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.