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130. Tin and inorganic tin compounds

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Preface

An agreement has been signed by the Dutch Expert Committee on Occupational Standards (DECOS) of the Health Council of the Netherlands and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the agreement is to write joint scientific criteria documents which could be used by the national regulatory authorities in both the Netherlands and in the Nordic countries.

The document on health effects of tin and inorganic tin compounds was written by MD Bente Westrum and Dr Yngvar Thomassen, both at the National Institute of Occupational Health, Norway and has been reviewed by DECOS as well as by NEG.

Editorial work was performed by NEG's scientific secretary, Jill Järnberg, and technical editing by Karin Sundström, both at the National Institute for Working Life in Sweden.

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Abbreviations

ALA	δ-aminolevulinic acid
ALAD	δ-aminolevulinic acid dehydratase
CHO	Chinese hamster ovary
LD_{50}	lethal dose for 50% of the exposed animals at single administration
LOEL	lowest observed effect level
NOEL	no observed effect level

Contents

1. Introduction

Bronze, an alloy of copper and tin, has been known since 2500 BC. The first inclusion of tin (Sn) in bronze was probably an accidental result of tin ore being found in copper ore; pure tin was most likely obtained at a later date (7). For the first time a workable metal with a low-melting point was available to fabricate durable weapons, ornaments, coins, cooking utensils, bells and statuary. Mining and melting became established industries, adjacent cities grew wealthy, the science of navigation advanced, trade flourished. Tin was mined in Spain, Britain and Central Europe. This thousand-year-old multifaceted civilisation declined with the advent of ironmongering.

The second great revolution began in 1810, when tin plate was first used for canning foods as a result of the military needs of the Napoleonic wars. Five decades were to elapse before canning of food became prevalent. Concurrently, an enormous increase in human exposures to tin spread throughout the civilised world (159).

This document reviews the literature on tin and its inorganic compounds. SnH_4 (stannane) is only referred to as a basic compound for the manufacturing of a large number of organotin compounds and is therefore not included in this document.

2. Substance identification

Pure tin is a silver-white, shiny metal with the atomic symbol Sn and belongs to the carbon group (group IVA). Tin's atomic number is 50 and it has an atomic weight of 118.71. Tin occurs naturally as the stable isotopes ^{112}Sn (0.97%), ^{114}Sn (0.65%), ^{115}Sn (0.36%), ^{116}Sn (14.5%), ^{117}Sn (7.7%), ^{118}Sn (24.2%), ^{119}Sn (8.6%), ^{120}Sn (32.6%), ^{122}Sn (4.6%) and ^{124}Sn (5.8%) (43).

The most commercially significant inorganic tin compounds include tin di-and tetrachloride, tin dioxide, potassium and sodium stannates, tin difluoride, tin difluoroborate and tin pyrophosphate.

Chemical formulas, molecular weights and CAS numbers of some tin compounds are listed in Table 1.

3. Physical and chemical properties

The melting point (232°C) of pure tin is low compared with those of the common structural metals, whereas the boiling point (2602°C) exceeds that of most metals except tungsten and the platinum group. Therefore, loss by volatilisation during

Table 1. Chemical identification of some tin compounds.

Chemical name	Synonyms	Chemical formula	Molecular weight	CAS-No
Potassium stannate		$K_2Sn(OH)_6$	298.9	12125-03-0
Sodium stannate		$Na_2Sn(OH)_6$	266.7	12209-98-2
Tin		Sn	118.7	7440-31-5
Tin(IV) bromide,	tin tetrabromide, stannic bromide	$SnBr_4$	438.3	7789-67-5
Tin(II) chloride,	tin dichloride, stannous chloride	$SnCl_2$	189.6	7772-99-8
Tin(IV) chloride	tin tetrachloride, stannic chloride	$SnCl_4$	260.5	7646-78-8
Tin(IV) chloride iodide	tin dichloride diiodide, stannic dichloride diiodide	$SnCl_2I_2$	443.4	13940-16-4
Tin(II) difluoroborate	stannous fluoroborate	$Sn(BF_4)_2$[a]	292.3	13814-97-6
Tin(II) fluoride	tin difluoride, stannous fluoride	SnF_2	156.7	7783-47-3
Tin(II) iodide	tin diiodide, stannous iodide	SnI_2	372.5	10294-70-9
Tin(IV) iodide	tin tetraiodide, stannic iodide	SnI_4	626.3	7790-47-8
Tin(IV) oxide	tin dioxide, stannic oxide,	SnO_2	150.69	18282-10-5
Tin(II) pyrophosphate	stannous pyrophosphate	$Sn_2P_2O_7$	411.32	15578-26-4
Tin(II) sulphate	stannous sulphate	$SnSO_4$	214.75	7488-55-3

[a]Available only in solution, as the solid form has not been isolated.

melting and alloying with other metals is insignificant. Only small quantities of some metals can be dissolved in pure liquid tin near its melting point but inter-metallic compounds are freely formed of which some are of metallurgical importance. Copper, nickel, silver and gold are appreciably soluble in liquid tin.

Tin coatings can be applied to most metal surfaces by electrodeposition while molten tin wets and adheres readily to clean iron, steel, copper, and copper-base alloys. This tin coating provides protection against oxidation of the base metal/ alloy and aids in subsequent fabrication because it is ductile and solderable (114).

Table 2. Physical and chemical properties of some tin compounds (110).

Compound	Melting point (°C)	Boiling point (°C)	Density (g/cm^3)	Solubility in water
Sn	231.9	2602	5.77[a] 7.27[b]	insoluble
$SnBr_4$	31	205	3.34	soluble
$SnCl_2$	247	623	3.90	soluble
$SnCl_4$	-33	114	2.23	soluble
SnF_2	213	850	4.57	soluble
SnI_2	320	714	5.28	slightly soluble
SnI_4	143	364.5	4.46	soluble
SnO	1080		6.45	insoluble
SnO_2	1630	1900	6.85	insoluble
$Sn_2P_2O_7$	Decomposes at 400°C		4.01	insoluble
SnS	880	1210	5.08	insoluble
$SnSO_4$	Decomposes at >378°C (SO_2)		4.15	reacts with

[a] Grey tin, cubic crystalline form.
[b] White tin, silvery tetragonal crystalline form, stable above 13°C.

The II (stannous) and IV (stannic) oxidation states are both reasonably stable and interconverted by moderately active reagents. The Sn^{2+}/Sn^{4+} potential is –0.15V and Sn(II) is well-known as a mild reducing agent. Because of its amphoteric nature, tin reacts with strong acids and strong bases but remains relatively resistant to neutral solutions. A thin oxide film forms on tin exposed to oxygen or dry air at ordinary temperatures; heat accelerates this reaction. Tin is easily attacked by hydrogen iodide and hydrogen bromide, and less readily by hydrogen chloride. Hot concentrated sulphuric acid reacts with tin forming tin disulphate, whereas the diluted acid reacts only slowly with tin at room temperatures. Reaction of tin with dilute nitric acid yields soluble tin nitrates; in concentrated nitric acid tin is oxidised to insoluble hydrated tin dioxide. Molten tin reacts with phosphorous forming a phosphide. Stannates are produced by the action of strong potassium or sodium hydroxide on tin (114). Physical and chemical properties of some tin compounds are listed in Table 2.

4. Occurrence, production and use

Tin is found throughout the Earth's crust at a few parts per million. The average concentration of particulate tin in air is near 1 ng/m^3 in the Northern Hemisphere. Higher values are observed in the urban atmospheres. The anthropogenic input of tin into the atmosphere appears to be dominated by emissions from waste incineration and nonferrous metal production (21).

Tin is mined chiefly as cassiterite (SnO_2). The other ores are complex sulphides, stannite (Cu_2FeSnS_4), and teallite ($PbZnSnS_2$) (7). The annual world production of tin has been quite stable at approximately 210 000-230 000 tons for decades, and out of this 15 000-20 000 tons is secondary metal recovered from scrape waste or

Table 3. Production of tin, unwrought[a]. Metric tons. Major tin producing countries (187).

Country	1994	1995	1996
Bolivia	15 539	17 709	16 733
Brazil	20 700	19 800	19 800
China	67 764	67 659	71 500
Indonesia	39 000	44 218	48 960
Malaysia	37 990	39 433	38 051
Thailand	7 634	8 246	10 983
United States	11 700	11 600	11 000
World production	215 598	223 703	229 046

[a] Production of virgin metal (primary) and tin derived from scrap (secondary). Tin alloys are included.

detinning. The major tin producing countries today are shown in Table 3. In the Western World, the tin produced is mainly secondary.

Metallic tin is obtained by smelting tin ore. The ore is mixed with salt and roasted at about 600°C, washed in water and then mixed with anthracite as a reducing agent and smelted at about 1500°C. After refining the tin is cast into bars (146, 147).

Because of its resistance to corrosion, tin is used as a protective coating for other metals. Another important property of tin is its ability to form alloys with other metals. $SnCl_4$ is used as a dehydrating agent in organic synthesis, a stabiliser for plastics, and as a chemical intermediate for other tin compounds. $SnCl_2$ serves as a reducing agent in manufacturing ceramics, glass and inks (85).

Dental amalgams contain varying proportions of tin (12-30%) (11). SnF_2 has been used as a prophylactic agent in preventive dentistry for decades. Sn(II) ions have a profound and long-lasting inhibiting effect on the oral micro flora *in vivo* (4). Topical application of SnF_2 appears to provide dentine with a layer of tin and fluoride, which may provide mechanical and chemical protection and may be of clinical significance in restorative dentistry. Sn(II) ions possess antibacterial activity whereas Sn(IV) ions do not (57, 61, 150, 152, 177).

The reducing agent Sn(II) is important in nuclear medicine as an essential component in diagnostic agents used to visualise blood, heart, lung, kidney and bone. Sn(II) has nearly ideal redox properties for the reduction of the visualising label technetium-99m (65, 136, 143).

Most of the operations associated with the extraction of tin ore are wet processes, but tin dust and oxide fumes may escape during bagging of concentrate, in ore rooms and during smelting operations (mixing-plant and furnace tapping), as well as during the periodic cleaning of bag filters used to remove particulate matter from smelter furnace flue gas (85).

Tin reclamation from tin plated steel trimmings, rejects from tin-can manufacturing companies, rejected plating coils from the steel industry, tin drosses and sludges, solder drosses and sludges, used bronze and bronze rejects

Table 4. Common uses and sources of exposure to tin and inorganic tin compounds (193).

Substance	Use	Occupations
Tin metal	Tin plating, solder and alloy production (common alloys are bronze, brass, gunmetal, bearing metal, type metal and pewter), manufacture of food cans	Workers in brass and bronze foundries, makers of pewter, solder, babbit metal, and type metal; manufacturers of cans and metal containers
Inorganic tin compounds	Manufacture of toothpaste, ceramics, drill glass, porcelain, enamel, textiles (used as mordant), and ink	Production workers

and metal type scrap also involve possible exposure to tin dusts and fumes (86). Common uses and exposures to tin today are shown in Table 4.

Tin production may also involve exposure to silica, lead and arsenic in the mining of the sulphide ores of tin, and to bismuth and antimony as well in the roasting and smelting process. Similarly, the preparation and use of tin alloys and solders present an exposure to these heavy metals. Tin mining may involve exposure to radon, thorium and uranium (7, 63, 64, 83, 130, 138, 139, 180).

Studies in the United Kingdom showed mean concentrations of Sn in diet of 1-2 mg/kg (60) or approximately 3 mg/day (166). The primary sources of tin were said to be canned goods (60).

5. Occupational exposure data

Analysis of dust samples collected from tin smelting works (see chapter 11.2.2 and (149)) showed that the dust fraction with particle size < 5 μm in diameter contained more than 33% of metallic tin and no silica. The concentrations of Sn (in mg/m^3) measured in the workroom air were: check sampling shed 2.22, dracco (filters for furnace gases) 1.10, smelting furnace man 1.55, refining furnace man 0.82, orehouse skipman 0.34, plumber 0.12, electrician 0.05 and engineer 0.02. The methods of sampling and analysis were not described (147).

An environmental survey to determine the type of exposure in a Chilean tin foundry showed air concentrations of metal tin between 8.6 and 14.9 mg/m^3 (131).

Tin concentrations in house dust were increased in homes of electric-cable splicers suggesting that the splicers were contaminating their homes with tin from work (145).

No systematic data on occupational exposure levels in tin production or processing are available.

The Norwegian occupational exposure database EXPO contains data from all samples analysed at the National Institute of Occupational Health in Oslo since 1984. Most of these samples have been collected due to the wish of different enterprises to control their exposures and are likely to represent "worst case measurements" (141). Of the 3407 air filters (8-hours personal monitoring)

Table 5. Branches and job functions in EXPO with air concentrations > 0.05 mg Sn/m^3.

Branch/job functions	No. of samples	Mean (mg Sn/m^3)	Range (mg Sn/m^3)
Defence activities/spraying	3	0.20	0.01-0.46
Metal coating/surface coating	2	0.32	0.20-0.45
Electronic production/surface coating	2	1.51	0.09-2.93
Railway repair/termite welding	6	1.07	0.01-5.68
Metal casting/cleaning	2	0.29	0.25-0.34

analysed for tin, 420 contained amounts above the detection limit (0.002 mg Sn/m^3). In Table 5, the branches and job functions with tin levels > 0.05 mg Sn/m^3 are listed. If some samples contained > 0.05 mg Sn/m^3, all values in the analysis are included to show the mean and range of concentrations.

6. Measurements and analysis of workplace exposure

When selecting samplers for aerosol collection their sampling characteristics should comply with internationally accepted sampling criteria (ISO, CEN, ACGIH). Presently, most measurements are not standardised and do not comply with these sampling criteria.

The method recommended by NIOSH for measuring airborne inorganic tin and its compounds, except oxides, is filter acid digestion and atomic absorption or inductively coupled plasma atomic emission spectrometry. If the aerosol phase is believed to contain SnO_2, the acid solution is centrifuged and the tin compounds in the supernatant are determined as above. The precipitate is then treated with alkali, rendering SnO_2 to a soluble stannate, and the determination is made as above (7). Other acid digestion procedures (aqua regia + hydrogen fluoride) are available for simultaneous measurements of total tin and other elements by e.g. inductively coupled plasma atomic emission, and mass spectrometry, respectively (20, 157). Radiochemical neutron activation analysis has been used for the measurement of tin in human biological materials at background levels (189). A field portable X-ray fluorescence spectrometer has been developed as a rapid, nondestructive, on site alternative for analysis of membrane filters used in NIOSH method 7300 for metals (10).

7. Toxicokinetics

7.1 Uptake

7.1.1 Oral uptake

In vitro experiments on the rat small intestine suggested that absorption of tin ($SnCl_4$) occurs by passive diffusion. The absorption of $SnCl_4$ was 7.65% after a single oral dose in rats. The presence of some organic acids resulted in enhanced absorption of tin from the gastrointestinal tract (98).

From a single oral dose of 20 mg/kg body weight of radioactive ^{113}Sn(II) or ^{113}Sn(IV) given to 24-hour fasted rats, an absorption of 2.8% and 0.6%, respectively, was estimated. Changing the anion complement from fluoride to citrate had no effect on the absorption. When the anion was pyrophosphate, the absorption was lowered. This was explained by the greater tendency of pyrophosphate to form insoluble complexes with tin (82).

References concerning the absorption of $SnCl_2$ report limited absorption, usually less than 5% (66, 67, 100, 176).

In rats and cats, no tin was recovered from the urine 24 hours after the ingestion of orange juice containing high levels of tin (7-20 mg/kg body weight) derived from containers. 99% of the tin ingested was recovered from the faeces in the rats indicating a very limited oral uptake (8).

Male Wistar rats were given $SnCl_2$ in their drinking water at three different concentration levels (0.44, 1.11, 2.22 mM) for 1-18 weeks. The cumulative dose was 17.7 mmol/kg body weight (corresponding to 2100 mg Sn/kg body weight) in the highest dose group. Blood tin increased significantly after 1 week at the highest dose and remained at a level of 16-60 pmol/g (~16-60 nmol/l) or 2-5 times the concentrations in the control group. In conclusion, despite the fact that mucosal barrier mechanisms effectively prevent tin absorption they can be overcome by very high tin doses (155).

Rabbits fed 2 mg $SnCl_2$/kg body weight for 5 days had blood concentrations of 2.3 µg Sn/l (19.4 nmol/l) after 24 hours. After 120 hours the concentration was 0.7 µg/l (5.9 nmol/l). Tin was not detected in the controls (208).

Approximately 50% of the dose was absorbed by man, when 0.11 mg Sn/day was ingested with the diet (control). From a test diet containing an additional 50 mg Sn/day as $SnCl_2$, only 3% was absorbed (90).

Four human volunteers with Sn blood levels of < 2 ng/ml (17 nmol/l) each consumed 60 mg Sn in the form of fruit juice from an unlacquered can. Blood samples were taken after 2, 5 and 24 hours. The 2 females had detectable tin blood levels of 3 ng/ml (25 nmol/l) only in the 5-hour samples. The 2 males had peak blood tin concentrations of 4.7 ng/ml (40 nmol/l) after 2 hours, and 3.9 ng/ml (33 nmol/l) after 24 hours, respectively. Remaining blood samples had undetectable amounts of tin (22).

Generally, data suggest that the oral uptake of tin is low, but may depend on dose, anion, and the presence of other substances.

7.1.2 Uptake by inhalation

No valid data on the uptake of inhaled inorganic tin are available.

7.1.3 Skin uptake

No data on the absorption of tin from dermal exposure are available.

7.2 Distribution

7.2.1 Animal data

A single oral dose of 20 mg/kg body weight of radioactive ^{113}Sn(II) or ^{113}Sn(IV) as fluoride or citrate was given to female Charles River and Cox Charles River rats. The tissue distribution of tin after 48 hours as a percentage of the administered Sn(II) or Sn(IV), respectively, was as follows: skeleton 1.0 and 0.24%, liver 0.08 and 0.02% and kidneys 0.09 and 0.02%. Comparing tin in tissues after the 1st and after the 28th days of oral administration of 20 mg/kg body weight, increased levels were seen only in bone, and were approximately proportional to the total amount of systemic exposure. Regarding soft tissues, the authors concluded that only liver and kidneys are likely to accumulate significant amounts of tin as a result of the oral ingestion of tin salts. No ^{113}Sn was found deposited in the brains of rats 48 hours after a single oral dose of 4 mg, after oral daily doses of 20 mg/kg body weight, 6 days/week for 4 weeks or after a single intravenous dose of 0.4 mg Sn(II) or Sn(IV) (82). Apparently, the blood-brain barrier for the most part excludes tin (67, 77, 82, 155).

Studies on the retention of the radionucleide ^{113}Sn administered as $SnCl_2$ intra-peritoneally in rats showed that most of the tin retained in the body was deposited in the bone, followed by muscle, pelt, liver and kidney. In contrast to all other organs, the relative amount of tin (as % of administered ^{113}Sn) in bone increased considerably (from 50% on day 1 to 65% on day 141) during this experiment (67). A study of the pharmacodynamics of several tin compounds in rabbits, using Sn(II) chelates administered with technetium-99m-labelled chelates showed that free Sn(II) ions localise mainly in bone. The distribution of ^{113}Sn in bone was similar to that of calcium and other bone-seeking metal ions (49).

Chiba et al reported Sn concentrations in unexposed mice of 0.1-0.29 mg/kg wet weight, and 0.69 mg/kg dry weight in bone (32).

The concentration of tin in the tibias of rats fed diets supplemented with tin (> 100 mg Sn/kg diet) were more than 5 times greater than the concentrations in the kidneys and nearly 20 times greater than the concentrations of tin in the liver. No other organs were analysed. Tin accumulated in the tibia and kidney in a dose-dependent manner at ≥ 100 mg/kg diet (92).

After lifelong administration of 0.4 mg Sn/kg body weight/day as $SnCl_2$ in the drinking water of rats, there was no significant increase in tin concentrations of examined organs; liver, kidney, heart, lung and spleen. Bone was not examined (160). In mice, a similar experiment showed tin levels of 1.2-4.5 mg/kg tissue in kidneys, liver, heart, lung, spleen and thyroid as opposed to less than 0.5 mg/kg in the control group (158).

A 2-year carcinogenesis study of $SnCl_2$ administered in feed (1000 or 2000 mg $SnCl_2$/kg) showed a dose-dependent difference in the concentration of tin in examined organs, i.e bone, liver and kidneys. Tin levels in bone were 9 and 38 mg/kg (low and high dose) in male rats, and 23 and 41 mg/kg, respectively in female mice. Tin concentrations in the kidneys were 17 and 30 mg/kg in male rats, and 0.7 and 0.9 mg/kg in female mice. In the liver Sn concentrations were 0.2

and 0.4 mg/kg (male rats) and 0.4 and 0.5 mg/kg (female mice). Untreated rats and mice had tin concentrations that were below the detectable limits (124). Dose estimates in mg/kg body weight are given in chapter 10.4.

Some data indicate that the tin content in the thymus is higher than in other representative organs. In 4 young adult dogs the tin concentration in thymus was about twice the concentrations in the spleen or muscle (168). Analysis in unexposed adult Lewis rats, adult COBS mice and adult A/KI mice showed thymus Sn concentrations of 20, 5.5 and 4.3 mg/kg, respectively. Tin concentrated in the thymus gland as the gland atrophied with age (169).

In pregnant rats fed 20 mg Sn/kg body weight/day as radioactive SnF_2 or SnF_4, no tin was found in foetal or placental tissues on the 10th day of pregnancy. Only small amounts of tin were found in the foetuses on day 21 (82).

In contrast, foetal tin values were elevated (0.8-1.3 mg Sn/kg) in Sprague-Dawley rats on the 20th day of gestation when the maternal diets contained tin salts (125 mg-625 mg Sn/kg feed). Untreated rats had foetuses containing 0.64 mg Sn/kg (182). Assuming a daily feed intake of 20 g/day and a body weight of 250 g the doses given correspond to 10-50 mg Sn/kg body weight/day.

7.2.2 Human data

With increasing age, tin levels seem to increase in the human lung, possibly because of inhalation of tin from polluted air. The tin content in human tissues was high in the United States and low in Africa, and seldom present in newborn babies in the United States (159).

Hamilton and co-workers determined the Sn content in tissue samples from adults who had died in accidents and found the highest concentrations in lymph nodes, lung, liver and kidney (1.5, 0.8, 0.4, 0.2 mg/kg wet weight, respectively), while levels in muscle and brain were lower (0.07 and 0.06 mg/kg wet weight, respectively). In bone 4.1 mg/kg ash was reported (76).

Median tin content in adult subjects of the United States in adrenals, lung, liver, kidney, spleen, muscle, and brain was 5.1, 3.4, 1.8, 1.5, 0.8 and < 0.4, < 0.3 mg/kg wet weight, respectively (183). In healthy Japanese males, concentrations of 9.8 mg/kg dry weight in hilar lymph nodes and 1.5 mg/kg dry weight in lung tissue were reported (181).

Chiba et al reported tin concentrations determined by atomic absorption spectrometry in several human organs. Mean concentrations (mg/kg dry weight, males, n=11-13) were: liver 1.05, kidney cortex 0.83, heart 0.75, lung 0.45, bone (rib) 0.61, testis 2.08 (32). The Sn concentration in human liver specimens from the United States (n=11) ranged from 0.14-0.17 mg/kg wet weight (determined by neutron activation analysis), and in Japanese human liver specimens (n=23) from 0.08 to 1.12 mg/kg wet weight (determined by atomic absorption spectrophotometry) (27). Sherman et al found that human thymus had an average tin concentration of 12.8 mg Sn/kg wet weight in two children (167).

In unexposed humans, blood tin concentrations of 2-9 µg/l (17-76 nmol/l) are reported (detection limit 2 µg/l) (76, 97). Corrigan et al found background tin

concentrations of 11.6±4.4 nmol/l (mean±SD) in plasma and 21.7±6.7 nmol/l in red blood cells in 12 humans (8 women, 4 men, mean age 77.8 years) (38).

Background concentrations below 1 µg Sn/l (8.4 nmol/l) in serum and urine are reported (157, 189) and a 95th upper percentile of 20 µg Sn/l (168 nmol/l) in urine in a group of 496 United States residents (132).

Marked concentrations of Sn were found in the hilar lymph nodes (100 mg/kg dry weight) and lungs (100 mg/kg dry weight) of one chromate refining worker in autopsy analysis of the internal organs of 7 metallic workers and 12 unexposed males in Japan. Elevated concentrations of Sn compared to unexposed were also observed in lung, spleen, liver and kidney of chromate plating and chromate refining workers (181).

7.2.3 Conclusion

Inorganic tin distributes mainly to bone but also to the lung, liver, kidney, and lymph nodes. Some data indicate that tin may have a higher affinity to thymus than to other organs. Animal data suggest that inorganic tin does not easily pass the blood-brain barrier.

7.3 Biotransformation

Tin cations are not rapidly reduced or oxidised in the organism (87). Hiles found that the differences in the relative affinity of the kidneys and liver for Sn(II) and Sn(IV) indicate a valence stability of the administered tin. He concluded that tin was not rapidly oxidised or reduced during absorption and systemic transportation (82).

According to the authors, the marked differences observed between $SnCl_2$ and $SnCl_4$ in their effects on the immune response in C57BL/6J mice (see chapter 10.7) suggested that these two oxidation states are not readily interconverted *in vivo* (50).

7.4 Excretion

7.4.1 Animal data

Absorbed tin is mainly excreted via the kidneys (67, 82, 87, 100, 192).

After a single oral dose of 20 mg/kg body weight of ^{113}Sn(II) or ^{113}Sn(IV) as fluoride or citrate given to female Charles River and Cox Charles River rats, approximately 50% of the absorbed tin was excreted within 48 hours. After a single intravenous dose of 2 mg/kg of ^{113}Sn(II) or ^{113}Sn(IV), 35 and 40%, respectively, was excreted in the urine. 12% of the Sn(II) appeared in the faeces, but only 3% of the Sn(IV), indicating that the biliary route is more important for Sn(II) than for Sn(IV) compounds (82).

^{113}Sn was given as $SnCl_2$ orally, intraperitoneally or intravenously to mice, rats, monkeys and dogs. After parenteral administration, whole-body activities could be described by 4-component exponential expressions, similar for all species

studied. Intravenously injected $SnCl_2$ in rats (0.3 μCi/rat) was eliminated with half-times of 0.4, 4.9, 25 and 90 days (67).

The biological half-time has been estimated to 10-20 days for Sn(II) in rat liver and kidney. In bone the half-time of Sn(II) and Sn(IV) is approximately 20-100 days (17, 18, 66, 82).

7.4.2 Human data

Eight adult males ate food containing 0.11 mg or 50 mg of Sn/day (as $SnCl_2$). Their urinary excretion was 29±13 μg (mean±standard deviation) and 122 ±52 μg/day, respectively (90).

In a review article by Magos, it is stated that in humans, 20% of absorbed tin was cleared with a half-time of 4 days, 20% with 25 days, and 60% with 400 days. No further details are given (111).

8. Biological monitoring

Up to the present very little information is available about tin in human biological materials even though adequate ultra-sensitive analytical techniques (inductively coupled plasma mass spectrometry and radiochemical neutron activation) have been developed for the measurement of tin at background levels (157, 189).

A method of biological monitoring demands knowledge of the relationship between exposure, external dose, toxicokinetics, internal dose and effects. Such relationships have not yet been established for inorganic tin and no relevant methods of biological monitoring are available.

9. Mechanism of toxicity

Even though tin is ubiquitous in animal tissues, no essential function has yet been shown beyond doubt to be tin-dependent (2, 24, 54, 82, 121, 162-164, 169, 185, 204).

Studies in animals show that inorganic tin interferes with the status of copper, iron and zinc, which may be due to impaired absorption of these metals (91, 134).

Haem is essential for cell respiration, energy generation and oxidative bio-transformation. Metal ions directly regulate cellular content of haem and haem proteins by controlling production of δ-aminolevulinic acid (ALA) syntethase and haem oxygenase. Thus, metal ions may impair the oxidative function of cells, particularly those dependent on cytochrome P-450. As a result, the biological impact of chemicals that are detoxified or metabolically transformed by the P-450 system is greatly altered (55, 112). Chelation of the metal ion into the porphyrin ring is not necessary in order to regulate the enzymes of haem synthesis and oxidation (113).

SnF_2 and other tin dihalides form complexes with haemoproteins such as hepatic cytochrome P-450 and haemoglobin (41).

Substitution of tin for the central iron atom of haem leads to a synthetic haem analogue (tin(IV)-protoporphyrin) that regulates haem oxygenase in a dual mechanism, which involves competitive inhibition of the enzyme for the natural substrate haem and simultaneous enhancement of new enzyme synthesis (51, 154).

$SnCl_2$ (~ 3-30 mg Sn/kg body weight, single subcutaneous dose) and Sn(II) tartrate (~ 9 mg Sn/kg body weight, single intraperitoneal dose) induce haem oxygenase in rat liver and kidney (55, 96, 99, 112). The Sn(II) ion is more potent as an inducer of haem oxygenase-1 in rat cardiac tissue than is the Sn(IV) ion, administered subcutaneously as tin citrate (single dose, 60 mg/kg of Sn) (119).

Treatment of young spontaneously hypertensive rats with $SnCl_2$ (63 mg/kg body weight/day of Sn, subcutaneously, twice weekly for 8 or 15 weeks), which selectively depletes renal cytochrome P-450 through increasing renal haem oxygenase activity, restores elevated blood pressure to normal (59, 102, 153).

Shargel and Masnyj found that the inhibition of hepatic mixed function oxidase enzyme activity in Charles River CD albino rats by SnF_2 (30 mg Sn/kg body weight, single intraperitoneal dose) was primarily due to the Sn(II) cation (165).

The activity of δ-aminolevulinic acid dehydratase (ALAD) in the erythrocytes of Harlan-Sprague-Dawley rats fed 2 g $SnCl_2$/kg diet for 21 days was 55% of that found in the controls (92). ALAD activity was clearly decreased in Wistar rats after 2 doses (total 4 mg Sn/kg) of $SnCl_2$ subcutaneously, intraperitoneally or intragastrically every other day, whereas 7 doses (total 14 mg/kg) resulted in almost complete enzyme inhibition (206). ALAD was inhibited by $SnCl_2$ but not by $SnCl_4$. The inhibition was rapidly reversed (28, 30). ALA synthetase and ALAD were inhibited by tin(II) tartrate (55).

Sn(II) concentrations of 1.5 µmol/l increased the activity of isolated and purified ALAD from human red blood cells by approximately 30%. At greater concentrations, tin was an inhibitor of the enzyme, probably due to binding to allosteric sites (48).

A protective effect of zinc with respect to ALAD activity in blood and ALA levels in urine was observed after combined administration of $SnCl_2$ and $ZnSO_4$ in rabbits (33). One subunit of the ALAD enzyme contains one zinc atom and eight sulphhydryl groups (186). Chiba and Kikuchi postulated that tin attacks one sulphhydryl group and binds weakly at the zinc-binding site of the enzyme (29). Injection of selenium (Na_2SeO_3) intraperitoneally simultaneously with $SnCl_2$ in ICR mice, completely protects ALAD from being inhibited by Sn. It has been suggested that selenium protects essential thiol groups in ALAD that are otherwise blocked by tin (25, 26, 31).

Adverse effects of feeding rats diets containing $SnCl_2$ (100 mg Sn/kg of food) for 4 weeks include copper depletion and reduction in hepatocellular antioxidant metalloenzyme activities of superoxide dismutase and glutathione peroxidase. Impairment in hepatocellular antioxidant protection favours the peroxidation of fatty acids (144).

Tin(II) tartrate (20 mg Sn/kg, single intraperitoneal injection) caused a decrease in glutathione in partially hepatoectomised Sprague-Dawley rats, allowing an increase in lipid peroxidation damaging the hepatocytic membranes (53). The inhibitory effect of tin on SH-containing enzymes, particularly hepatic glutathione reductase and glucose 6-phosphate dehydrogenase, may be caused by the SH-group forming a metal mercaptide complex with coordinate covalent bonds leading to decreased catalytic activity. The depression in enzyme levels may also be due to the interaction of tin with the biological ligands not directly involved in the active centre of the enzyme but through the formation of an unacceptable substrate complex for enzyme catalysis (56).

$SnCl_2$ given intravenously in mice resulted in significant inhibition of the P-450 cytochrome dependent hepatic drug metabolising enzymes such as azo-reductase and aromatic hydroxylase (19).

Pretreatment of mice with $SnCl_2$ (50 mg/kg body weight, daily for 2 days) induced the coumarin 7-hydroxylase in liver and kidney (58).

$SnCl_2$ (2 mg Sn/kg body weight/day) given orally had inhibitory effects on calcium content, acid and alkaline phosphatase activity and collagen synthesis in Wistar rat femoral bone (197-200). $SnCl_2$ orally (60 mg Sn/kg body weight/day for 3 days) in rats also suppressed insulin secretion and inhibited hepatic phosphorylase activity (201, 202), active transport of calcium and mucosal alkaline phosphatase activity in the duodenum and increased bile calcium contents (195, 203).

$SnCl_2$ exposure caused a dose-dependent increase in the cerebral and muscle acetylcholinesterase activity in rats given 1.11 and 2.22 mM in drinking water (highest cumulative dose corresponding to 2100 mg Sn/kg body weight) whereas no effect was seen at 0.44 mM. The authors concluded that neurochemical effects of $SnCl_2$ seem to occur only with extreme brain tin burdens and are therefore probably not relevant (155).

Studies of frog neuromuscular transmission suggest that activation of the N-type calcium channel is involved in the $SnCl_2$ induced increase in calcium entry into the nerve terminals (79). $SnCl_2$ itself may facilitate the transmitter release from nerve terminals in the mammalian (mouse) as well as in the amphibian (frog) species (80).

An intraperitoneal dose of $SnCl_2$ (5-30 mg Sn/kg) suppressed gastric secretion. The mechanism of inhibition was assumed to be associated with an inhibition of nerve transmission as well as reduction of gastrin release from G cells (194, 196).

Corrigan et al reported significant higher plasma and red blood cell Sn concentrations in patients with Alzheimer's disease (plasma 21.6 and red blood cells 32 nmol/l) than in those with multiinfarct dementia (12.4 and 19.9 nmol/l) and controls (11.6 and 21.7 nmol/l) (38, 39). There were negative correlations between tin levels and the red blood cell polyunsaturated fatty acid levels in the Alzheimer patients, and the authors suggested that Sn is involved in lipid peroxidation in that illness (39).

In conclusion, tin cations have the ability to influence the biosynthesis and induce the biodegradation of cytochrome P-450. Some data indicate that Sn(II) may be more potent in that respect than Sn(IV). In addition, tin seems to have an inhibitory effect on the activity of several other enzymes. Thus, tin may alter drug metabolism. An effect of $SnCl_2$ on nerve transmission is reported.

10. Effects in animals and in vitro studies

10.1 Irritation and sensitisation

Solutions of 1% or 2% $SnCl_2$ and 0.25% or 0.5% SnF_2 in distilled water on pieces of gauze were applied to the abraded skin of rabbits for 18 hours. Intraepidermal pustules with complete destruction of the epidermis were induced. The stratum corneum remained intact. Sites patch tested with 0.5% $SnCl_2$ or 0.1% SnF_2 (water) showed no pustules but a polymorphonuclear infiltration of leucocytes. When the solutions were applied to intact skin there was no effect (174).

Larsson et al determined non-irritant levels of $SnCl_2$ and $SnCl_4$ in alcohol on skin (5%) and on oral mucosa (3% and 0.05% respectively) in Sprague-Dawley rats. Each test solution was openly applied to the test site for 1 minute, followed 6 hours later by histologic examination of the tissue response. Lesions of allergic contact type could not be found in the oral rat mucosa (103).

An irritating effect of $SnCl_2$ feeding on the alimentary tract of Wistar rats was reflected by a diffusely reddened gastric and duodenal mucosa as well as by mucosal hypertrophy and hyperplasia visible in the entire small bowel at autopsy (47) (for dose regimen see chapter 10.3).

Janssen et al found ridge-like villi, increased migration of epithelial cells along the villus, a decreased number of villi per unit surface and increased total length of the rat small intestine after feeding rats 250 and 500 mg $SnCl_2$/kg diet (88).

Metallic tin was non-toxic in a study using human epithelium-fibroblast co-culture for assessing mucosal irritancy of metals used in dentistry. Cell viability and prostaglandin E_2 release from the cultures were used as markers for the irritative potential of the test materials and these markers were not significantly reduced compared to untreated controls (156).

When guinea-pigs were exposed by inhalation to $SnCl_4$ at 3000 mg/m^3 for 10 minutes daily for "several months", only transient irritation of the eyes and nose developed (133).

10.2 Effects of single exposure

$SnCl_2$ (100 µmol/l) as well as SnO_2 (up to 1000 µmol/l) were nontoxic towards rabbit alveolar macrophages in single-element incubations (101), but there was a synergistic effect on the depression of superoxide anion radical release in solutions where Sn^{2+} was combined with Cd^{2+} or Ni^{2+} (71).

Silica containing 97% crystalline SiO_2 (50 mg), SnO_2 (50 mg) or a mixture of SnO_2-SiO_2 (25 mg each in 1 ml saline) dust were instilled intratracheally in rats. Autopsies were performed on day 10, 20 and 30. The *in vivo* cytotoxicity (cellular metabolic activity, lysozyme content and total protein content in rat broncho-alveolar lavage), interleukin-1 release from rat pulmonary cells and fibrogenic effects (lung dry weight, collagen content of the whole lung and pathological grading) after dusting correlated well with the free SiO_2 content in the dusts. SnO_2 tended to inhibit the effect of SiO_2 in the rat lungs. The effects of SnO_2 alone were poorly described (190).

Rats were experimentally exposed to 50 mg of metallic tin dust in saline from a tin smelting works by a single intratracheal administration. Four months later the authors described X-ray changes of widespread tiny densities throughout the rat lungs; changes which they found similar to the X-ray changes earlier seen in workers exposed to the same compound. Histologically, there was no fibrous response of any kind up to a year in the rats (146).

Intraperitoneal injections in guinea pigs with dusts from various stages in the process of a foundry reducing Bolivian tin ore concentrate to metal bars caused "an inert type of reaction", defined by the authors as dust gathered in flattened nodules with no change for months, histologically abundant macrophages with subsequent fibroblastic reaction, and no necrosis (131).

Data on the lethal dose for 50% of the exposed animals at single administration (LD_{50}) for $NaSn_2F_5$ and $SnCl_2{\cdot}2H_2O$ are given in Table 6. Major toxic symptoms in rats and mice were ataxia, general depression, fore and hindleg weakness advancing to flaccid paralysis prior to death. Rats dosed orally developed diarrhoea. Rats, given either Sn compound, displayed swollen and discolorated kidneys by autopsy on the 4th day, microscopically tubular necrosis and tubular regeneration. Further data from this experiment suggest that both F and Sn contribute to the toxicity of $NaSn_2F_5$ (37).

Rats receiving $NaSn_2F_5$ (~23 mg Sn/kg) or $SnCl_2{\cdot}2H_2O$ (~23 mg Sn/kg) intraperitoneally showed necrosis of the proximal tubules and regeneration of tubular cells with scar formations, while rats given NaF showed limited focal lesions (205).

A study by Chmielnicka et al demonstrated a clear derangement of the various stages in the haem synthesis in rabbits after oral administration of a single dose of $SnCl_2$. This effect was seen at a dose of 100 mg Sn/kg body weight, but not at 10 mg Sn/kg. A protective effect of zinc with respect to ALAD activity in blood and ALA levels in urine was observed after the combined administration of tin and zinc (33).

Male Swiss Webster mice given single intravenous doses of some radio pharmaceuticals containing $SnCl_2$ as a reducing agent, showed a significant inhibition of P-450 cytochrome dependent hepatic drug metabolising enzymes such as azo-reductase and aromatic hydroxylase at a dose level of ~ 0.1 mg Sn/kg body weight of $SnCl_2{\cdot}2H_2O$. The cytochrome P-450 content was also significantly reduced (19).

Table 6. 24-hour LD_{50}-data in mice and rats treated with $NaSn_2F_5$ or $SnCl_2 \cdot 2H_2O$ (37).

Species	Administration mode	LD_{50} (mg Sn/kg)
$NaSn_2F_5$		
Rats, male	intravenous	9
Rats, female	intravenous	9
Mice, male	intravenous	13
Rats, male	intraperitoneal	50
Rats, female	intraperitoneal	43
Mice, male	intraperitoneal	54[a]
Rats, male	oral	383
Mice, male	oral	396
Rats, male	oral (fasted)	149
Rats, female	oral (fasted)	146
$SnCl_2 \cdot H_2O$		
Rats, male	intravenous	15
Rats, male	intraperitoneal	136
Rats, male	oral	1678
Rats, male	oral (fasted)	1197

[a] 48-hour data given.

Gross and histological examination of various tissues from three species of animals showed no fibrosis, neoplasia, or other adverse effects following intravenous administration of SnO_2 or Sn particles at high doses. The species, doses, and times from dosing to examination were: rats 250-1000 mg SnO_2/kg, 200-800 mg Sn/kg, 4-26 months; rabbits 250 mg SnO_2/kg, 200 mg Sn/kg, 6-26 months; and dogs, similar doses as rabbits, 4-5 years (62).

10.3 Effects of short-term exposure

Weanling Wistar rats were fed diets containing 0, 0.03, 0.10, 0.30 or 1.00% of various salts or oxides of tin *ad libitum* for periods of 4 or 13 weeks. End points examined included mortality, body-weight change, diet utilisation, measurements of blood, urine and biochemical parameters, organ weights and gross and micro-pathology. No adverse effects were noted with any levels of Sn(II) oleate, SnS, SnO or SnO_2. Severe growth retardation, decreased food efficiency, slight anaemia and slight histological changes in the liver were observed with ≥ 0.3% $SnCl_2$, Sn(II) orthophosphate, sulphate, oxalate and tartrate. The no observed effect level (NOEL) of tin salts examined was 0.1%, or 22-33 mg Sn/kg body weight/day, in an unsupplemented diet, which contained a liberal amount of iron and copper. The authors stated that the level might be lower in diets marginal in iron and copper. Dietary supplements of iron had a markedly protective effect against tin-induced anaemia, whereas a decrease in dietary iron aggravated the condition. The growth depression caused by tin was not alleviated by enriching the diet with iron and copper (45, 46).

In rats, ≤ 100 mg Sn/kg diet as $SnCl_2$ (~ 7 mg Sn/kg body weight/day) for 27 days had little effect on the metabolism of copper. Rats fed 500 mg Sn/kg diet (~39 mg Sn/kg body weight/day) had reduced levels of copper in plasma, liver and kidneys. Only small changes in iron metabolism were observed. Tin levels of ≥ 500 mg/kg diet were associated with numerous disturbances in the metabolism of zinc. Moderate variations in dietary zinc levels did not significantly affect the levels of minerals in tissues (91, 92).

Dietary levels of 100 mg Sn/kg diet in weanling rats for 4 weeks reduced copper levels significantly in the duodenum, liver, kidney and femur, and zinc levels in the kidney and femur (140, 144).

Oral administration of $SnCl_2$ (2 mg Sn/kg body weight/day) in rabbits for 1 month decreased zinc and copper concentration in bone marrow and increased iron concentrations in liver and kidneys (207). Beynen et al found that iron status (tissue iron, haemoglobin, hematocrit, red blood cell count, plasma iron, total iron binding capacity and transferrin saturation) in rabbits was not influenced by dietary tin concentrations < 100 mg Sn/kg diet as $SnCl_2$ for 28 days. Higher dietary intake of tin caused a decrease in these parameters. Food intake and body weights were not reported (12).

A study in Wistar rats fed on diets containing various concentrations of tin (1, 10, 50, 100 and 200 mg Sn/kg as $SnCl_2$) for 28 days showed that iron, copper and zink tissue and plasma concentrations were seemingly unaffected at 1 mg and slightly decreased at 10 mg Sn/kg diet (~ 0.7 mg Sn/kg body weight/day). Greater effects were seen at 50 mg/kg diet (~ 3.5 mg Sn/kg body weight/day). The blood haemoglobin concentration and percentage transferrin saturation decreased in a linear manner as the level of dietary Sn increased. Analysis of variance and test for linear trend was used for the statistical evaluation (134).

Growth retardation, slight anaemia, increased relative weights of the kidneys and liver, irritation of the gastrointestinal tract, "mild" histological changes in the liver and varying degrees of pancreatic atrophy were observed in Wistar rats fed $SnCl_2$ for 13 weeks (gradually increased from 163 mg Sn/kg body weight/day in week 0-4 to 310 mg Sn/kg/day in week 8-13) (47).

Janssen et al investigated the effects of 0, 250 or 500 mg Sn/kg diet (as $SnCl_2$) in a 4-week study on weanling Wistar rats. Haemoglobin was decreased and body weights reduced in a dose-related way in the tin-fed groups. Crypt depth, villus length and cell turnover were increased in parts of the intestine. In week 4, the estimated doses of tin were about 25 and 50 mg Sn/kg body weight/day, respectively (88).

Oral doses of 2 mg Sn/kg body weight/day as $SnCl_2$ for 5 days did not affect the process of haem biosynthesis in rabbits. Examined indices were ALAD in whole blood, liver, kidneys, brain, spleen, and bone marrow, concentrations of free erythrocyte protoporphyrins, activity of ALA synthetase in the liver and bone marrow, urine ALA, and co-proporphyrins (208).

In rabbits, a daily oral dose of 10 mg Sn/kg body weight as $SnCl_2 \cdot 2H_2O$ for 4 months caused transient anaemia in the 6-10th week. A transient high iron

serum concentration, a high total iron binding capacity and saturation index were also observed (34).

A 30-day toxicity study of $NaSn_2F_5$ in albino Wistar rats resulted in depressed growth in a dose-related manner after 15 and 30 days. The daily oral doses of $NaSn_2F_5$ were 20, 100 and 175 mg/kg body weight. Degenerative changes of the proximal tubular epithelium of the kidneys were observed in 15-20% of the animals in the groups receiving 175 mg/kg. At 15 days a dose-related decrease in haemoglobin was found, significant only in males in the two highest dose groups. Serum glucose levels were decreased at both 15 and 30 days, possibly related to reduced food intake. The dose of 20 mg/kg (~13.4 mg Sn/kg body weight) produced only minimal toxicity according to the authors (36).

The distal epiphysis compressive strength decreased significantly in the femoral bone in Wistar rats administered 300 mg Sn/kg drinking water (as $SnCl_2$) and laboratory chow contaminated with 52.4 mg Sn/kg of diet for 4 weeks. Feed and water intake was not reported (127).

The calcium content in the tibia of rats fed 100 mg Sn/kg diet as $SnCl_2$ (~7 mg Sn/kg body weight/day) for 28 days was decreased (92).

Oral doses of 1.0 mg Sn/kg at 12-hours intervals for 28 days given to male Wistar rats produced an increase in the Sn content of the femoral diaphysis and epiphysis, thus resulting in decreased calcium content in bone, and also in decreased acid and alkaline phosphatase activities in the femoral epiphysis (198).

The dose-effect relationship of oral doses of $SnCl_2$ on biochemical indices in Wistar rats was studied by Yamaguchi et al. Oral doses of 0.3, 1.0 and 3.0 mg Sn/kg body weight were given twice daily for 90 days. The 6.0 mg/kg/day dose caused significant decreases in femur weight, calcium concentration, lactic dehydrogenase and alkaline phosphatase activities in serum, succinate dehydrogenase activity in the liver, and calcium content and acid phosphatase activity in the femoral diaphysis and epiphysis. The 2.0 mg/kg/day dose produced a significant reduction in succinate dehydrogenase activity in the liver, and the calcium content and acid phosphatase activity in the femoral diaphysis. At the 0.6 mg/kg/day dose, a slight non-significant decrease in calcium content in the femoral epiphysis was observed. The results suggested that the LOEL of inorganic tin orally administered would be 0.6 mg/kg body weight/day (197).

In conclusion, depressed growth, anaemia, a decreased calcium content in bone, interference with the status of iron, copper and zink, and decreased enzyme activities are reported in animals after short term administration of some tin compounds including $SnCl_2$. The anion may influence toxicity.

10.4 Effects of long-term exposure and carcinogenicity

Long Evans rats fed 5 µg Sn/ml (~0.4 mg/kg body weight/day) as $SnCl_2$ in drinking water from weaning until natural death were compared to an equal number of controls. Growth was not affected. Significantly lessened longevity was found in female rats given tin. There were increased incidences of fatty

degeneration of the liver and of vacuolar changes in the renal tubules in the animals fed tin. These effects were not observed in Charles River mice. Tin was not tumorigenic or carcinogenic (158, 160).

From life term studies on the effect of trace elements on spontaneous tumours in Long-Evans rats it was concluded that the oral ingestion of tin cannot be considered carcinogenic at the given dose, 5 µg $SnCl_2$/ml drinking water or 0.34-0.38 mg Sn/kg body weight/day. According to the authors this corresponds to approximately 25 mg of tin daily for a 70-kg man (95).

Stoner et al reported no significant difference in lung tumour production in strain A mice compared to controls after multiple intraperitoneal injections of $SnCl_2$ for 30 weeks. Total doses given were 240, 600 and 1200 mg/kg body weight and the numbers of surviving animals/initial number were 18/20, 12/20, 4/20, respectively (175).

Male and female Fischer F344 rats and B6C3F1 mice received 1000 (low dose) or 2000 mg (high dose) $SnCl_2$/kg food for 105 weeks. Feed and water were available *ad libitum*. Mean body weight gain and feed consumption of dosed and control rats were comparable. Doses in mg Sn/kg body weight/day are calculated from feed consumption and body weights for male rats and female mice (Table 7). Survival appeared to depend on the dose for female mice (controls 38/50, low dose 33/50, high dose 28/50). For male rats survival rates were 37/50, 39/50, 30/50, respectively. Primary tumours occurring with statistically significant changes in incidence are summarised in Tables 8 and 9. Such tumours occurred in male rats and female mice only. C-cell adenomas of the thyroid gland were significantly increased in low-dose male rats. Thyroid C-cell adenomas and carcinomas (combined) occurred in male rats with a significant positive trend and the incidence in either dosed group was significantly higher than seen in the controls. Adenomas of the lung in male rats occurred with a significant positive trend. The incidence of female mice with either hepatocellular adenomas or carcinomas exhibited a significant dose-related trend, and histiocytic lymphomas in female mice also occurred with a significant positive trend. However, compared to historic control incidences for this laboratory in about 300 animals, the tumour incidence was not significantly increased except for male rats at the low dose.

Lack of dose-response relationship, variable (7-20%) occurrence of these tumours in untreated animals and no increase in hyperplastic changes in the tin-treated animals weaken a possible carcinogenic effect of inorganic tin.

Based on this study, $SnCl_2$ given orally in feed was judged by the NTP not to be carcinogenic for male or female Fischer 344 rats or B6C3F1 mice, although C-cell tumours of the thyroid gland in male rats may have been associated with the administration of the chemical (124).

Tin foil imbedded subcutaneously in Wistar rats did not cause any tumour induction (129).

Table 7. Calculated doses in the NTP 105-week study (124).

Species	Week	Low dose (mg Sn/kg bw/day)	High dose (mg Sn/kg bw/day)
Male rats	5	41	89
	25	30	68
	62	26	55
	104	20	35
Female mice	5	182	348
	26	134	272
	65	92	203
	104	137	290

Table 8. Primary tumours in male rats fed $SnCl_2$ in the NTP 105-week study (124).

Male rats	Control diet	Low dose	High dose
C-cell-adenoma (thyroid)	2/50	9/49[a]	5/50
C-cell-adenoma or carcinoma (thyroid)	2/50	13/49[a]	8/50[a]
Lung adenoma[b]	0/50	0/50	3/50

[a] $p<0.05$, Fisher´s Exact test.

[b] $p<0.05$, Cochran-Armitage Trend.

Table 9. Primary tumours in female mice fed $SnCl_2$ in the NTP 105-week study (124).

Female mice	Control diet	Low dose	High dose
Hepatocellular adenoma or carcinoma[b]	3/49	4/49	8/49
Histiocytic malignant lymphoma[b]	0/50	0/49	4/49

[b] $p<0.05$, Cochran-Armitage Trend-

Intracranial implants of metallic tin cylinders in Marsh mice gave a local response of gliosis, but no fibrous capsules or related neoplasms (13). Intrathoracic injection of tin needles in Marsh mice resulted in persisting engulfed needles by giant cells with some adjacent nodular fibroplasia and a new network of capillaries. The metal particles were not tumorigenic (14). Intraperitoneal implantation of tin cylinders led to development of fibrous capsules (15).

The available animal data suggest that metal tin and $SnCl_2$ are not carcinogenic although one study concludes that C-cell tumours of the thyroid gland in male rats may have been associated with the administration of $SnCl_2$.

10.5 Mutagenicity and genotoxicity

In the Ames test using various *Salmonella* strains (TA 1535, TA 100, TA 1538, TA 98 and TA 1537), SnF_2 was slightly mutagenic in strain TA 100, but only in the presence of a metabolic activation system (S9 liver fraction from Aroclor-pretreated rats) and on one type of medium (72). $SnCl_2$ tested in the same strains, with or without the activation system, was not mutagenic in doses of 0.033-10 mg/plate (137).

Kada et al reported the absence of effect ($SnCl_2$, $SnCl_4$ and $SnSO_4$) in the Rec-assay in *Bacillus subtilis*, but indicated a high toxic effect of $SnCl_2$ and $SnCl_4$ on

bacteria (94). $SnCl_4$ tested in the Rec-assay test with *Bacillus subtilis* in concentrations up to 10 mg/test showed no genotoxicity (75).

Strains of *Escherichia coli* presenting mutations on specific genes for the repair of DNA were treated with $SnCl_2$ (5-75 µg/ml, corresponding to 26-395 µmol/l). The results indicate that $SnCl_2$ could be capable of inducing and/or producing lesions in DNA. This capability was confirmed by the lysogenic induction of *E. coli* K 12 and by microscopic observation of *E. coli* B filamentation (9).

The presence of catalase, reactive oxygen scavengers or metal-ion chelators in *E. coli* cultures treated with $SnCl_2$ abolished the lethal effect and suggested the participation of reactive oxygen species in the toxicological effect of $SnCl_2$ (42).

Survival rates in *E. coli* were most affected in the strain double mutant on specific genes for the repair of DNA damage after incubation with $SnCl_2$. Near-UV illumination inhibited the lethal effect of $SnCl_2$ in *E. Coli* AB 1157 (wild type strain) (170).

The SOS chromotest, a simple colorimetric assay of the induction of the bacterial gene sfiA in *E. coli*, indicated effects at 2-3 mmol/l of $SnCl_2$, but the interpretation was difficult because of a clear cyotoxic effect on the bacteria (128). $SnCl_4$ did not produce DNA-damage in the SOS chromotest (75).

$SnCl_2$ at concentrations of 50, 150, 350 and 500 µmol/l produced dose-related DNA damage, as detected by alkaline sucrose gradient analysis in Chinese hamster ovary (CHO) cells. Treatment of cells with Sn(IV) as $SnCl_4$ produced no such DNA damage. There was no loss in colony formation 6 days after either treatment (116).

Tin(II) as $SnCl_2$ (5, 10, 25 or 50 µmol/l) was readily taken up by human white blood cells and caused a dose-dependent increase in DNA strand breaks that was more extensive than equimolar amounts of chromium(VI), a known carcinogen and DNA damaging agent. Exposure to tin(II) also interfered with the lymphocytes´ ability to be stimulated by the polyvalent mitogen Concanavalin A. Tin(IV) as $SnCl_4$ did not cause DNA damage and, in contrast to other studies, was not taken up by cells. The authors state that the relevance of these findings to human health is not known. The values for tissue bound tin from environmental exposure are 2-3 orders of magnitude below the levels at which DNA damage was observed *in vitro* after an exposure of 30 minutes (115).

$SnCl_4$ at 10 and 20 µg/ml (38-76 µmol/l) increased the frequency of chromosomal aberrations, micronuclei and sister chromatide exchanges to a statistically significant level in human lymphocytes *in vitro* when compared to the untreated control. Mitotic index and cell cycle kinetics were depressed. The effects were directly proportional to the concentrations used (179).

Cultures of human peripheral blood lymphocytes from 27 male donors were incubated with 2 or 4 µg $SnCl_4 \cdot 5\ H_2O$/ml (5.7-11.4 µmol/l) for 70 hours. Both doses of $SnCl_4$ induced chromosome aberrations in the cells. Approximately 11 and 13% of the cells, respectively, were damaged compared to 4.5% in the control cultures. Sister chromatid exchanges were about twice as frequent in both tin cultures compared with controls. A reduction in cell cycle kinetics (replicative

index) was observed (70). Incubation of human lymphocytes from 52 donors with $SnCl_4$, 4 µg/ml (11.4 µmol/l, assuming crystallisation water) for 48 hours, resulted in significant elevations of damaged cells, chromosome aberrations, micronuclei formation and depression of the mitotic index in both sexes (69).

Intraperitoneal doses of 9.8-39.5 mg SnF_2/kg body weight at 0 and 24 hours in NMRI-mice gave no significant increase in micronucleated polychromatic erythrocytes from mouse bone marrow. In *Drosophila melanogaster* fed 1.25 mM SnF_2 in 5% saccharose, no significant increase in sex-linked recessive mutations was observed (72). $SnCl_2$ was non-genotoxic in the *Drosophila* wing spot test (184).

To conclude, *in vitro* studies have shown that $SnCl_2$ causes DNA damage in human white blood cells, CHO cells, and in *E. coli*. The effects on human white blood cells and CHO cells were dose-dependent. DNA damage in human lymphocytes *in vitro* has been shown after treatment with $SnCl_4$.

10.6 Reproductive and developmental studies

Theuer et al investigated the placental transfer in Sprague-Dawley rats given various fluorides and tin salts (SnF_2, $NaSn_2F_5$, $NaSn_2Cl_5$) (125 mg-625 mg Sn/kg feed). Untreated rats had foetuses containing 0.64 mg Sn/kg. Foetal tin values were found to be elevated (0.8-1.3 mg Sn/kg) when the maternal diets contained tin salts. The greatest number of foetal resorptions was found in groups fed sodium pentafluorostannite, but the observation was not considered toxicologically significant (182).

10.7 Other studies

Intraperitoneal or intravenous injections of metallic tin powder (200 mg in saline) in Lewis rats produced a striking plasmacellular hyperplasia in the draining lymph nodes and spleen (106, 108). Depending on the genetic characteristics of the subjects, the lymph node response to metallic tin in rats varied from a slight banal response to insoluble foreign particles, to an exuberant granulomatous hyperplasia (August rats), and intense plasmacellular hyperplasia (Lewis rats and F1 hybrids of Lewis rats) (105). Pretreatment with tin salts in drinking water prevented the plasmacellular response to subsequently injected metallic tin as long as 2 months after the pretreatment (107). The production of plasma cell hyperplasia by metallic tin and the prevention of such response by tin salts are unique to this metal (104).

The effect of tin compounds on the immune response to sheep red blood cells in mice was studied. $SnCl_2$ and $SnCl_4$ (approximately 5 and 3.5 mg Sn/kg body weight, respectively) intraperitoneally in mice had a number of effects on parameters reflecting humoral and cell-mediated immune responses (50).

Subacute administration of $SnCl_2$ (~ 20 mg Sn/kg body weight for 3 days) intraperitoneally in mice suppressed parameters of both the primary and secondary immune response, suggesting that tin supresses part of the immune response in

which IgM antibody production is important, and that the IgG production in the primary response is suppressed or delayed (81).

Jones et al found a significant increase in LD_{50} values in ICR mice following intraperitoneal injections of salts of several metal ions including Sn(II) (as $SnCl_2$) subsequent to pretreatment with the same ion (93).

Intratracheally injected $SnCl_2$ in saline followed by bacterial infection (aerosolised Group C *Streptococcus* sp.) increased the mortality with 36 and 87% in mice at a single dose of 0.01 and 0.1 mg, respectively (~ 6 and 60 µg Sn, corresponding to 0.24 and 2.4 mg Sn/kg body weight). Similar effects were seen with e.g. fly ashes, carbon, bentonite**,** and a number of metal oxides. According to the authors, in the case of soluble metals, inhalation exposure yields similar results (78).

In conclusion, data imply that tin chlorides have an effect on mouse immune response. Injections of metallic tin in the rat seem to produce a plasmacellular hyperplasia in lymph nodes and spleen, an effect that may be prevented by pretreatment with tin salts.

11. Observations in man

11.1 Effects by contact and systemic distribution

11.1.1 General effects

In 10-11 humans, $SnCl_2$ (36 mg Sn) given with $^{65}ZnCl_2$ solutions (0.5, 4 and 6 mg of Zn, respectively) or with turkey test meals (4 mg of ^{65}Zn) inhibited ^{65}Zn absorption, measured by whole body counting of the retention of ^{65}Zn after 7-10 days. According to the authors, the dose required to inhibit Zn absorption under the conditions in this study were well in excess of those ordinarily found in the diet (188). Solomons et al were unable to demonstrate clear inhibition of the plasma appearance of zinc after 1- 4 hours in human volunteers ingesting a single dose of 12.5 mg Zn and 25, 50 and 100 mg Sn given as $SnCl_2$ (172).

11.1.2 Skin

Patch tests with metallic tin in 73 nickel-sensitive patients revealed 6 positive allergic and 4 doubtful reactions. The low frequency of doubtful reactions made it unlikely that metallic tin is irritant (117).

Patch testing with 1% $SnCl_2$ in petrolatum and a tin disc suggested that some patients are sensitised to tin. A low frequency of doubtful reactions suggested that metallic tin and $SnCl_2$ at 1% were non-irritating. However, irritant reactions were frequent in patients tested with 10% and 5% $SnCl_2$ in petrolatum (44).

In 199 patients with suspected allergic reactions to metals, 13 had positive patch tests with 2% $SnCl_2$ in petrolatum (26 metals tested) (142).

One out of 50 craftsmen in the ceramics industry had a positive reaction by patch testing with 2.5% elementary tin in petrolatum (68).

A worker producing metal patterns for body parts on trucks, exposed to airborne dust from an alloy that used to contain tin, had dermatitis around the eyes, forehead and wrists. He had a positive patch test to 1% $SnCl_2$ in petrolatum. The case is reported as an occupational allergic dermatitis due to tin (122).

In conclusion, in a few studies positive patch test reactions to metallic tin and $SnCl_2$ but only one case of occupational allergic dermatitis are reported. Considering the widespread use of tin and the unclear clinical relevance of the positive patch test reactions it is unlikely that tin is a contact allergen.

11.1.3 Respiratory system

No clinical or experimental reports on acute effects by inhalation of inorganic tin have been identified. Metal fume fever caused by inorganic tin has not been documented (16).

11.1.4 Gastrointestinal tract

Several authors report acute gastrointestinal illness following the intake of canned fruit or fruit juice.

As a result of the detinning of unlacquered cans by corrosion 200-2000 mg Sn/kg of food have been reported (23, 73). Estimated doses ingested are 30-200 mg during a short period of time, i.e. drinking a glass of tomato juice (5, 118, 178, 191). Symptoms most frequently reported are nausea, abdominal cramps, vomiting and diarrhoea. Median incubation period was 1 hour (range 15 minutes to 14 hours), and median duration of symptoms 12 hours (range 0.5 hours to 3 weeks) (5).

Toxic signs (nausea and diarrhoea) followed the drinking of tin-containing fruit juices by 5 human volunteers only at Sn levels of approximately 1400 mg/l, corresponding to a single dose of approximately 330 mg or 4.4-6.7 mg/kg body weight (LOEL) and above. No effects were observed after the ingestion of approximately 130 mg Sn, or 1.7-2.6 mg Sn/kg (NOEL). The authors stated that there was no evidence from their experiments that toxicity was due to the absorption of tin and that the most likely cause was local irritation of the mucous membranes of the alimentary tract (8).

11.2 Effects of repeated exposure

11.2.1 General effects

Eight adult males were given mixed diets containing 0.11 mg Sn/day (control diet) and 50 mg Sn/day (test diet, 50 mg of additional Sn as $SnCl_2$ in fruit juice) for 20 days each in a cross-over design. There was no effect on the faecal and urinary excretion rates of copper, iron, manganese, magnesium and calcium. Zinc and selenium excretion rates were moderately changed. Hematocrit and serum ferritin levels were not affected (74, 89, 90). A mean body weight of 76 kg leads to an estimated LOEL of 0.7 mg Sn/kg/day in this study.

The uremic patient might be especially prone to accumulate trace elements from the usual environmental sources. Elevated tin levels have been found in

muscle, serum, liver and kidney of these patients. As tin affects kidney enzyme activity in animals (chapter 9), it is suggested that tin might be involved in a degenerative feedback effect in uremic patients (125, 151).

In a Belgian case-control study (n=272), a significantly increased risk (odds ratio 3.72, 95% confidence interval 1.22-11.3) of chronic renal failure was found for occupational exposure to tin. Exposures were scored independently by 3 industrial hygienists (126).

11.2.2 Respiratory system

There are several case reports of workers exposed to SnO_2 dust and fumes for 3 years or more in tin smelting works, scrap metal recovery plants and hearth tinning. The only positive finding is the chest roentgenograms presenting a pneumoconiosis called stannosis (6, 35, 40, 52, 135, 161, 171, 173). In general, no information on exposure levels is available.

Dundon and Hughes presented a case report of a "peculiar widespread mottling of both lung fields by discrete shadows" in the chest roentgenogram in a man who 10 years later died from cancer of the prostate. He had been employed in industry tending a detinning furnace for 18 years. The employment was terminated 18 years before death. At autopsy, 1100 mg Sn/kg wet weight of lung tissue was found (52).

Robertson et al examined the employees, including pensioners, from a tin smelting works and described chest X-ray changes in 121 out of 215 workers. The changes were widespread, tiny, dense shadows; or softer, larger, more nodular opacities. Typical changes were found in workers handling raw ore, smelting furnace house workers and refinery furnace men. The employment time was at least 3 years, and up to nearly 50 years. None of the men had any clinical symptoms or signs referable to pneumoconiosis. None of the films suggested fibrosis or significant emphysema (146, 149). Lung function studies of forced expiratory volume and airway resistance showed no disability, whatever the radiographic category. The population at the tin smelting works had lower mortality (131 deaths) than expected when compared to the male population in the United Kingdom (expected 166) in the period 1921-55 (147). Dust concentrations from the tin smelting works were given in chapter 5, e.g. 2.22 mg tin/m^3 in the check sampling shed, but the methods of sampling and analysis were not described (147).

Autopsy findings were given by Robertson et al for 7 workers with abnormal radiographs. None had died of pulmonary disease. Aggregates of macrophages containing dust were seen around respiratory bronchioles and less commonly around segmental bronchi, in the alveoli, in the interlobular septa and in the perivascular lymphatics. The mild focal emphysema observed was assumed to be clinically insignificant and was considerably less severe than that seen in coal workers pneumoconiosis. No fibrosis was present. Chemical and X-ray diffraction analysis showed that the lungs contained SnO_2. X-ray emission microanalysis identified tin in a minute particle of dust in lung phagocytes (148).

Hlebnikova (1957, cited in (87)) made a survey over a number of years of workers exposed to condensation aerosols formed during the smelting of tin and consisting mainly of SnO_2. Total silica concentration in the aerosols did not exceed 3%. Total dust concentration in air varied between 3 and 70 mg/m^3. Workers developed pneumoconiosis after 6-8 years of employment. No cases of pneumoconiosis were observed 10 years after the dust concentration had been reduced to 10 mg/m^3. No further details are given (87).

Symptoms like wheezing, cough, chest pain and dyspnoea on exertion reported in workers handling $SnCl_4$ were probably due to elevated levels of hydrogen chloride formed by the combination of $SnCl_4$ and water in the presence of heat (109).

11.2.3 Conclusion

Occupational exposure to SnO_2 dust or fumes induces stannosis with no indication of fibrosis or apparent disability beyond chest X-ray opacities. An increased risk of chronic renal failure is reported. Excretion rates of zinc and selenium were moderately changed in subjects given 0.7 mg Sn/kg body weight/day.

11.3 Genotoxic effects

No data are available.

11.4 Carcinogenic effects

Some reports from China are concerned with the health of tin miners. There were 1724 lung cancer cases registered at the Yunnan Tin Corporation in the period 1954-1986, of which 90% had a history of working underground. Assumed contributing factors included diet, arsenic, radon and tobacco (63, 138, 139, 180). Tin was not considered a carcinogenic factor in these studies.

An increased mortality from cancer of the lung was present among Cornish tin miners. There was a clear relation between exposure to radon and death from lung cancer (64, 83).

11.5 Reproductive and developmental effects

No data are available.

12. Dose-effect and dose-response relationships

12.1 Single/short-term exposures

12.1.1 In vitro

$SnCl_2$ causes DNA damage in human white blood cells, CHO cells, and in *E. coli*. The effects on human white blood cells and CHO cells are dose-dependent. DNA

damage in human lymphocytes has been shown after treatment *in vitro* with $SnCl_4$ (115, 116).

12.1.2 Animals

Oral, short-tem studies where the dose is given or possible to estimate are summarised in table 10.

The LOEL for $SnCl_2$ given orally with respect to calcium content in rat bone, is ~ 0.6 mg Sn/kg body weight/day for 90 days (197). The decrease in calcium content is dose-dependent.

The LOEL for $SnCl_2$ orally with respect to interference with the status of iron, copper and zink in rats is ~ 0.7 mg Sn/kg body weight/day for 28 days. Also, blood haemoglobin levels decrease with increasing Sn levels (0.07-13.2 mg/kg body weight). Analysis of variance and test for linear trend suggests that there is a dose-effect relationship for these effects (134).

In mice, an increased susceptiblility to bacterial infection was observed after a single intratracheal injection of $SnCl_2$ at a dose corresponding to 0.24 mg/kg body weight (78).

12.1.3 Humans

The NOEL of acute ingestion of $SnCl_2$ with respect to gastrointestinal illness is approximately 1.7-2.6 mg Sn/kg body weight (8).

The LOEL for $SnCl_2$ administered orally for 20 days with respect to interference with the excretion of zink and selenium is 0.7 mg Sn/kg body weight/day. Excretion rates are moderately changed at this level (74, 89, 90).

Positive patch test reactions to tin have been reported (44, 68, 117, 122, 142). However, only one case of occupational allergic contact dermatitis is published (122). 5% $SnCl_2$ in petrolatum is irritant, whereas 1% $SnCl_2$ in petrolatum is not (44). In view of the widespread occurrence of tin, it is probably not a relevant contact allergen.

12.2 Long-term exposures

12.2.1 Animals

Oral long-term studies where the dose is given or possible to estimate are summarised in Table 11.

The LOEL for $SnCl_2$ orally in rats in life-long exposures with respect to degenerative changes in the liver and kidney is ~ 0.4 mg Sn/kg body weight/day (160).

Available data suggest that metal tin and $SnCl_2$ are not carcinogenic although one study concludes that C-cell tumours of the thyroid gland in male rats may have been associated with the administration of $SnCl_2$ (124).

Table 10. Dose-effect relationships from oral, short-term, animal studies

Exposure regimen	Dose	Species	No of animals per dose group (controls)	Effect	Reference
$SnCl_2$ for 90 days, 2 daily doses	0.6 mg Sn/kg bw/day	Weanling male Wistar rats	6 (6)	Non-significant decrease in femoral epiphysis calcium content.	(197)
	2.0 mg Sn/kg bw/day			Significantly decreased femoral calcium content, succinate dehydrogenase activity in liver, acid phosphatase activity in femur.	
	6.0 mg Sn/kg bw/day			Significantly decreased femoral weight and calcium content, and inhibition of several enzymes. The decrease in femoral calcium content and enzyme activity was dose-dependent.	
$SnCl_2$ in diet for 28 days	0.07, 0.7, 3.5, 7, 13.2 mg Sn/kg bw/day (1, 10, 50, 100, 200 mg Sn/kg diet)	Male Wistar rats aged 3 weeks	7 (7)	Plasma, kidney, spleen and tibia iron, haemoglobin and transferrin saturation decreased in a linear dose-effect manner. Significant inverse response of plasma, liver, kidney, spleen and tibia Cu levels and plasma, kidney and tibia Zn levels. Effects from ~ 0.7 mg/kg bw/day on mineral status.	(134)
$SnCl_2$ for 28 days, 2 daily doses	2.0 mg Sn/kg bw/day	Weanling male Wistar rats	5 (5)	Decreased calcium content and decreased phosphatase activities in femoral bone.	(198)
$SnCl_2$ for 5 days	2 mg Sn/kg bw/day	Female rabbits	5 (5)	No adverse effects on haem biosynthesis observed.	(208)

Table 10. Cont.

Exposure regimen	Dose	Species	No of animals per dose group (controls)	Effect	Reference
$SnCl_2$ for 1 month	2 mg Sn/kg bw/day	Male rabbits	5 (5)	Decreased zinc and copper concentrations in bone marrow, increased iron concentrations in liver and kidneys.	(207)
$SnCl_2$ for 4 months	10 mg Sn/kg bw/day	Female rabbits	6	Transient anaemia, high s-iron, total iron binding capacity and saturation index.	(34)
Sn(II) oleate, SnS or SnO_2 in diet for 4 weeks, or SnO in diet for 13 weeks	0.03, 0.10, 0.3 or 1.0% of compound	Weanling Wistar rats	10 males, 10 females (10+10)	No adverse effects noted.	(46)
$SnCl_2$, Sn(II) ortho-phosphate, sulphate, oxalate and tartrate in diet for 4 weeks, or $SnCl_2$ in diet for 13 weeks	~7-10 mg Sn/kg bw/day (0.03% of compound)	Male rats, Sprague-Dawley	10 males, 10 females (10+10)	No adverse effects noted.	(46)
	~22-33 mg Sn/kg bw/day (0.1% of compound)			No adverse effects noted.	
	~70-100, ~220-330 mg Sn/kg bw/day (0.3, 1.0% of compound)			≥ 70-100 mg Sn/kg bw/day growth retardation, reduced food efficiency, anaemia, histological liver changes, more severe in the groups given 220-330 mg Sn/kg bw /day.	

Table 10. Cont.

Exposure regimen	Dose	Species	No of animals per dose group (controls)	Effect	Reference
$SnCl_2$ in diet for 21-27 days	~7 mg Sn/kg bw/day (100 mg Sn/kg diet, 15 or 52 mg Zn/kg diet)	Male rats, Sprague-Dawley	7 (7)	≥ 7 mg Sn/kg bw decreased calcium content of the tibias.	(91, 92)
	~13-14 mg Sn/kg bw/day (200 mg Sn/kg diet) 15, 30 or 52 mg Zn/kg diet)			≥ 13-14 mg Sn/kg bw decrease in absorption of zinc.	
	~39 mg Sn/kg bw/day (500 mg Sn/kg diet, 15 or 30 mg Zn/kg diet)			≥ 39 mg Sn/kg bw decreased retention of zinc in tibia, kidney, liver and plasma, decreased copper levels in plasma, liver and kidney.	
	~142 mg Sn/kg bw/day (2000 mg Sn/kg diet, 15 mg Zn/kg diet)				
$SnCl_2$ in diet for 4 weeks	25 and 50 mg Sn/kg bw/day (250 and 500 mg Sn/kg diet)	Weanling male Wistar rats	10 (10)	Decreased haemoglobin, dose-dependent decrease in body weight, growth, feed intake, length and weight of small intestine. Increased intestinal crypt depth and villus length.	(88)
$NaSn_2F_5$ by gavage for 30 days	13.4 mg Sn/kg bw/day (20 mg $NaSn_2F_5$/kg bw/day)	Male and female Wistar rats	20 (20)	No adverse effects noted.	(36)
	67 mg Sn/kg bw/day (100 mg $NaSn_2F_5$/kg bw/day)			≥ 67 mg/kg bw dose-dependent growth retardation.	
	117 mg Sn/kg bw/day (175 mg $NaSn_2F_5$/kg bw/day)			15-20% of rats had degenerative changes in kidney tubular epithelium.	

Table 11. Dose-effect and dose-response relationships. Long-term exposure, oral studies in animals only.

Exposure	dose	Species	No of animals per dose group (controls)	Effect or response	Reference
$SnCl_2$ in drinking water for life	0.34-0.38 mg Sn/kg bw/day (5 µg/ml)	Long-Evans rats, males and females	94 (82)	No significant change in tumour incidence.	(95)
$SnCl_2$in drinking water for life	0.4 mg Sn/kg bw/day (5 µg Sn/ml)	Long-Evans rats, male and female	~100 (100)	Reduced longevity in females, increased incidence of liver and kidney histopathological changes, no tumorigenic or carcinogenic effects observed.	(160)
$SnCl_2$ in drinking water for life	0.4 mg Sn/kg bw/day (5 µg Sn/ml)	Charles River mice, male and female	108 (80)	No toxicity of tin was demonstrable.	(158)
$SnCl_2$ in diet for 105 weeks	1000 or 2000 mg/kg diet Calculated doses given in Table 7.	Fischer344 rats B6C3F1 mice	50 males, 50 females (50+50) 50 males, 50 females (50+50)	See Tables 8 and 9. $SnCl_2$ given orally in feed was judged by the NTP not to be carcinogenic for male or female Fischer 344 rats or B6C3F1 mice, although C-cell tumours of the thyroid gland in male rats may have been associated with the administration of the chemical.	(124)

12.2.2 Humans
Several case reports on inhalation exposure to SnO_2 dust or fumes in humans were found, but systematic data on exposure levels are not available. Exposure time was 3-50 years. No symptoms or signs of impaired lung function were found, but there were abnormal findings in radiographs and at autopsy. Aggregates of macrophages containing dust but no fibrosis were observed (6, 35, 40, 52, 87, 135, 146, 148, 149, 161, 171, 173).

13. Previous evaluations by national and international bodies

The ACGIH and the NIOSH/OSHA recommend an occupational exposue limit of 2 mg/m^3 in the interest of minimising the potential of stannosis (1, 123).

In the US Environmental Protection Agency Gene-Tox Program the overall evaluation placed $SnCl_2$ in the limited negative category for carcinogenicity (120).

$SnCl_2$ was classified as a chemical with equivocal evidence of carcinogenicity in a review of 301 chemicals tested by the US National Toxicology Program (3).

IARC stated in 1987 that inorganic fluorides used in drinking water, including SnF_2, are not classifiable as to their carcinogenicity to humans (84).

14. Evaluation of human health risks

14.1 Groups at extra risk

Workers with renal disease might be at extra risk of renal effects by exposure to tin. Johnson et al suggested that chronic exposure of man to moderate levels of tin in food probably is important mainly to those individuals who chronically consume low levels of zinc and thus often are in a marginal nutritional status regarding zinc (the elderly, children and pregnant women).

14.2 Assessment of health risks

14.2.1 Exposure
Occupational exposure to tin and its inorganic compounds is described by inhalation or skin contact during the handling of tin ore, smelting and industrial processing of tin. Data on exposure levels are scarce.

Canned food from unlaquered cans may contain high levels of tin.

14.2.2 Effects
Deposition of tin particles in the lungs of exposed workers has been associated to stannosis, with no indication of fibrosis. No apparent disability beyond X-ray opacities is found. There are no data on the possible absorption from the lungs.

Irritant reactions to skin (humans and animals) and mucosa (animals) have been shown for $SnCl_4$ and $SnCl_2$. Allergic dermatitis in humans has been suggested. No data on the possibility of skin absorption is available.

When tin is absorbed from the gut it may interfere with the status of other metals (animals, humans) and/or cause changes in enzyme levels (animals) in blood, liver, kidney and bone and degenerative changes in liver and kidney (animals).

$SnCl_2$ was considered not carcinogenic in rats and mice, with the possible exception of C-cell tumours in the thyroid gland in male rats.

In vitro experiments have shown effects on enzyme activities, and DNA-damage in human white blood cells, CHO cells and *E. coli*.

14.2.3 Assessment

The literature on long-term inhalation of inorganic tin consists of case reports in humans, with poor exposure assessment and old methods of examination. Reports on effects concerning micropathology and cell toxicity in the respiratory system are scarce. The information is insufficient to assess the health risk to the lungs.

Tin absorbed from the gastrointestinal tract may affect the mineral status in animals and humans. On acute ingestion, the irritative symptoms of nausea and diarrhoea are likely to prevent the ingestion of doses that might represent a further health risk. For the chronic ingestion during weeks and months, the critical effect of absorbed tin might be the decrease of calcium content in bone (rats) for short-time exposures, but interference with the status of minerals is observed at about the same levels of exposure (0.6-0.7 mg/kg body weight) in both animals and humans. In older studies, degenerative changes in liver and kidney are observed at even lower levels (0.4 mg/kg) in life-time exposure in rats. The exact doses of exposure in mg/kg body weight are difficult to estimate due to the study designs and lack of information in the reports. The available reports on metallic tin and $SnCl_2$ are not sufficient to classify tin as a contact allergen.

14.3 Scientific basis for an occupational exposure limit

Data for the concentration of tin in workplace air, in body fluids and organ concentrations in workers and toxic effects are scarce. Effects on enzymes and the concentration of other elements in tissues and fluids are not sufficiently documented and evaluated for a critical effect to be established. This is also true for *in vitro* experiments showing cytogenetic changes in human white blood cells, CHO cells and *E. coli*. Although there are some indications that occupational exposures may cause adverse effects the available data are insufficient for forming a scientific basis for an occupational exposure limit.

15. Research needs

Systematic data on occupational exposure levels of inorganic tin in air are needed as are data on blood or tissue levels in workers exposed to known levels of inorganic tin in their working atmospheres. There are also few data on background blood or tissue levels of tin in unexposed humans.

If absorption from occupational exposure is confirmed in the future, further investigations into the effects on enzymes and mineral status and dose-effect relationships of inorganic tin on the haematopoietic system, bone, liver and kidney in humans are necessary. Animal inhalation studies are also lacking.

Data on irritative effects (eye, respiratory tract) are needed. The lung effects described should be more thoroughly examined by modern laboratories of lung function, radiology and micropathology. The observed DNA-damage *in vitro* should lead to further studies in humans. Further studies according to modern protocols on carcinogenicity in animals are also needed.

16. Summary

Westrum B, Thomassen Y. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards. 130. Tin and inorganic tin compounds.* Arbete och Hälsa 2002;10:1-48.

Exposure to inorganic tin occurs in the mining and smelting of tin ore, in tin plating, solder, alloy, toothpaste, ceramics and textile production. Acute gastrointestinal illness follows the intake of food containing high levels of tin. Tin absorption from the gut is < 5%. Tin is deposited in bone, liver, kidneys, and lymph nodes. Effects of tin are growth retardation, anaemia, changes in enzyme activities, interactions with the absorption and excretion of calcium, copper, iron and zinc, and morphological changes in liver and kidney. $SnCl_2$ was considered not carcinogenic in rats and mice, with the possible exception of C-cell tumours in the thyroid gland in male rats. Tin chlorides produce DNA-damage *in vitro*. $SnCl_2$ is irritating to skin. Inhalation of SnO_2 may cause X-ray changes (stannosis), but no apparent pulmonary dysfunction and no fibrosis. Data are insufficient for identification of a scientific basis for an occupational exposure limit.

Key words: bone, gastrointestinal, kidney, liver, mineral status, occupational exposure limits, skin, $SnCl_2$, stannosis, tin, toxicity.

17. Summary in Norwegian

Westrum B, Thomassen Y. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards. 130. Tin and inorganic tin compounds.* Arbete och Hälsa 2002;10:1-48.

Eksponering for uorganisk tinn forekommer i tinngruver og smelteverk, i produksjon av tinnvarer, lodding, legeringer, tannkrem, keramikk og tekstiler. Inntak av mat med høyt nivå av tinn gir akutt magetarm sykdom. Absorpsjon av tinn fra tarmen er < 5%. Absorbert tinn blir avsatt i bein, lever, nyre og lymfeknuter. Effekter av tinn er veksthemming, anemi, endringer i enzymaktivitet, interaksjon med absorpsjon og utskillelse av av kalsium, kopper, jern og sink og morfologiske endringer i lever og nyre. $SnCl_2$ ble vurdert som ikke kreftfremkallende hos rotter og mus, med et mulig unntak for C-celle svulster i skjoldbruskkjertelen hos hannrotter. Tinnklorider gir DNA-skade *in vitro*. $SnCl_2$ irriterer hud. Inhalasjon av tinn kan gi røntgenologiske forandringer (stannose), men tilsynelatende ingen reduksjon i lungefunksjon og ingen fibrose. Data er utilstrekkelige for å identifisere et vitenskapelig grunnlag for en grenseverdi for eksponering i arbeidet.

Nøkkelord: bein, lever, magetarm sykdom, nyre, grenseverdi for eksponering i arbeid, $SnCl_2$, stannose, tinn, toksisitet.

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19. Data bases used in search of literature

In the search for literature the following data bases were used:

- American Chemical Society
- Arbline
- CISDOC
- HSELINE
- Medline
- NIOSTIC
- RILOSH
- Toxline

Last search was performed in March 2002.

Appendix 1

Occupational exposure limits for tin and inorganic tin compounds in air.

Country	mg/m^3	Comments	Year	Ref
Denmark	2	as Sn	2000	1
Finland	2	as Sn	1998	2
	5	as Sn, tin oxide, fume	1998	2
Germany	-		2001	3
Iceland	2	as Sn	1999	4
Netherlands	2	as Sn, except SnO_2, SnH_4	2001	5
	2	SnO_2		
Norway	2	as Sn	2001	6
Sweden	-	-	2000	7
United Kingdom	2	as Sn, except SnH_4	1998	8
	4	short-term	1998	8
USA (ACGIH)	2	as Sn, metal	2002	9
		as Sn, oxide and inorganic compounds, except SnH_4	2002	9
(NIOSH)	2	as Sn, except oxides	2000	10
	2	as Sn, SnO, SnO_2	2000	10
(OSHA)	2	as Sn, except oxides	2000	10

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