sci 1:144-49, 1970

139. Farnsworth M, Pekola J: Determination of small amounts of tin with dithiol. Anal Chem 26:735-37, 1954

140. Farnsworth M, Pekola J: Determination of tin in inorganic and organic compounds and mixtures. Anal Chem 31:410-14, 1959

141. Adcock LH, Hope WG: A method for the determination of tin in the range 0.2 to 1.6 ug, and its application to the determination of organotin stabiliser in certain foodstuffs. Analyst 95:868-74, 1970

142. Thomas B, Tann HL: Pesticide residues in foodstuffs in Great Britain--XV. Triphenyltin residues in potatoes. Pestic Sci 2:45-47, 1971

143. Corbin HB: Rapid and selective pyrocatechol violet method for tin. Anal Chem 45:534-37, 1973

144. Metallic Impurities in Organic Matter Sub-Committee: The determination of small amounts of tin in organic matter--Part I. Amounts of tin up to 30 μg. Analyst 92:320-23, 1967

145. Koch J, Figge K: [Analysis of methyltin stabilizers.] J Chromatogr 109:89-100, 1975 (Ger)

146. Engberg A: A comparison of a spectrophotometric (quercetin) method and an atomic-absorption method for the determination of tin in food. Analyst 98:137-45, 1973

147. Marr IL: Microanalytical determination of tin in organotin compounds. Talanta 22:387-94, 1975

148. Eberle AR, Lerner MW: Determination of tin and molybdenum in nuclear reactor and other materials--Extraction and spectrophotometric determination with 8-quinolinol. Anal Chem 34:627-32, 1962

149. Sawyer R: Determination of dialkyltin stabilizers in aqueous extracts from PVC and other plastics. Analyst 92:569-74, 1967

150. Honigschmid-Grossich R: [Dibutyl tin chloride.] Z Anal Chem 191:463, 1962 (Ger)

151. Strafford N: A colorimetric method for the determination of minute amounts of tin in organic matter. Mikrochim Acta 2:306-13, 1937

152. Adamson JH: The colorimetric determination of dialkyltin compounds dissolved in fats and olive oil. Analyst 87:597-98, 1962

153. Newman EJ, Jones PD: Separation and determination of small amounts of tin--A report of work undertaken on behalf of the Metallic Impurities in Organic Matter Sub-committee of the Analytical Methods Committee. Analyst 91:406-10, 1966

154. Tonge BL: The gas chromatographic analysis of butyl-, octyl-, and phenyl-tin halides. J Chromatogr 19:132-84, 1965

155. Helberg D: [Contribution to the analysis of organotin stabilizers--II. Thin-layer chromatographic detection of bis-(2-ethylhexyl)tin compounds and quantitative determination of dialkyltin compounds.] Dtsch Lebensm-Rundsch 63:69-71, 1967 (Ger)

156. Vernon F: The fluorimetric determination of triphenyltin compounds. Anal Chim Acta 71:192-95, 1974

157. Bock R, Gorbach S, Oeser H: [Analysis of triphenyl tin compounds.] Angew Chem 70:272, 1958 (Ger)

158. Nangniot P, Martens PH: [Application of chrono-amperometry by anodic redissolution for the determination of traces of triphenyltin acetate.] Anal Chim Acta 24:276-79, 1961 (Ger)

159. Kreshkov AP, Kuchkarev EA: [Spectrographic determination of germanium, tin and lead in metallo-organic compounds.] Zavod Lab 32:558-59, 1966 (Rus)

160. Chromy L, Mlodzianowska W, Uhacz K, Warchol R: Antifouling paints based on organotin compounds--Part II. Spectrographic determination of microgram amounts of bis-(tri-n-butyltin) oxide in aqueous solutions. J Oil Colour Chem Assoc 53:121-26, 1970

161. Gilman H, King WB: A method for the quantitative analysis of tin in organic compounds. J Am Chem Soc 51:1213-26, 1929

162. Capacho-Delgado L, Manning DC: Determination of tin by atomic absorption spectroscopy. Spectrochim Acta 22:1505-13, 1966

163. George GM, Albrecht MA, Frahm LJ, McDonnell JP: Atomic absorption spectrophotometric determination of dibutyltin dilaurate in finished feeds. J Assoc Off Anal Chem 56:1480-82, 1973

164. 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. Geneva, World Health Organization, 1974, pp 440-52

165. 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. Rome, The Food and Agriculture Organization of the United Nations and the World Health Organization, 1971, pp 521-42

166. Threshold Limit Values for 1965, adopted at the 27th Annual Meeting of the American Conference of Governmental Industrial Hygienists, Houston. ACGIH, 1965, p 15

167. American Conference of Governmental Industrial Hygienists, Committee on Threshold Limit Values: Documentation of the Threshold Limit Values for Substances in Workroom Air, ed 3. Cincinnati, ACGIH, 1971, pp 150-51, 224-25, 256, 258, 349-50

168. American Conference of Governmental Industrial Hygienists: Threshold Limit Values for Chemical Substances in Workroom Air. Cincinnati, ACGIH, 1975, p32

169. Permissible Levels of Toxic Substances in the Working Environment, Occupational Safety and Health Series. Geneva, International Labour Office, 1970, vol 20, pp 239, 353

170. Summary plant observation report and evaluation. Menlo Park, California, Stanford Research Institute, April 1976, 68 pp (submitted to NIOSH under Contract No. CDC-99-74-31)

IX. APPENDIX I

METHOD FOR SAMPLING ORGANOTINS IN AIR

This sampling method is adapted from NIOSH Method No. P & CAM 173 [116] and No. 127 [121]. However, no report was found in the literature in which these sampling techniques were combined. Although this method of sampling is recommended, other methods shown to be at least equivalent may be used.

General Requirements

Collect personal samples in the breathing zone of individual employees, without interfering with the employees' freedom of movement. Enough samples should be collected to permit calculation of a TWA concentration to evaluate the exposure of each employee at every operation or location in which there is occupational exposure to organotins. Record the sampling locations and conditions, equipment used, time and rate of sampling, and any other pertinent information.

Equipment for Air Sampling

(a) Filter: Membrane filter with a pore size of 0.8 μm mounted with backup pad in a 2- or 3-piece closed-face cassette.

(b) Large charcoal tubes: Glass tubes with both ends flame-sealed, 11 cm long with an 8-mm outer diameter and a 6-mm internal diameter, containing two sections of 20/40-mesh activated coconut-shell

charcoal separated by a 2-mm portion of polyurethane foam. The adsorbing section contains 400 mg of charcoal, the backup section 200 mg. A 3-mm portion of polyurethane foam is placed between the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in front of the adsorbing section. Tubes meeting these specifications are designated commercially as "large."

(c) Battery-operated personal sampling pump: The pump should have a means for attachment, such as a clip, to the employee. All pumps and flowmeters must be calibrated using a calibrated test meter or other reference, as described in the Section on Calibration of Equipment.

Calibration of Equipment

Since the accuracy of an analysis can be no greater than the accuracy with which the volume of air is measured, the accurate calibration of a sampling pump is essential. The frequency of calibration required depends upon the use, care, and handling to which the pump is subjected. Pumps should be recalibrated if they have been abused or if they have just been repaired or received from the manufacturer. Maintenance and calibration should be performed on a routine schedule, and records of these should be maintained.

Ordinarily, pumps should be calibrated in the laboratory both before they are used in the field and after they have been used to collect a large number of field samples. The accuracy of calibration depends on the type of instrument used as a reference. The choice of calibration instrument will depend largely upon where the calibration is to be performed. For laboratory testing, a spirometer or soapbubble meter is recommended,

although other calibration instruments, such as a wet test meter or dry gas meter, can be used. The actual setups will be similar for all instruments.

The calibration setup for a personal sampling pump with a membrane filter followed by a charcoal tube is shown in Figure XII-1. Since the flowrate given by a pump depends on the pressure drop across the sampling device, in this case a membrane filter followed by a charcoal tube, the pump must be calibrated while operating with a representative filter and charcoal tube in line. Instructions for calibration with the soapbubble meter follow. If another calibration device is selected equivalent procedures should be used.

(a) Check the voltage of the pump battery with a voltmeter to ensure adequate voltage for calibration. Charge the battery if necessary.

(b) Break off the tips of a charcoal tube to produce openings at least 3 mm in diameter.

(c) Assemble the sampling train as shown in Figure XII-1.

(d) Turn on the pump and moisten the inside of the soapbubble meter by immersing the buret in the soap solution and drawing bubbles up the inside until they are able to travel the entire length of the buret without bursting.

(e) Adjust the pump flow controller to provide the desired flowrate.

(f) Start a soapbubble up the buret and measure with a stopwatch the time the bubble takes to move from one calibration mark to another.

(g) Repeat the procedure in (f) at least 3 times, average the results, and calculate the flowrate by dividing the volume between the preselected marks by the time required for the soapbubble to traverse the

distance. If, for the pump being calibrated, the volume of air sampled is the product obtained by multiplying the number of strokes times a stroke factor (given in units of volume/stroke), the stroke factor is the quotient obtained by dividing the volume between the two preselected marks by the number of strokes.

(h) Data for the calibration include volume measured, elapsed time or number of strokes, pressure drop, air temperature, atmospheric pressure, serial number of the pump, date, and the name of the person performing the calibration.

Collection of Samples

(a) Break both ends of the large charcoal tube to provide openings of at least 3 mm, which is half the internal diameter of the tube. A smaller opening may cause a limiting orifice effect which would reduce the flow through the tube.

(b) Assemble a sampling train consisting of a 0.8-μm membrane filter followed by a large charcoal tube with a portable, battery-operated personal sampling pump. The smaller section of charcoal in the tube is used as a backup section and should therefore be placed nearest the sampling pump. Tubing may be used to connect the back of the tube to the pump. The front of the tube should be connected directly to the filter holder by a minimum length of tubing. The tube is supported in a vertical position for sampling to prevent channeling. When the environment to be sampled contains organotins only as vapor, the membrane filter may be eliminated. When only low-volatility particulate organotins are present,

the charcoal tube may be eliminated from the sampling train.

(c) The recommended sampling flowrate is 1 liter/minute. The calibrated flowrate should be established as accurately as possible, using the manufacturer's directions.

(d) Measure and record the temperature and pressure of the atmosphere being sampled.

(e) Record the initial and final counter readings. The sample volume is obtained by multiplying the number of counter strokes times the stroke factor.

(f) Immediately after sampling, seal the filter container and cap the charcoal tubes with the plastic caps provided with commercially available tubes. Do not use rubber caps.

(g) Treat at least one filter and one charcoal tube in the same manner as the sample tubes (break, seal, ship), but do not draw air through them. This filter and tube will serve as a blank.

X. APPENDIX II

ANALYTICAL METHOD FOR ORGANOTINS

This analytical method is adapted from a pyrocatechol violet method for the rapid and selective determination of tin [143].

Principle of the Method

(a) A known volume of air is drawn through a membrane filter followed by a charcoal tube to collect organotin particulate and vapor.

(b) The organic matter (filter and charcoal) is destroyed by treatment with sulfuric and nitric acids, leaving tin(IV) in solution in sulfuric acid.

(c) The tin is separated from the sulfuric acid, insoluble matter, and any elements that would interfere in the colorimetric measurement (molybdenum, titanium, high amounts of heavy metals or phosphate). This separation is carried out by extracting the tin as tin(IV) iodide with n-hexane from a strong sulfuric acid solution of potassium iodide. The tin is extracted from the hexane with a dilute solution of sulfuric and citric acids.

(d) The tin is measured directly in this solution at 660 nm after adding a mixed reagent of pyrocatechol violet and cetyl trimethyl ammonium bromide, a quaternary salt catalyst.

Range and Sensitivity

(a) The detection limit is in the range of 0.04-0.08 μg of tin at a concentration of 0.004-0.01 ppm in organic materials, which must be digested with strong mineral acids.

(b) The optimal amount of tin is up to 10 μg in the sample.

(c) Relative standard deviations of 0.55-1.4% have been obtained in the range of 1-10 μg of tin in various types of organic samples.

Interferences

(a) Metals which have shown positive interference are: Ge(IV), Mo(VI), Ti(IV), Ga(III), Sb(III), Sb(V), Bi(III), Cr(III), Cr(VI), Cu(II), Ni(II), Hg(II), Zr(IV), Fe(II), and Fe(III). These interferences are removed during the separation procedure.

(b) Elements and radicals which have shown no interference (error less than ± 0.001 μg of tin) at the maximum indicated level are: NO3 (200 mg); K, Li, Mg, Na, NH4 (100 mg); Al (50 mg); B4O7, Br, ClO3, IO3, IO4, PO2 (20 mg); CNS, I (10 mg); NO2, S2O8 (4 mg); Ag, As, Cd, Ce, Co, In, La, Mn, Th, U, V, Zn, Zr (2 mg); Se, Tl (1 mg); Sr, Te (0.1 mg).

Advantages of the Method

(a) It provides one basic method suitable for determining many different organotins.

(b) The sampling device is small and portable, and involves no liquids.

(c) The analysis is readily accomplished.

(d) No elaborate equipment is required.

Disadvantages of the Method

(a) Sampling rate is limited by the decreased adsorption efficiency of charcoal at higher flowrates.

(b) Pressure drop becomes excessive at higher flowrates.

(c) Organic compounds in high concentrations in the environment sampled may displace organotins from the charcoal.

Apparatus

(a) Spectrophotometer.

(b) Digestion vessels: narrow-mouth flasks of various capacities.

(c) Separatory funnels: pear-shaped type with Teflon stopcock and capacities of 125 and 250 ml.

(d) Cuvettes: 5-cm or 10-cm cells.

Reagents

(a) Acids: reagent-grade concentrated hydrochloric, nitric, and sulfuric acids; citric acid; and L-ascorbic acid.

(b) Pyrocatechol violet: both catechol violet, B.D.H. Chems., Ltd., Prod. No. 20022, and pyrocatechol sulfone phthalein, Eastman 7589, have been found to be satisfactory.

(c) Cetyl tri-methyl ammonium bromide (CTAB).

(d) Potassium iodide.

(e) Tin.

Reagent Solutions

(a) Standard tin solutions:

(1) 500 μg/ml: Dissolve 0.2500 g of pure tin in 150 ml of concentrated hydrochloric acid. Dilute to 500 ml with water.

(2) 10 μg/ml in 20% w/v sulfuric acid and 10% citric acid: Place exactly 10 ml of standard tin solution, 500 μg/ml, in a flask or beaker of resistant glass, and add 50 ml of concentrated sulfuric acid and 5 ml of concentrated nitric acid. Heat to evolution of strong fumes of sulfuric acid and cool. Add concentrated sulfuric acid to bring to a total of 100 g. Place in a cooling bath and cautiously dilute with 150-200 ml of water. Cool to room temperature and add a water solution of 50 g of citric acid. Transfer to a 500-ml volumetric flask, dilute to volume, and mix well.

(3) 0.5 μg/ml: Prepare fresh in 5% w/v sulfuric acid and 2.5% w/v citric acid.

(4) 0.025 μg/ml: Prepare fresh in 5% w/v sulfuric acid and 2.5% w/v citric acid.

(b) Sulfuric-citric acid solution: 5 g of sulfuric acid and 2.5 g of citric acid/100 ml in water. This mixed solution is used in preparing the calibration curve.

(c) CTAB solution: 5.5 mg/ml CTAB in water.

(d) Sensitized pyrocatechol violet solution: For each 100 ml of solution, dissolve 12 mg of pyrocatechol violet in water, add 2 ml of CTAB solution, and dilute to volume. Prepare fresh daily as needed.

(e) Acid-iodide wash solution: Mix one volume of sulfuric acid with two volumes of water and cool. Add one volume of potassium iodide,

20% w/v. Prepare fresh as needed.

(f) Ascorbic acid: 5% w/v in water. Prepare fresh daily as needed.

Preparation of Calibration Curve

(a) Place a measured amount, 1-20 ml, of standard tin solution, 0.5 μg/ml, in a 50-ml volumetric flask.

(b) Dilute to 20 ml with a measured amount of sulfuric-citric acid solution, 5% and 2.5% w/v, respectively.

(c) Add 2 ml of ascorbic acid, 5% w/v, and dilute to 40 ml.

(d) Add 5 ml of sensitized pyrocatechol violet solution and dilute to 50 ml.

(e) After 30 minutes, measure the absorbance at 660 nm in a 10-cm cell.

(f) Repeat with the next dilution. After each reading, rinse the cell twice with water, once with 2M hydrochloric acid, twice with water, and three times with the next solution to be read.

(g) Plot absorbance readings against amount of tin.

Analytical Procedure

A blank is carried through the entire procedure along with the samples.

(a) Preparation of Sample

Details of sample preparation vary with the nature of the organotins present. Appropriate pretreatment or separation procedures may be required

if more than one organotin is present and if quantitative determination of each organotin is required. In general, the membrane filter and first section of charcoal from the charcoal tube are analyzed together. The backup section of the charcoal tube is analyzed separately to verify that breakthrough of the first section has not occurred. The filter and charcoal are digested by treatment with nitric and sulfuric acids. After elimination of organic matter and volatile acids (including traces of nitric acid), the tin is present as tin(IV) in a known amount of concentrated sulfuric acid.

(b) Separation of Tin

(1) Dilute the known volume of sulfuric acid digest (one volume) with two volumes of water, mix, and cool to room temperature.

(2) Add one volume of potassium iodide solution, 20% w/v, and mix.

(3) Transfer to a 250-ml separatory funnel. Rinse the digestion vessel with 2-3 volumes of n-hexane and add rinsings to the funnel.

(4) Extract for 1 minute and allow to settle for 5-10 minutes.

(5) Draw off the aqueous solution and transfer the hexane containing the tin(IV) to a second (125-ml) separatory funnel by pouring from the neck of the first funnel. Rinse the extraction funnel with a few milliliters of hexane and add to the main portion.

(6) Add to the 125-ml funnel, including the funnel containing the reagent blank, exactly 20 ml of standard tin solution, 0.025 μg/ml, freshly prepared in 5% w/v sulfuric acid and 2.5% w/v citric acid.

(7) Shake the hexane and acid wash for 30 seconds to 1 minute and allow to separate.

(8) Draw the aqueous phase into a 50-ml volumetric flask.

(9) Wash the hexane with two 10-ml portions of water, allowing the phases to separate for 5 minutes each time, and combine in the volumetric flask. Make to volume. Let stand overnight.

(c) Measurement of Tin

(1) Add 2 ml of a 5% w/v ascorbic acid solution to each aqueous extract to be read. Prepare a mixed reagent as follows: For each 100 ml (sufficient for 20 readings), place 12 mg of pyrocatechol violet in a container and dissolve in water. Add 2 ml of CTAB solution (0.55% w/v), swirl gently, and dilute to 100 ml. Mix well.

(2) Add exactly 5 ml of the mixed reagent to the sample flask, dilute to volume, and mix.

(3) Do the same to each of the other samples at about 4-minute intervals.

(4) Measure each solution after 30 minutes by filling a 5-cm or 10-cm cell and reading the absorbance at 660 nm.

(5) Deduct the absorbance of the blank from that of the samples.

(6) Convert the corrected absorbances to tin by means of the calibration curve.

Calculations

The concentration of tin in air can be expressed as milligrams of tin/cubic meter of air, which is numerically equal to micrograms of tin/liter of air:

$$\text{mg tin/cu m} = \mu\text{g tin/V}$$

where:

μg tin = micrograms of tin from the calibration curve
V = volume of air sampled (in liters) at 25 C and 760 mmHg

XII. APPENDIX III

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or

competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity,

or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 degrees Fahrenheit (21.1 degrees Celsius); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

> Skin Contact--single short contact, possible adverse effects; prolonged or repeated contact, mild to severe dermatitis.
>
> Eye Contact--highly irritating with possibility of severe corneal damage.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill," or "incineration." Warnings such as "comply with local, state, and federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or US Bureau of Mines approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.

MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO. EMERGENCY TELEPHONE NO.
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA		
BOILING POINT, 760 MM HG		MELTING POINT
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)
APPEARANCE AND ODOR		

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL.	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY _____

ADDRESS _____

DATE _____

TABLE XII – 1

PROPERTIES AND USES OF ORGANOTIN COMPOUNDS

COMPOUND	FORMULA	Molecular Weight	Tin Content (%)	Appearance	Melting Point (C)	Boiling Point (C)	Solubility		Uses			
							H_2O	Organic Solvents	Catalyst	Stabilizer	Biocide	* Other
MONOORGANOTINS												
Bis(butyltin) trisulfide	$[(C_4H_9)_2Sn_2S_3]_2$	895.28	53.0							X		
Monobutyltin trichloride	$(C_4H_9)SnCl_3$	282.08	42.1						X			2,10,11
Monoethyltin trichloride	$(C_2H_5)SnCl_3$	254.11	46.7						X			
Monooctyltin trichloride	$(C_8H_{17})SnCl_3$	338.12	35.1	Colorless liquid	–63	98		Sol				11
Monophenyltin tribromide	$(C_6H_5)SnBr_3$	435.45	27.3						X			
Monophenyltin trichloride	$(C_6H_5)SnCl_3$	302.10	39.3						X			
DIORGANOTINS												
Bis(dibutylacetatotin) oxide	$[(C_4H_9)_2SnOOC_2H_3]_2O$	599.58	39.6						X	X		
Bis(dibutylchlorotin) oxide	$[(C_4H_9)_2SnCl)_2O]_2$	1,104.88	43.0		110-112				X			
Bis(dimethylacetatotin) oxide	$[(CH_3)_2SnOOC_2H_3]_2O$	431.46	55.0		236					X		
Bis(dipropylchlorotin) oxide	$[(C_3H_7)_2SnCl)_2O]_2$	992.80	47.8		121-122				X			
Bis(dipropylpropionatotin) oxide	$[(C_3H_7)_2SnOOC_2H_3]_2O$	543.54	43.7						X			
Dibutyltin bis(i-octylthioglycolate)	$(C_4H_9)_2Sn(SCH_2CO_2C_8H_{17}\text{-}i)_2$	639.11	18.6	Slightly yellow liquid					X	X	X	1,3
Dibutyltin diacetate	$(C_4H_9)_2Sn(OOC_2H_3)_2$	350.81	33.8	Colorless liquid	10	142-145	Insol	Sol	X	X	X	3
Dibutyltin diacetylacetone	$(C_4H_9)_2Sn[(CH_3CO)_2CH]_2$	430.87	27.5							X		
Dibutyltin dibenzylsulfide	$(C_4H_9)_2Sn(SCH_2C_6H_5)_2$	479.03	24.8							X		
Dibutyltin dibromide	$(C_4H_9)_2SnBr_2$	392.74	30.2	Small needles	20	118-170	Insol		X			
Dibutyltin dibutoxide	$(C_4H_9)_2Sn(OC_4H_9)_2$	378.85	31.3						X			
Dibutyltin dicaprylate	$(C_4H_9)_2Sn(O_2CC_7H_{15}\text{-}n)_2$	518.93	22.9		-22				X	X	X	
Dibutyltin dichloride	$(C_4H_9)_2SnCl_2$	303.83	39.1	White needles	113.6	142	Sol(hot)	Ether, benzene, alcohol	X	X	X	10
Dibutyltin diethoxide	$(C_4H_9)_2Sn(OC_2H_5)_2$	322.81	36.8						X	X		
Dibutyltin di(2-ethylhexoate)	$(C_4H_9)_2Sn(O_2CCHC_2H_5C_4H_9)_2$	518.93	22.9						X	X	X	

TABLE XII – 1 (CONTINUED)
PROPERTIES AND USES OF ORGANOTIN COMPOUNDS

COMPOUND	FORMULA	Molecular Weight	Tin Content (%)	Appearance	Melting Point (C)	Boiling Point (C)	Solubility		Uses			
							H_2O	Organic Solvents	Catalyst	Stabilizer	Biocide	Other *
Dibutyltin difluoride	$(C_4H_9)_2SnF_2$	270.77	43.8							X	X	
Dibutyltin diiodide	$(C_4H_9)_2SnI_2$	486.57	24.4									2
Dibutyltin dilaurate	$(C_4H_9)_2Sn(OOCC_{11}H_{23})_2$	631.55	18.8	Liquid or low-mp solid depending on type & purity	27		Insol	Insol	X	X	X	13
Dibutyltin dimethoxide	$(C_4H_9)_2Sn(OCH_3)_2$	294.79	40.3						X			2,12
Dibutyltin di(methylmaleate)	$(C_4H_9)_2Sn(O_2CCH{:}CHCO_2CH_3)_2$	490.87	24.2							X		
Dibutyltin distearate	$(C_4H_9)_2Sn(O_2CC_{17}H_{35})_2$	799.13	14.9						X	X	X	
Dibutyltin maleate	$(C_4H_9)SnO_2CCH{:}CHCO_2$	346.81	34.2	White powder			Insol	Insol in almost all	X	X		13
Dibutyltin methoxide acetate	$(C_4H_9)_2Sn(OOC_2H_3)OCH_3$	322.80	36.8						X			
Dibutyltin oxide	$(C_4H_9)_2SnO$	248.92	47.7	White powder			Insol	Insol	X	X		2,7, 10,11
Diethyltin dibenzoate	$(C_2H_5)_2Sn(OOCC_6H_5)_2$	418.89	28.3							X		
Diethyltin dicaprylate	$(C_2H_5)_2Sn(O_2CC_7H_{15\text{-}n})_2$	462.89	25.6						X			
Diethyltin dichloride	$(C_2H_5)_2SnCl_2$	247.63	47.9						X	X		5
Diethyltin dimethoxide	$(C_2H_5)_2Sn(OCH_3)_2$	238.75	49.7						X			
Diethyltin oxide	$(C_2H_5)_2SnO$	192.81	61.6	White powder	Infusible		Insol	Insol [sol in HCl, conc alkali]	X		X	
Diethyltin sulfide	$(C_2H_5)_2SnS$	208.79	56.8	Slightly yellow liquid					X	X	X	9,13
Dimethyltin dibutylsulfide	$(CH_3)_2Sn(SC_4H_9)_2$	326.91	36.3						X	X	X	
Dimethyltin dihydride	$(CH_3)_2SnH_2$	150.71	78.8						X			
Dimethyltin dimethoxide	$(CH_3)_2Sn(OCH_3)_2$	210.73	56.3		86							12
Dimethyltin oxide	$(CH_3)_2SnO$	164.70	72.1	White powder	Infusible		Insol	Insol [sol in NaOH]	X			
Dimethyltin sulfide	$(CH_3)_2SnS$	180.78	65.6		148					X		
Dioctyltin dichloride	$(C_8H_{17})_2SnCl_2$	415.75	28.5						X			2
Dioctyltin oxide	$(C_8H_{17})_2SnO$	360.85	32.9						X	X		
Diphenyltin dibromide	$(C_6H_5)_2SnBr_2$	432.72	27.4	Colorless crystals	38	230		Alcohol,ether	X			
Diphenyltin dichloride	$(C_6H_5)_2SnCl_2$	343.81	34.5	"	42	333-337	Very slightly sol	Alcohol, ether, ligroin	X			13

TABLE XII – 1 (CONTINUED)
PROPERTIES AND USES OF ORGANOTIN COMPOUNDS

COMPOUND	FORMULA	Molecular Weight	Tin Content (%)	Appearance	Melting Point (C)	Boiling Point (C)	Solubility		Uses			
							H_2O	Organic Solvents	Catalyst	Stabilizer	Biocide	Other *
Diphenyltin oxide	$(C_6H_5)_2SnO$	288.90	41.1	Colorless powder	Infusible		Insol	Insol [sol in conc acids]		X		
TRIORGANOTINS												
Bis(tributyltin) oxide (Trade names: TBTO, Tributyl oxide)	$[(C_4H_9)_3Sn]_2O$	595.62	39.9	Yellow liquid		254	Insol	Sol	X		X	2,8, 10,12, 13
Bis(triethyltin) oxide	$[(C_2H_5)_3Sn]_2O$	427.50	55.5						X			
Bis(triisobutyltin) oxide	$[(C_4H_9)_3Sn]_2O$	595.62	39.9								X	
Bis(triphenyltin) oxide	$[(C_6H_5)_3Sn]_2O$	715.74	33.2						X			
Bis(tripropyltin) oxide	$[(C_3H_7)_3Sn]_2O$	511.56	46.4								X	
N_1N-bis(tributyltin) diphenylurea	$[(C_4H_9)_3SnNC_6H_5]_2CO$	789.77	30.1						X	X	X	
N_1O-bis(tributyltin) N-phenylcarbamate	$(C_4H_9)_3SnNC_6H_5CO_2Sn(C_4H_9)_3$	714.70	33.2						X	X	X	
Tributyltin acetate	$(C_4H_9)_3Sn(OOC_2H_3)$	349.08	34.0	White, waxy solid		80–83	Insol	Benzene, methyl alcohol			X	2,8, 10,11
Tributyltin benzoate	$(C_4H_9)_3SnOOCC_6H_5$	410.88	28.9								X	
Tributyltin borate	$(C_4H_9)_3SnBO_2$	332.62	35.7								X	8
Tributyltin butoxide	$(C_4H_9)_3SnOC_4H_9$	362.85	32.7						X			
Tributyltin fluoride	$(C_4H_9)_3SnF$	308.81	38.4			341–342				X		
Tributyltin hydride	$(C_4H_9)_3SnH$	290.81	40.8						X		X	5
Tributyltin iodide	$(C_4H_9)_3SnI$	416.71	28.5								X	
Tributyltin isocyanate	$(C_4H_9)_3SnNCO$	331.83	35.8						X		X	
Tributyltin isothiocyanate	$(C_4H_9)_3SnNCS$	347.89	34.1			150–153			X		X	
Tributyltin laurate	$(C_4H_9)_3SnO_2CC_{11}H_{23}$	488.93	24.3						X	X	X	
Tributyltin methoxide	$(C_4H_9)_3SnOCH_3$	320.82	37.0						X		X	
Tributyltin oleate	$(C_4H_9)_3SnO_2C(CH_2)_7CH{:}CHC_8H_{17}$	570.99	20.8						X			
Tributyltin phenoxide	$(C_4H_9)_3SnOC_6H_5$	382.87	31.0						X			
Tricyclohexyltin hydride	$(C_6H_{11})_3SnH$	368.87	32.2			147–150			X			
Tricyclohexyltin hydroxide (Trade names: Plictran, DOWCO–213)	$(C_6H_{11})_3SnOH$	384.87	30.8								X	

TABLE XII – 1 (CONTINUED)
PROPERTIES AND USES OF ORGANOTIN COMPOUNDS

COMPOUND	FORMULA	Molecular Weight	Tin Content (%)	Appearance	Melting Point (C)	Boiling Point (C)	Solubility		Uses			
							H_2O	Organic Solvents	Catalyst	Stabilizer	Biocide	Other *
Tricyclopropyltin chloride	$(C_3H_5)_3SnCl$	277.41	42.8								X	
Triethyltin acetate	$(C_2H_5)_3Sn(OOC_2H_3)$	264.77	44.8						X			8
Triethyltin azide	$(C_2H_5)_3SnN_3$	247.93	47.9								X	9
Triethyltin chloride	$(C_2H_5)_3SnCl$	241.33	49.2	Colorless liquid	15.8	208–210	Sol	Sol	X		X	
Triethyltin hydride	$(C_2H_5)_3SnH$	206.75	57.4						X			
Triethyltin isocyanate	$(C_2H_5)_3SnNCO$	247.77	47.9						X		X	
Triethyltin methoxide	$(C_2H_5)_3SnOCH_3$	236.76	50.1							X		
Trihexyltin chloride	$(C_6H_{13})_3SnCl$	409.32	29.0									12
Triisobutyltin chloride	$(C_4H_9)_3SnCl$	325.49	36.5		30.2	174					X	
Triisopropyltin chloride	$(C_3H_7)_3SnCl$	283.41	41.9			134–137					X	
Triisopropyltin hydride	$(C_3H_7)_3SnH$	248.78	47.7			68–70			X			
Trimethyltin bromide	$(CH_3)_3SnBr$	243.70	48.7	Colorless crystals or liquid	27	165	Sol	Sol	X			
Trimethyltin chloride	$(CH_3)_3SnCl$	199.24	59.6	Colorless crystals	37	154	Slightly sol	"	X			
Trimethyltin hydride	$(CH_3)_3SnH$	164.80	72.0	Colorless, oily liquid		59–61	"	"	X			
Trimethyltin hydroxide	$(CH_3)_3SnOH$	180.72	65.7		118				X		X	12
Triphenyltin acetate (Trade names: Brestan, Fertin acetate, Linostanol)	$(C_6H_5)_3Sn(OOC_2H_3)$	408.89	29.0								X	8
Triphenyltin bromide	$(C_6H_5)_3SnBr$	429.92	27.6	Colorless crystals	120.5	249	Insol	Sol	X		X	
Triphenyltin chloride	$(C_6H_5)_3SnCl$	385.46	30.8	"	106	240	"	"			X	13,14
Triphenyltin fluoride	$(C_6H_5)_3SnF$	369.01	32.2	Fine prisms	357		"	Slightly sol			X	
Triphenyltin hydroxide (Trade names: DOWCO-186, Du-Ter, Fentin, TPTH)	$(C_6H_5)_3SnOH$	367.02	32.3	White powder	118		"	Insol in nearly all	X		X	2,10
Triphenyltin isothiocyanate	$(C_6H_5)_3SnNCS$	407.95	29.1		171–172							9
Triphenyltin methoxide	$(C_6H_5)_3OCH_3$	380.88	31.2								X	
Tripropyltin chloride	$(C_3H_7)_3SnCl$	283.41	41.9	Colorless liquid	-23.5	123		Sol			X	
Tripropyltin fluoride	$(C_3H_7)_3SnF$	266.96	44.5	Flat prisms	275						X	

TABLE XII – 1 (CONTINUED)
PROPERTIES AND USES OF ORGANOTIN COMPOUNDS

COMPOUND	FORMULA	Molecular Weight	Tin Content (%)	Appearance	Melting Point (C)	Boiling Point (C)	Solubility		Uses			
							H_2O	Organic Solvents	Catalyst	Stabilizer	Biocide	Other *
Tripropyltin hydride	$(C_3H_7)_3SnH$	248.78	47.7						X			
Tris(2–cyanoethyl)tin acetate	$(NCCH_2CH_2)_3Sn(OOC_2H_3)$	339.80	34.9							X	X	
Tris(tributyltin) borate	$[(C_4H_9)_3Sn]_3BO_3$	928.24	38.4								X	8
Tris(tripropyltin) borate	$[(C_3H_7)_3Sn]_3BO_3$	802.15	44.4								X	8
TETRAORGANOTINS												
Allyltriphenyltin	$(C_6H_5)_3Sn(CH_2CHCH_2)$	390.90	30.4						X			
Tetraallyltin	$(CH_2{:}CHCH_2)_4Sn$	282.81	41.9						X			
Tetrabenzyltin	$(C_6H_5CH_2)_4Sn$	483.23	24.6	Colorless prisms	42–43		Insol	Sol in some	X			
Tetrabutyloxyacetatoditin oxide	$Sn_4C_{40}H_{80}O_8$ $[(Bu_2SnOAc)O(Bu_2SnOH)]_2$	1,163.16	40.8						X	X		
Tetraethyltin	$(C_2H_5)_4Sn$	234.94	50.5	Colorless liquid	–112	181	Slightly sol	Sol	X			2,3
Tetraisopropyltin	$(C_3H_7)_4Sn$	291.05	40.8						X			
Tetramethyltin	$(CH_3)_4Sn$	178.85	66.4	Colorless liquid	–54.8	78	Insol	Sol in some	X			1
Tetra–n–butyltin	$(C_4H_9)_4Sn$	347.21	34.2	Colorless liquid (distinct unpleasant odor)	–97	145 (11 mmHg)	"	Sol	X	X	X	1,2,4, 5,7
Tetra–n–octyltin	$(C_8H_{17})_4Sn$	571.59	20.8	Liquid		268	"					1
Tetraphenyltin	$(C_6H_5)_4Sn$	427.12	27.8	Colorless, tetragonal crystals	226	420	"	Sol in benzene, pyradine, chloroform, acetic acid; slightly sol in alcohol	X	X		5,6
Tetrapropyltin	$(C_3H_7)_4Sn$	291.05	40.8	Colorless liquid		222–225	"	Sol	X			3
Tetravinyltin	$(CH{:}CH_2)_4Sn$	226.87	52.3	"		55–57			X			
Trimethylphenyltin	$(CH_3)_3Sn(C_6H_5)$	240.92	49.3			62–63						6

* Other Uses: 1 – solvent, 2 – in flame resistant polyester, 3 – metal plating agent, 4 – gasoline additive, 5 – effect on spreading coefficient of solder, 6 – anti fogging agent, 7 – improves adhesion of polychloroprene, 8 – wood preservative, 9 – antiwear additive, 10 – curing agent, 11 – thermal or electrical coating, 12 – water repellant coating, 13 – antioxidant or corrosion inhibitor, 14 – film additive.

TABLE XII-2

ESTIMATED DEDI DOSES AND EFFECTS ON HUMANS
TREATED ORALLY WITH STALINON

Subjects		Estimated Total DEDI (mg)	Total No. Capsules	Symptom Lag Time* (days)	Outcome	Reference
Sex	Age					
M	31	750	50	14	Fatal	22
F	15	675	45	-	Nonfatal	24
F	27	450 - 600	30 - 40	-	Fatal	22
M	22	525	35	19	"	22
F	26	450	30	2 - 3**	Nonfatal	22
F	15	420	28	10	Fatal	22
M	12	395	25	-	"	24
F	12	380	24	-	"	24
F	24	330	22	7	Nonfatal	22
M	17	300	20	14	"	26
M	5	225	15	-	"	24
F	3.5	210	12	1	"	26
M	22	175	120***	-	"	25
F	9	45	3	-	"	24

*Estimated time of appearance of first symptoms from beginning of treatment, except where otherwise noted
**From completion of treatment
***Treatment consisted of drops rather than capsules.

TABLE XII-3

PERCENT MORTALITY IN MICE AFTER
INHALATION* ADMINISTRATION OF SIX ORGANOTINS

Compound	Concentration (mg/l)	% Mortality in 10 Days
Triethyltin bromide	3.4	100(3 d)
	1.6	65
Tripropyltin bromide	3.2	60
	1.7	5
Tributyltin bromide	5.2	100(4 d)
	2.7	100(5 d)
	2.0	70
	1.0	10
Tributyltin iodide	1.3	7
	0.9	0
Tributyltin hydride	2.0	0
	1.5	0
Tetramethyltin	10.8	100(1 d)
	2.5	25

*Single 10-minute exposure

From Glass et al [16]

TABLE XII-4a

PERCENT MORTALITY IN MICE
AFTER ORAL ADMINISTRATION OF TETRABUTYLTIN

Dose (mM/kg)	Percentage of Mortality after:									
	Hours					Days				
	3	4	6	10	12	1	2	3	4	30
2	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	10	30	30
8	0	0	0	0	20	20	40	50	80	80
10	0	0	20	30	30	30	100	100	100	100
40	0	50	50	50	50	100	100	100	100	100

From Caujolle et al [50]

TABLE XII-4b

PERCENT MORTALITY IN MICE
AFTER ORAL ADMINISTRATION OF TETRAISOBUTYLTIN

Dose (mM/kg)	Percentage of Mortality after:											
	Hours				Days							
	1	2	6	12	1	2	3	4	6	8	10	30
0.5	0	0	0	0	0	0	0	0	0	0	0	0
1	0	10	10	10	10	40	40	40	40	40	40	40
3	0	10	10	10	20	60	70	70	80	80	80	80
4	0	0	0	0	0	0	30	50	70	70	70	70
10	0	0	0	0	0	40	40	80	90	90	90	90
20	0	0	50	50	70	80	80	80	80	80	100	100

From Caujolle et al [50]

TABLE XII-4c

PERCENT MORTALITY IN MICE
AFTER ORAL ADMINISTRATION OF TETRAAMYLTIN

Dose (mM/kg)	Percentage of Mortality after:												
	Hours						Days						
	3	4	6	10	12	18	1	2	3	4	6	8	30
1	0	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	20	20
4	0	0	0	0	0	0	0	0	30	50	50	50	50
8	0	0	0	0	0	0	0	0	10	20	80	80	80
10	0	0	0	0	0	20	40	40	100	100	100	100	100
20	0	0	0	10	10	10	50	100	100	100	100	100	100
40	0	30	40	50	50	70	100	100	100	100	100	100	100

From Caujolle et al [50]

TABLE XII-4d

PERCENT MORTALITY IN MICE
AFTER ORAL ADMINISTRATION OF TETRAISOAMYLTIN

Dose (mM/kg)	Percentage of Mortality after:									
	Hours		Days							
	10	12	1	2	3	4	6	8	10	30
0.25	0	0	0	0	0	0	0	0	0	0
0.50	0	0	0	0	0	0	0	0	10	10
1	0	0	0	0	0	20	30	30	30	30
2	0	0	10	40	40	40	40	40	40	40
3	0	0	40	50	50	50	50	50	50	50
4	0	10	10	30	30	40	40	40	40	40
10	0	0	0	20	40	80	80	80	80	80
20	0	10	30	30	80	80	80	80	80	80
25	0	20	20	40	100	100	100	100	100	100

From Caujolle et al [50]

TABLE XII-5

COMPARISON OF CHEMICAL STRUCTURE AND TOXICITY
IN ORGANOTIN COMPOUNDS OF THE GENERAL FORMULA R3SnR' OR R3SnX

Compound A (LD50 in mg/kg)	Compound B (LD50 in mg/kg)	Change in Structure	Average Change in Toxicity (B:A)*
Triparaxylyltin bromide [(CH3)2C6H3]3SnBr (34.0)	Trimesityltin bromide [(CH3)3C6H2]3SnBr (92.0)	Substitute R3 = [(CH3)3C6H2]3 for R3 = [(CH3)2C6H3]3	2.6
"	Trinaphthyltin bromide (C10H8)3SnBr (193.0)	Substitute R3 = (C10H8)3 for R3 = [(CH3)2C6H3]3	5.7
"	p-Tetraxylyltin [(CH3)2C6H3]3Sn [(CH3)2C6H3] (2,290.0)	Substitute R' = [(CH3)2C6H3] for X = Br	62.7
Trimesityltin bromide [(CH3)3C6H2]3SnBr (92.0)	Trinaphthyltin bromide (C10H8)3SnBr (193.0)	Substitute R3 = (C10H8)3 for R3 = [(CH3)3C6H2]3	2.1
"	Trimesityltin iodide [(CH3)3C6H2]3SnI (152.0)	Substitute X = I for X = Br	1.7
"	Trimesitylmethyltin [(CH3)3C6H2]3SnCH3 (greater than 3,000)	Substitute R' = CH3 for X = Br	Greater than 50
"	Trimesitylmethyltin [(CH3)3C6H2]3SnC2H5 (1,870.0)	Substitute R' = C2H5 for X = Br	20.3
"	Trimesityl-n-octyltin [(CH3)3C6H2]3SnC8H17 (2,000.0)	Substitute R' = C8H17 for X = Br	21.7

TABLE XII-5 (CONTINUED)

COMPARISON OF CHEMICAL STRUCTURE AND TOXICITY
IN ORGANOTIN COMPOUNDS OF THE GENERAL FORMULA R3SnR' OR R3SnX

Compound A (LD50 in mg/kg)	Compound B (LD50 in mg/kg)	Change in Structure	Average Change in Toxicity (B:A)*
Trimesityltin bromide [(CH3)3C6H2]3SnBr (92.0)	Trimesitylisoamyltin [(CH3)3C6H2]3SnC5H11 (660.0)	Substitute R' = C5H11 for X = Br	30
Trimesitylisoamyltin [(CH3)3C6H2]3SnC5H11 (660.0)	Trimesitylmethyltin [(CH3)3C6H2]3SnCH3 (greater than 3,000)	Substitute R' = CH3 for R' = C5H11	7
"	Trimesitylethyltin [(CH3)3C6H2]3SnC2H5 (1,870.0)	Substitute R' = C2H5 for R' = C5H11	2.8
Trimesitylethyltin [(CH3)3C6H8]3SnC2H5 (1,870.0)	Trimesitylmethyltin [(CH3)3C6H2]3SnCH3 (greater than 3,000)	Substitute R' = CH3 for R' = C2H5	3
Trimesityl-n-octyltin [(CH3)3C6H2]3SnC8H17 (2,000.0)	"	Substitute R' = CH3 for R' = C8H17	2.5
"	Trimesitylethyltin [(CH3)3C6H2]3SnC2H5 (1,870.0)	Substitute R' = C2H5 for R' = C8H17	0
"	Trimesitylisoamyltin [(CH3)3C6H2]3SnC5H11 (660.0)	Substitute R' = C5H11 for R' = C8H17	3

*Statistical analysis using the Litchfield and Wilcoxon method

From Kolla and Zalesov [52]

TABLE XII-6

COMPARATIVE ORAL TOXICITY OF DIALKYLTIN DICHLORIDES* IN RATS

Alkyl Group	Effects at Each Dose Level		
	40 mg/kg	80 mg/kg	160 mg/kg
Methyl	No weight loss; no bile-duct lesion	No weight loss; no bile-duct lesion	Death on d 4 with marked weakness in both; no bile-duct lesion
Ethyl	"	One death; lung congestion; no effect on one; no bile-duct lesion	Death in both on d 4; no lesions
Propyl	"	One ill, killed d 5, no lesion; no effect in one	One died d 2; pulmonary congestion, weight loss in one; recovery, slight bile-duct lesion
Isopropyl	No weight loss; very slight bile-duct lesion	Slight weight loss, mild bile-duct lesion	Some weight loss, bile-duct lesion
Butyl	One death; bile-duct lesion; weight loss in one	Death, bile-duct lesion in both; severe liver lesion in one	Both very ill with weight loss; severe bile-duct lesion
Pentyl	Weight loss in both; some bile-duct damage	One died d 5, no necropsy; one with weight loss, adrenals red, bile-duct lesion	Weight loss in both, adrenals very dark at necropsy, slight bile-duct lesion
Hexyl	Weight loss in one resulting in death, no bile-duct lesion; one unaffected	Weight loss in both; recovery; adrenals very dark at necropsy; no bile-duct lesion	Weight loss in both; one death; no bile-duct lesion

TABLE XII-6 (CONTINUED)

COMPARATIVE ORAL TOXICITY OF DIALKYLTIN DICHLORIDES* IN RATS

Alkyl Group	Effects at Each Dose Level		
	40 mg/kg	80 mg/kg	160 mg/kg
Octyl	No weight loss or bile-duct lesion (50 mg/kg)	No weight loss; bile duct lesion (100 mg/kg)	Weight loss in one, no cause found (200 mg/kg)
2-Ethyl-hexyl	No ill effects	No weight loss; bile-duct lesion	No ill effects

*Compounds were administered orally to pairs of female rats on normal diet according to the following schedule: 40 mg/kg given on 1st and 4th days; 80 mg/kg on 1st and 4th days, except hexyl given only on 1st day; 160 mg/kg given on 1st day only, except butyl and octyl given also on 4th day. Rats were observed for 10 days from first dose.

From Barnes and Stoner [60]

TABLE XII-7

COMPARATIVE TOXICITY OF DIALKYLTIN DICHLORIDES
APPLIED PERCUTANEOUSLY TO RATS*

Alkyl Group	Skin Lesions and General Effects	Bile-Duct Lesion
Methyl	Necrosis of superficial layers of skin with black eschar formation; no deep-seated inflammation; slight weight loss	None
Ethyl	Slight superficial necrosis with patchy eschar; generalized deep-seated edema and subcutaneous inflammation	"
Propyl	Weight loss; 2/3 died; white patchy necrosis of skin with deeper inflammation and edema	Slight
Isopropyl	Some weight loss; dry necrosis of skin; no eschar; deeper edema and inflammation	Moderate
Butyl	Little superficial damage to skin but some edema of subcutaneous tissues; death in 1/3	Marked
Pentyl	Irritability; no obvious skin lesions or subcutaneous edema; dark adrenals in one rat	Slight
Hexyl	No weight loss; no skin lesions	None
Octyl	"	"

*The tin salts, 80 mg/kg, were dissolved in 0.1 ml dimethylphthalate and applied on 5 successive days to the clipped skin of groups of three rats. Rats were observed for 12 days, and at necropsy the skin lesions and condition of the bile duct were examined.

From Barnes and Stoner [60]

TABLE XII-8

EFFECTS OF DIALKYLTIN DICHLORIDES
ADMINISTERED INTRAVENOUSLY TO RATS*

Alkyl Group	Number of Deaths at Each Dose Level				Effects
	5 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg	
Methyl	-	0	0	2	No obvious cause of death; no bile-duct lesions in survivors
Ethyl	-	0	1	4	Death in 2-24 hr; no obvious cause; slight bile-duct lesions in survivors
Propyl	0	3	4	-	Death usually within 12 hr; some pleural effusion; moderate bile-duct lesions in survivors
Isopropyl	0	0	4	-	Death in 2-72 hr; weight loss; moderate bile-duct lesions in survivors
Butyl	0	4	4	-	Death in 1-18 hr; considerable lung damage; severe bile-duct lesions in survivors
Pentyl	0	1	4	-	Death in 1-18 hr; pleural effusion often marked; moderate bile-duct lesions in survivors
Hexyl	0	2	4	-	Death in 2-4 hr; moderate bile-duct lesions in survivors
Octyl	0	4	4	-	Death usually within 4 hr; no gross lung damage; no bile-duct lesions in survivors

TABLE XII-8 (CONTINUED)

EFFECTS OF DIALKYLTIN DICHLORIDES
ADMINISTERED INTRAVENOUSLY TO RATS*

Alkyl Group	Number of Deaths at Each Dose Level				Effects
	5 mg/kg	10 mg/kg	20 mg/kg	40 mg/kg	
2-Ethyl-hexyl	0	4	2**	-	Death in 4-18 hr; no bile-duct lesions
Trimethyl-hexyl	0	4	2**	-	"

*Intravenous injections in 0.05 ml Tween 80 into female rats in groups of four, except where otherwise noted
**Only two rats in these groups

From Barnes and Stoner [60]

TABLE XII-9

TIN CONCENTRATIONS IN ORGANS OF MALE RATS
FED DI-N-OCTYLTIN OXIDE FOR 2 YEARS

DOTO in Diet (ppm)	Tin Concentration (ppm)					
	Liver	Kidneys	Heart	Testes	Lean Muscle	Fat
Control	*	*	*	*	*	*
9.6	**	0.1	*	*	*	*
24	**	0.1	*	*	*	*
39	0.2	0.4	*	**	*	*
72	0.2	0.2	**	0.3	*	*
98	0.8	0.4	0.1	0.1	*	*
295	2.0	1.6	0.3	0.2	0.1	*

*Probably 0.05 ppm, based on sensitivity of method
**Probably 0.05-0.08 ppm, based on sensitivity of method

From Banks et al [84]

TABLE XII-10

TIN CONCENTRATIONS IN ORGANS OF MALE DOGS
FED DI-N-OCTYLTIN OXIDE FOR 2 YEARS

DOTO in Diet (ppm)	Tin Concentration (ppm)							
	Liver	Brain	Kidneys	Heart	Fat	Lean Muscle	Blood	Urine
Control	0.3	*	*	*	**	**	**	**
9.6	8.2	0.4	0.5	0.2	0.2	*	-	-
24	11.0	0.5	0.6	0.2	0.2	0.1	-	-
39	13.4	0.4	0.7	0.2	0.3	0.1	-	-
72	25.1	1.6	1.4	0.7	0.7	0.2	0.1	*
98	26.9	1.6	1.3	0.4	0.4	0.2	-	-
295	34.5	3.3	2.3	0.9	0.8	0.4	0.2	0.1

*Probably 0.05-0.08 ppm, based on sensitivity of method
**Probably 0.05 ppm, based on sensitivity of method

From Banks et al [84]

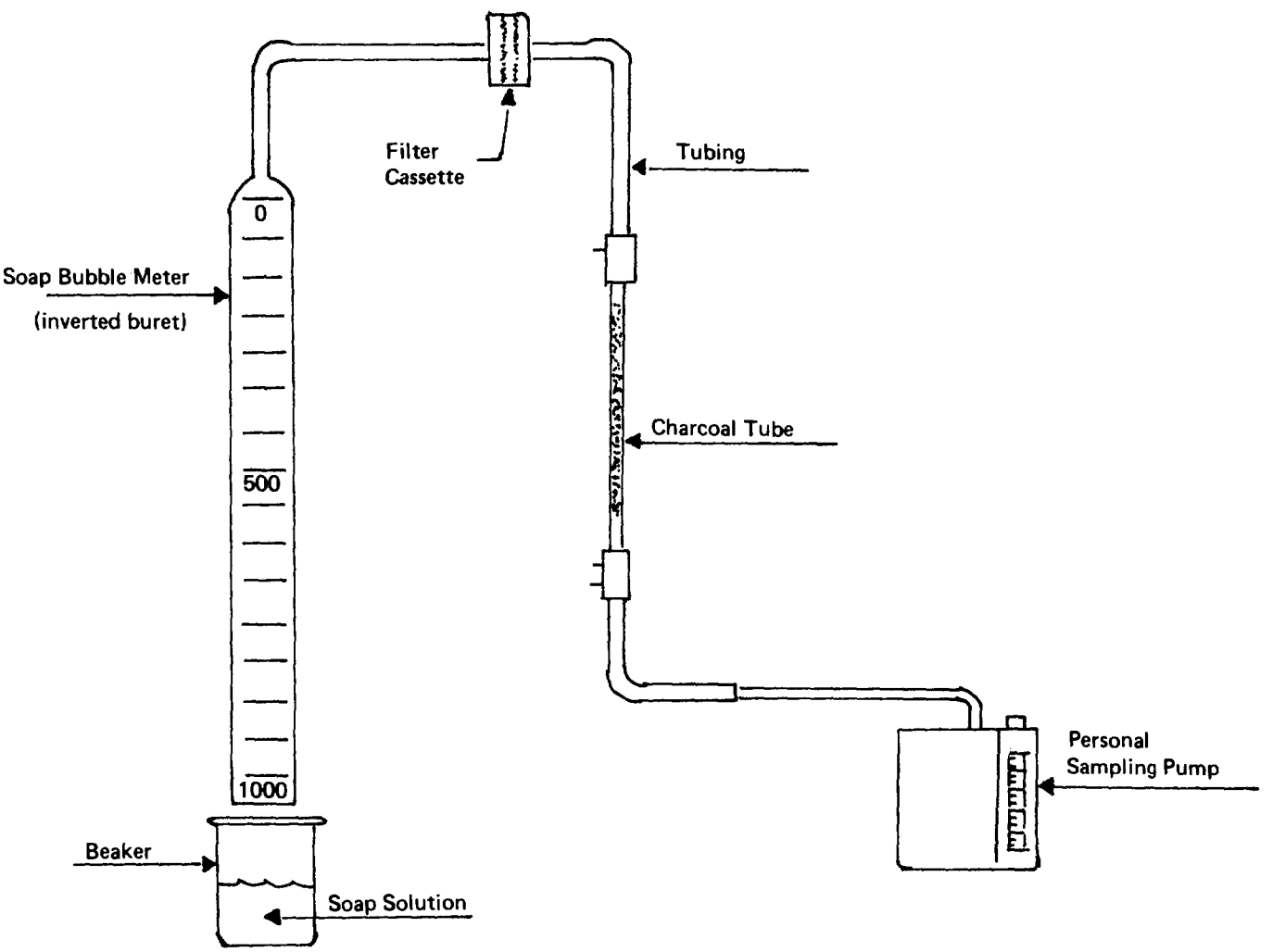


FIGURE XII-1 - CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH FILTER CASSETTE AND CHARCOAL TUBE

☆ U.S. GOVERNMENT PRINTING OFFICE: 1977—757-057/5753

DEPARTMENT OF
HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH
ROBERT A. TAFT LABORATORIES
4676 COLUMBIA PARKWAY, CINCINNATI, OHIO 45226

OFFICIAL BUSINESS
PENALTY FOR PRIVATE USE, $300

POSTAGE AND FEES PAID
U.S. DEPARTMENT OF H.E.W.
HEW 399

DHEW (NIOSH) Publication No. 77-115