
Tin and inorganic tin compounds

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Aan de Staatssecretaris Sociale Zaken en Werkgelegenheid

Onderwerp : Aanbieding advies 'Tin and inorganic tin compounds'
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Mijnheer de staatssecretaris,

Bij brief van 3 december, nr DGV/BMO-U-932542, verzocht de Staatssecretaris van Welzijn, Volksgezondheid en Cultuur namens de Minister van Sociale Zaken en Werkgelegenheid de Gezondheidsraad om gezondheidskundige advieswaarden af te leiden ten behoeve van de bescherming van beroepsmatig aan stoffen blootgestelde personen.

In dat kader bied ik u hierbij een advies aan over tin en anorganische tinverbindingen. Dit advies is opgesteld door de Commissie WGD van de Gezondheidsraad en beoordeeld door de Beraadsgroep Gezondheid en Omgeving.

Ik heb dit advies vandaag ter kennisname toegezonden aan de Minister van Volksgezondheid, Welzijn en Sport, de Minister van Sociale Zaken en Werkgelegenheid en de Staatssecretaris van Volkshuisvesting, Ruimtelijke Ordening en Milieu.

Hoogachtend,

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Tin and inorganic tin compounds

Health-based recommended occupational exposure limit

Dutch Expert Committee on Occupational Standards,
a committee of the Health Council of the Netherlands,
in cooperation with the Nordic Expert Group for
Criteria Documentation of Health Risks from Chemicals

to:

the Minister and State Secretary of Social Affairs and Employment

No. 2005/06OSH, The Hague, June 9, 2005

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues...” (Section 21, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

Most Health Council reports are prepared by multidisciplinary committees of Dutch or, sometimes, foreign experts, appointed in a personal capacity. The reports are available to the public.

This report can be downloaded from www.healthcouncil.nl.

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Samenvatting

Vraagstelling

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid leidt de Commissie WGD van de Gezondheidsraad gezondheidkundige advieswaarden af voor stoffen in lucht waaraan mensen beroepsmatig blootgesteld kunnen worden. Deze aanbevelingen vormen de eerste stap in een drietrapsprocedure die moet leiden tot wettelijke grenswaarden, aangeduid als maximaal aanvaarde concentraties (MAC-waarden).

Het voorliggende rapport is samengesteld in samenwerking met de Nordic Expert Group (NEG). Het gezamenlijke rapport over de gevolgen van beroepsmatige blootstelling aan tin en anorganische tinverbindingen, gepubliceerd in Zweden in 2002 (Arbete och Hälsa 2002:10), is geïncorporeerd als deel 2 van het huidige document. Deel 1 bestaat voornamelijk uit een samenvatting van de meest relevante gevolgen van blootstelling aan zwavelwaterstof en een gezondheidkundige evaluatie van deze stof. De conclusies van de commissie zijn gebaseerd op wetenschappelijke publicaties die vóór februari 2004 zijn verschenen.

Fysische en chemische eigenschappen

Tin is een metaal met een smeltpunt van 232°C en een kookpunt van 2602°C. De stof heeft twee valenties, II en IV.

Tinverbindingen kunnen worden verdeeld in twee groepen: de oplosbare zouten (zoals SnBr_4 , SnCl_2 , SnCl_4 , SnF_2 , SnI_2 , SnI_4) en de onoplosbare zouten (zoals SnO , SnO_2 , SnP_2O_7 , SnS , SnSO_4). Het smeltpunt van de oplosbare zouten ligt tussen -33 en 143°C en de onoplosbare zouten hebben een hoger smeltpunt ($>880^\circ\text{C}$). Het kookpunt van de oplosbare zouten varieert tussen 11 en 714°C , terwijl het kookpunt van de onoplosbare zouten hoger is dan 1200°C . SnP_2O_7 en SnSO_4 ontleden bij temperaturen $>378\text{-}400^\circ\text{C}$.

Tin wordt voornamelijk ontgonnen als cassiteriet (SnO_2), en gebruikt als coating op andere metalen ter bescherming tegen corrosie. Daarnaast wordt tin veel gebruikt in legeringen met andere metalen.

Monitoring

Voor de bepaling van anorganisch tin (behalve tin oxide) in de lucht, adviseert NIOSH een methode waarbij het filter wordt behandeld met een zure oplossing waarna met behulp van spectrometrie de hoeveelheid tin wordt bepaald. Radiochemisch neutrone activatie wordt gebruikt voor het meten van tin in menselijk biologisch materiaal.

Grenswaarden

De huidige bestuurlijke MAC-waarde (8 uur tgg) in Nederland voor tin en anorganische tin verbindingen is 2 mg Sn/m^3 . Deze waarden is niet gebaseerd op een advies van de Commissie WGD of de Europese SCOEL. In Denemarken, Finland, IJsland, Noorwegen, Groot Britannië en de USA (ACGIH, NIOSH and OSHA) geldt ook een grenswaarde van 2 mg Sn/m^3 (tgg 8 uur). Daarnaast is in Groot Britannië ook een STEL van 4 mg/m^3 (tgg 15 minuten) van kracht.

Kinetiek

De orale opname van tin en anorganische tinverbindingen is laag. Tin accumuleert in botten, longen, lymfklieren, de lever en de nieren. Eenmaal opgenomen tin wordt voornamelijk weer via de nieren uitgescheiden.

Effecten

Mensgegevens

De gegevens over de effecten van het inademen van tin en anorganische tinverbindingen op mensen zijn zeer beperkt. Bij mensen die dertig tot vijftig jaar zijn blootgesteld aan tinoxide, zijn er weliswaar geen effecten op de longfunctie waargenomen maar er zijn wel kleine afwijkingen te zien op longfoto's en bij bipten. Ook zijn er ophopingen van (stof bevattende) macrofagen in de longen te zien, ook stannose of stoflongen genoemd. Er is echter geen sprake van fibrose van de longen als gevolg van blootstelling aan tin.

Oplosbare anorganische tindeeltjes kunnen interfereren met de selenium- en zinkgehalten in het lichaam. De betekenis hiervan is echter niet bekend. SnCl_2 in petrolatum kan de huid irriteren (positief in patch testen), er is tot nu toe echter maar een casus beschreven met contact dermatitis.

Het drinken van fruitsappen uit blikjes die tin bevatten kan misselijkheid en diarree veroorzaken. Irritatie van het maag-darmkanaal is mogelijk gerelateerd aan de concentratie van vrije tin-ionen en niet aan de hoeveelheid totaal opgenomen tin.

Diergegevens

Er zijn geen gegevens beschikbaar over de effecten van inhalatoire blootstelling aan tin en anorganische tinverbindingen op proefdieren. SnCl_2 lijkt niet irriterend te zijn voor de huid, maar bij ratten is wel irritatie van het spijsverteringskanaal waargenomen. Sensibilisatie als gevolg van blootstelling aan SnCl_2 of SnCl_4 is niet beschreven.

Bij ratten die eenmalig oraal werden blootgesteld aan metallisch tin, waren op röntgenfoto's afwijkingen van de longen te zien (geen fibrose). De orale LD_{50} voor anorganisch tin is 146-396 mg Sn/kg lichaamsgewicht (lg) voor NaSn_2F_5 en 1197-1678 mg Sn/kg lg voor $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$.

Blootstelling van ratten aan oplosbare anorganische tinverbindingen via de voeding leidt tot groeivertraging, verminderde voedselopname, lichte bloedarmoede en kleine histopathologische afwijkingen in de lever. In een studie waarin ratten gedurende 28 dagen worden blootgesteld aan 0.7 mg Sn/kg lg, zijn verlaagde ijzer-, koper- en zinkniveaus in weefsel en bloed gemeten.

In een 90-dagen-studie met Wistar ratten, werd een dosis-gerelateerde afname van de hoeveelheid calcium in botten gerapporteerd na een tweemaal daagse orale blootstelling aan 0.3 mg/kg lg (totaal 0.3 mg/kg lg/dag) en hoger.

Na levenslange blootstelling aan 0.4 mg Sn/kg lg via het drinkwater, zijn bij ratten veranderingen in de lever en in de niertubuli te zien. Op basis van een NTP studie concludeert de commissie dat SnCl₂ en metallisch tin waarschijnlijk niet carcinogeen zijn voor F344 ratten en B6C3F1 muizen, hoewel de onderzoekers een associatie tussen blootstelling en de ontwikkeling van C-cel tumoren in de schildklier van mannelijke ratten niet volledig uitsluiten.

SnCl₂ veroorzaakt DNA schade in *E. coli*, CHO-cellen (Chinese Hamster Ovary cellen) en humane witte bloedcellen. De effecten in CHO and humane witte bloedcellen was dosisafhankelijk. SnCl₄ induceert ook chromosomale schade in humane lymfocyten. Deze effecten zijn mogelijk gerelateerd aan de vorming van reactieve zuurstofdeeltjes en de binding aan DNA.

Evaluatie en advies

De Commissie WGD is van mening dat op basis van de fysisch chemische eigenschappen, drie groepen van tinverbindingen onderscheiden moeten worden voor het afleiden van een gezondheidskundige advieswaarde:

Metallisch tin

Wat betreft metallisch tin is de commissie van mening dat er onvoldoende gegevens beschikbaar zijn over de effecten na korte of langdurige blootstelling. Er kan daarom geen advieswaarde (158-minuten of 8-uur) worden voorgesteld.

Oplosbare anorganische tinverbindingen

Er zijn geen gegevens over de effecten van kortdurende en langdurige inhalatoire blootstelling aan oplosbare anorganische tinverbindingen op mensen en proefdieren. De commissie is van mening dat de gegevens over de effecten na orale blootstelling beperkt zijn en van onvoldoende kwaliteit. De beschikbare studies onderzoeken slechts een gering aantal toxicologische eindpunten, waardoor geen compleet beeld van de toxiciteit van deze verbindingen beschikbaar is. Daarnaast betwijfelt de commissie de relevantie van de orale blootstelling voor de risicobeoordeling na inhalatoire blootstelling. De commissie concludeert daarom dat er onvoldoende gegevens zijn om een advieswaarde (15-minuten of 8-uur) voor te stellen.

Onoplosbare anorganische tinverbindingen

Er zijn geen gegevens over de effecten van kortdurende blootstelling aan onoplosbare anorganische tinverbindingen. De commissie is daarom van mening dat een advieswaarde (15-minuten, STEL) niet kan worden afgeleid.

Wanneer mensen langdurig via de lucht aan SnCl_2 worden blootgesteld, kunnen ze stannose (stoflongen) krijgen. Dit heeft echter geen gevolgen voor de longfunctie. Informatie over de blootstelling in deze studie is echter zeer beperkt of afwezig. Ook zijn er geen gegevens over de effecten van inhalatoire blootstelling bij dieren. Orale blootstelling aan onoplosbaar anorganisch tin veroorzaakt groeivertraging en bloedarmoede bij knaagdieren. De commissie betwijfelt echter de relevantie van de orale blootstelling voor de risicobeoordeling na inhalatoire blootstelling.

De Commissie WGD is daarom van mening dat er onvoldoende gegevens zijn voor het vaststellen van een gezondheidkundige advieswaarde (8 uur).

Gezondheidkundige advieswaarde

De commissie is van mening dat er onvoldoende gegevens zijn voor het afleiden van een gezondheidkundige advieswaarde (gedurende 15 minuten of 8 uur) voor metallisch tin en voor de oplosbare en onoplosbare anorganische tinverbindingen.

Executive Summary

Scope

At request of the Minister of Social Affairs and Employment, The Health Council of the Netherlands sets health-based recommended occupational exposure limits (HBR-OEL) for toxic substances in workplace air. These recommendations are made by the Council's Dutch Expert Committee on Occupational Standards (DECOS). It constitutes the first step in a three step procedure which leads to legally binding occupational exposure limits.

The present report on tin and inorganic tin compounds was prepared in cooperation with the Nordic Expert Group (NEG). The joint report on the consequences of occupational exposure to tin and inorganic tin compounds, published in Sweden in 2002 (Arbete och Hälsa 2002:10), is included in part 2 of this document. Part 1 mainly consists of a summary of the most important health effects and a health hazard assessment by DECOS.

The committee's conclusions are based on scientific publications obtained from data retrieval systems from prior to February 2004.

Physical and chemical properties

Tin is a metal with a melting point of 232°C and a boiling point of 2602°C. Tin has two oxidation states, the II (stannous) and IV (stannic) state.

Tin compounds can be divided in soluble (such as SnBr_4 , SnCl_2 , SnCl_4 , SnF_2 , SnI_2 , SnI_4) and insoluble salts (such as SnO , SnO_2 , SnP_2O_7 , SnS , SnSO_4). The soluble salts have melting points between -33 and 143°C and boiling points between 11 and 714°C . The insoluble compounds have much higher melting points ($>880^\circ\text{C}$) and boiling points $>1200^\circ\text{C}$. SnP_2O_7 and SnSO_4 decompose at temperatures >378 - 400°C .

Tin is mined chiefly as cassiterite (SnO_2). Tin is mainly used as a protective coating for other metals due to its resistance to corrosion. Another important property is its ability to form alloys with metals.

Monitoring

The method recommended by NIOSH for monitoring airborne inorganic tin and its compounds (except oxides), is filter acid digestion and subsequent atomic absorption spectrometry (AAS) or inductively coupled plasma atomic emission spectrometry.

Radiochemical neutron activation analysis has been used for the measurement of tin in human biological materials.

Current limit values

In the Netherlands, the present administrative MAC-value is 2 mg/m^3 as Sn for tin and inorganic tin compounds. This exposure limit is not based on an advice of DECOS or the european SCOEL (Scientific Committee on Occupational Exposure Limits). In Denmark, Finland, Iceland, Norway, the United Kingdom (UK) and the USA (ACGIH, NIOSH and OSHA) 2 mg/m^3 as Sn is recommended as occupational exposure limit. In addition, in the UK a short-time value of 4 mg/m^3 is available.

Kinetics

Oral uptake of tin and inorganic tin compounds is low. Tin accumulates in the bone, the lungs, the lymph nodes, the liver and the kidney. Absorbed tin is mainly excreted via the kidneys.

Effects

Human data

Only limited human information is available concerning the effects of tin (compounds) after inhalatory exposure. In humans exposed to SnO₂ dust or fumes for 3-50 years, no effects on lung function were found despite abnormal findings in radiographs and at autopsy. Aggregates of dust-containing macrophages in the lungs were found presenting a pneumoconiosis called stannosis. No fibrosis of the lungs associated with exposure was reported. Increased incidences of lung cancer in tin-miners were not attributed to exposure to tin.

Soluble inorganic tin compounds (SnCl₂) may interfere with the status of selenium and zinc in the human body. SnCl₂ (5%) in petrolatum may be a skin irritant (positive patch tests). However, only one case of occupational contact dermatitis has been described.

General findings associated with acute and short-term oral exposure of humans after drinking of tin-containing fruit juices include nausea and diarrhea. These symptoms are attributed to irritation of the mucosal surfaces. This gastrointestinal irritation is probably related to the concentration of free stannous ions present at the gastro-intestinal mucosa and not the absolute amount of ingested tin.

Animal studies

No data are available concerning the effects of inhalatory exposure in experimental animals.

SnCl₂ does not appear to be a skin irritant in animal studies. Irritation of the alimentary tract after feeding of SnCl₂ was observed in rats. No sensitisation due to SnCl₂ or SnCl₄ in alcohol was reported.

Single oral administration of 50 mg metallic tin dust in saline to rats gave X-ray changes and tiny densities in the lungs after 4 months (without fibrosis). Oral LD50 values for inorganic tin salts are 146-396 mg Sn/kg bw for NaSn₂F₅ and 1197-1678 mg Sn/kg bw for SnCl₂·2H₂O.

Dietary exposure of Wistar rats to various soluble salts of tin led to growth retardation, decreased food efficiency, slight anaemia (decreased Hb-levels) and slight histopathological changes in the liver. Decreases of iron, copper and zinc tissue- and plasma levels were reported after 28-day exposure of rats to 0.7 mg Sn/kg bw.

In a 90-day study in Wistar rats, which were exposed orally 2 times per day to 0.3, 0.6 and 1.0 mg Sn/kg bw a dose-related decrease in calcium content in the bone was reported at 0.6 mg/kg bw/day (2 times 0.3 mg/kg bw) and above.

At 0.4 mg Sn/kg bw rats showed fatty degenerative changes in liver and vacuolar changes in the renal tubules after life-time exposure in drinking water. In a NTP study SnCl₂ (1000 and 2000 mg/kg food for 105 weeks) and metallic tin were concluded to be non-carcinogenic to F344 rats and B6C3F1 mice, although an association between treatment and the development of C-cell tumours of the thyroid gland in male rats was not fully excluded by the authors.

SnCl₂ induced DNA damage in *E. coli*, CHO-cells (Chinese Hamster Ovary cells) and human white blood cells. The effects in CHO and human white blood cells were dose dependent. SnCl₄ induced chromosomal damage in human lymphocytes. The effects may be correlated with formation of reactive oxygen species and binding to DNA.

Hazard Assessment and recommended occupational exposure limit

DECOS is of the opinion that for the hazard assessment three groups of tin should be considered based on the physical and chemical properties.

Tin metal

For tin (metal), the committee is of the opinion that no data are available concerning the effects after acute, short-term and long-term exposure. Therefore, no health based occupational exposure limit (15 minutes or 8 hours) can be derived.

Soluble inorganic tin compounds

No data are available concerning the effects of acute, short-term and long-term inhalatory exposure to soluble inorganic tin compounds in man and experimental animals. The committee considers the human and animal data after oral exposure limited and in general of low quality (poor study design and limited information). The repeated dose studies reported only established particular end-points and as such do not provide complete toxicological information. In addition, the committee doubts the relevance of these oral data for the risk assessment after inhalatory exposure. Therefore, DECOS is of the opinion that the available data do not allow to derive a health based occupational exposure limit (15 min and 8 hour).

Insoluble inorganic tin compounds

No data are available concerning the effects of acute and short-term exposure (both inhalatory and oral) to soluble inorganic tin compounds in man and experimental animals. Therefore, the committee concluded that a health based occupational exposure limit (15 min, STEL) can not be derived.

Long-term inhalatory exposure to SnO₂ induces stannosis (pneumoconiosis) in man. However, no sign of impaired lung-functions were observed. No systematic exposure data are available. No data concerning the effects after inhalatory exposure in experimental animals were available. Oral exposure may lead to growth retardation or anemia in rodents. However, the committee doubts the relevance of the oral studies for the risk assessment after inhalatory exposure. In conclusion, DECOS considers the data after long-term exposure insufficient to derive a health based occupational exposure limit (8 hours).

Health based recommended occupational exposure limit

DECOS concludes that at present the available data are insufficient as scientific basis for an occupational exposure limit for tin(metal), soluble and insoluble inorganic tin compounds.

Part 1 Health Council: Tin and inorganic tin compounds

DECOS basis for hazard assessment

Scope

1.1 Background

In the Netherlands occupational exposure limits for chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by The Dutch Expert Committee on Occupational Standards (DECOS), a committee of the Health Council of the Netherlands, at the request of the Minister of Social Affairs and Employment (Annex A). The purpose of the committee's evaluation is to set a health-based recommended occupational exposure limit for the concentration of the substance in air, provided the database allows the derivation of such value.

In the next phase of the three-step procedure the Social and Economic Council advises the Minister on the feasibility of using the health based value as a regulatory Occupational Exposure Limit (OEL) or recommends a different OEL. In the final step of the procedure the Minister of Social Affairs and Employment sets the official Occupational Exposure Limit.

1.2 Committees and procedures

This document contains the assessment of the health hazard of tin and inorganic tin compounds and is a co-production of the DECOS and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). It is a

result of an agreement between both groups to prepare jointly scientific criteria documents, which can be used by the national regulatory authorities in the Netherlands and the Nordic countries for establishing exposure limits. The members of the DECOS and NEG are listed in annex B.

The joint draft document on the harmful effects of tin and inorganic tin compounds has been prepared by MD B Westrum and Dr Y Thomassen from the National Institute of Occupational Health, Norway. In addition, the draft was reviewed first by the NEG and subsequently by DECOS. The final document was published by the Swedish National Institute of Occupational Health (Arbete och Hälsa 2002:10) and is included in Part 2 of this report.

Part one contains a brief summary of the relevant effects from the final document in part two, supplemented with additional published data. DECOS used the data from both parts in assessing a health based recommended occupational exposure limit for tin and inorganic tin compounds. The first draft of part one was prepared by W.M.L.G. Gubbels-van Hal, from NOTOX BV, 's-Hertogenbosch, by contract with the Dutch Health Council.

In 2004, the Health Council released a draft of this report for public review. The individuals and organisations that commented on the draft are listed in annex C. The committee has taken these comments into account in deciding on the final version of the report.

1.3 Data

In the sections below, the first part is a short summary of the findings from the report of the NEG on Tin and inorganic tin compounds (see part two)*, while any additional information retrieved from the literature search is included in the paragraph 'additional information'.

Starting point in searching literature (for part one of this document) on health effects of exposure to tin and inorganic tin compounds was the report of the NEG on Tin and inorganic tin compounds (see part 2 of this report). Unless otherwise indicated, data were retrieved from this document. In addition, literature was retrieved from the on-line databases Medline and Toxline starting from 2001. The final search has been carried out in February 2004. The searches were performed using CAS 7440-31-5, tin and stann? as search profile.

* References from part two are referred to as 'NEGXX'

Kinetics

2.1 Toxicokinetics

Summary of the data in Arbete och Hälsa 2002:10 (part two)

Generally animal data suggest that the oral absorption of tin and tin compounds is low, but may differ depending on dose, anion and the presence of other substances. No information on uptake via the dermal or inhalatory route is available. Inorganic tin compounds do not easily pass the blood-brain barrier. After oral ingestion of tin salts, tin is found to accumulate in the bone and to a lesser extent in the liver and kidneys. When tin salts were administered to pregnant rats, no tin was found in fetuses on day 10 of pregnancy. However, on day 20-21 of gestation small amounts of tin were detected.

In humans the highest concentrations of tin due to environmental pollution (concentrations not indicated) were found in bone, lungs, lymphnodes, liver and kidney. Some data indicate that tin has a higher affinity to the thymus than to other organs.

Tin cations (Sn(II) and Sn(IV)) are not rapidly reduced or oxidized. These two oxidation states of the metal are not easily interconverted *in vivo*.

Absorbed tin is mainly excreted via the kidneys. Half-life in female Charles River rats was 48 hours. 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 relevant methods for biological monitoring of tin and inorganic tin compounds are available, because no knowledge on the relationship between exposure, external dose, toxicokinetics, internal dose and effects is available.

Additional information

In a human volunteer study (n=20), the serum tin concentrations were not elevated after drinking tomato-juice containing <0.5, 161, 264, 529 mg tin (as SnCl₂) per kg body weight¹ and remained below the detection limit of 10 µg/l serum. The authors concluded that the absorption of tin from the gastrointestinal is minimal in humans.

2.2 Mechanism of toxicity

Summary of the data in Arbete och Hälsa 2002:10 (part two)

Tin is not known to be an essential mineral. It interferes with the status of iron, copper and zinc. Tin cations have the ability to influence the biodegradation of cytochrome P-450. Some data indicate that Sn(II) may be more potent than Sn(IV). In addition tin seems to have an inhibitory effect on the activity of several other enzymes amongst others: δ-aminolevulinic acid dehydratase, superoxide dismutase, glutathion peroxidase, glutathion reductase and glucose 6-phosphate dehydrogenase. Thus, tin may alter metabolism. An effect of SnCl₂ on nerve transmission is reported (via altered calcium fluxes).

Additional information

Stannous chloride (SnCl₂) induced cytotoxicity in several *Escherichia coli* strains. Simultaneous treatment with reactive oxygen species scavengers completely protected the cells against cytotoxic damage². The authors concluded that SnCl₂ toxicity is related with the generation of reactive oxygen species.

Effects

3.1 Observations in humans

3.1.1 Irritation and sensitisation

Summary of the data in Arbete och Hälsa 2002:10 (part two)

Only one case of occupational allergic contact dermatitis was published (Nielsen *et al*, 1998)^{NEG122}. *

A few human patch tests, applying 2% SnCl₂ or 2.5% metallic tin in petrolatum, were positive, suggesting that sensitisation to tin had occurred (Menné 1987, Rammelsberg 1986, de Fine Livarius 1993, Gaddoni 1993)^{NEG117, NEG142, NEG44, NEG68}.

In patients, tested with 5% and 10% SnCl₂ in petrolatum, irritant reactions of skin were frequent (de Fine Olivarius 1993)^{NEG44}. At lower concentrations, the patch tests showed doubtful irritant reactions.

Considering the widespread use of tin and tin compounds and the limited number of positive reports on contact allergy (combined with the unclear clinical relevance of the positive patch-test reactions), the committees find it unlikely that tin (compounds) is a contact allergen.

* See references in part two

Additional information

No new data were found.

3.1.2 *Acute and short-term toxicity*

Summary of the data in Arbete och Hälsa 2002:10 (part two)

No studies are available concerning the effects of tin and tin compounds after inhalatory exposure.

In humans, nausea and diarrhoea was reported after drinking of tin-containing fruit juices (corresponding to a single dose of 4.4-6.7 mg Sn/kg bw). No effects were observed after ingestion of approximately 1.7-2.6 mg Sn/kg bw (Benoy 1971)^{NEG8}.

In 8 male volunteers receiving mixed diets containing tin (0.11 and 50 mg Sn/day as SnCl₂) for 20 days, moderate changes in excretion rates of zinc and selenium were reported at the highest concentration. Based on a mean body weight of 76 kg a LOAEL of 0.7 mg Sn/kg bw/day was derived from this study (Greger 1981, Johnson 1982a and b)^{NEG73, NEG89, NEG90}.

Several authors reported acute gastrointestinal illness (nausea, abdominal cramps, vomiting and diarrhoea) following intake of canned fruit or fruit juice (Barker 1972, Benoy 1971)^{NEG5, NEG8}. The doses ingested were 30-200 mg Sn during a short period of time. The authors stated that the observed effects were due to local irritation of the mucous membranes of the alimentary tract. A NOAEL of 1.7-2.6 mg kg bw was suggested based on these studies*.

Additional information

In 2003, Boogaard *et al*³ studied the acute effects of ingesting tomato juice or tomato soup containing tin (as SnCl₂). The results of this study demonstrated that tin levels up to 267 mg Sn/kg tomatosoup cause no adverse effects.

3.1.3 *Longterm toxicity*

Summary of the data in Arbete och Hälsa 2002:10 (part two)

Humans, inhalatory exposed to SnO₂ dust or fumes for 3-50 years, showed no effects on lung function (forced expiratory volume and airway resistance), despite abnormal findings in radiographs and at autopsy. Aggregates of dust-containing macrophages in the lungs were found presenting a pneumoconiosis called stannosis (Barták 1948, Cole 1964, Cutter 1949, Dundon 1950, Robertson 1961,

* The DECOS is of the opinion that this gastro-intestinal irritation is probably related to the concentration of free stannous ions present at the gastro-intestinal mucosa and not the absolute amount of ingested tin.

Schuler 1958, Sluis-Cremer 1989, Spencer 1954)^{NEG6, NEG35, NEG40, NEG52, NEG148, NEG161, NEG171, NEG173}. No fibrosis of the lungs associated with inhalatory exposure was reported (Robertson 1961, EHC 1981)^{NEG148, NEG87}. In most of these studies, no information on the exposure levels were available. Only one study concerning tin miners reported an exposure concentration of 2.22 mg tin/m³ (Robertson 1961^{NEG148}, no details on sampling method nor on method of analysis).

In a Belgian case control study, an increased risk of chronic renal failure was reported after occupational exposure to tin (Nuijts 1995)^{NEG126}.

Several reports concerning tin miners indicated an increased incidence of lung cancer (Forman 1992, Qiao 1989a and b, Taylor 1989)^{NEG63, NEG138, NEG139, NEG180}. The authors of these reports, however, did not identify tin as the carcinogenic factor. Assumed contributing factors included diet, radon, arsenic, silica and tobacco.

Additional information

Chen *et al*⁴ studied the risk for lung cancer among tin miners in China. The authors found a clear dose-response relation for silicoses in tin miners and exposure to dust (total dust and respirable crystalline silica dust). In 2002, Chen *et al*⁵ could not confirm this relation in another study in tin miners. In both studies, however, the increased risk of lung cancer was not related to exposure to tin or tin compounds.

3.2 Observations in animals

3.2.1 Irritation and sensitisation

Summary of the data in Arbete och Hälsa 2002:10 (part two)

SnCl₂ does not appear to be a skin irritant in animal studies. Only application (1 or 2% SnCl₂ and 0.25 or 0.5% SnF₂) to abraded skin of rabbits for 18 hours induced intraepidermal pustules and complete destruction of the epidermis (Stone 1968)^{NEG174}.

Irritation of the alimentary tract after SnCl₂ feeding was observed in rats (der Meulen 1974, Janssen 1985)^{NEG47, NEG88}.

Application of non-irritant levels of SnCl₂ and SnCl₄ in alcohol on skin and oral mucosa of Sprague Dawley rats did not lead to lesions of contact allergy (Larsson 1990)^{NEG103}.

Additional information

No new data were found.

3.2.2 Toxicity due to single exposure

Summary of the data in Arbete och Hälsa 2002:10 (part two)

Single oral administration of 50 mg metallic tin dust in saline to rats gave X-ray changes, tiny densities in the lungs after 4 months. Histopathologically no fibrous response was found one year after exposure (Robertson 1960)^{NEG146}.

Oral LD50 values for inorganic tin salts are 146-396 mg Sn/kg bw for NaSn_2F_5 and 1197-1678 mg Sn/kg bw for $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$.

SnO_2 did not induce any signs of toxicity in rats (250-1000 mg/kg bw), rabbits and dogs (250 mg/kg bw). SnCl_2 at 100 mg Sn/kg bw affected haem synthesis in rabbits (Chmielnicka 1992)^{NEG33}. 0.1 mg Sn/kg bw in mice reduced cytochrome P-450 activity significantly (Burba 1983)^{NEG19}.

Additional information

No new data were found.

3.2.3 Toxicity due to short time exposure

Summary of the data in Arbete och Hälsa 2002:10 (part two)

Dietary (oral) exposure of Wistar rats for 4 and 13 weeks to various salts and oxides of tin (0, 0.03, 0.10, 0.30 and 1.00% in food) led to a NOAEL of 0.1% (22-33 mg Sn/kg bw) based on growth retardation, decreased food efficiency, slight anaemia and slight histopathological changes in the liver. Dietary supplements of iron had a marked protective effect against tin-induced anaemia, while growth depression was not affected by enriching the diet with iron and copper (de Groot 1973 a and b)^{NEG45, NEG46}.

The NOAEL for SnCl_2 in Wistar rats fed orally 1, 10, 50, 100 and 200 mg Sn/kg diet (equivalent to 0.07, 0.7, 3.5, 7 and 13.2 mg Sn/kg bw/day) during 28 days was 0.07 mg/kg bw/day. At 0.7 mg/kg bw/day and above iron, copper and zinc tissue and plasma levels were (slightly) decreased. Blood haemoglobin levels decreased with increasing Sn levels. Both effects showed a dependency of dose (Pekelharing 1994)^{NEG134}.

In a 90-day study in Wistar rats exposed orally 2 times per day to 0.3, 0.6 and 1.0 mg Sn/kg bw a LOAEL of 0.6 mg Sn/kg bw/day (2 times 0.3 mg Sn/kg) was found. A dose-related decrease in calcium content in the bone was reported at 0.6 mg/kg bw/day and above (Yamaguchi 1980)^{NEG197}.

Tin chlorides have an effect on mouse immune response (Hayashi 1984)^{NEG81}. However, the route of administration in the studies investigating effects on the immune system is either intraperitoneal or intratracheal. The committees regard both routes as less relevant for occupational situation.

Injections (i.v. or i.p.) of metallic tin in the rat produced a plasma cellular hyperplasia in lymph-nodes and spleen, an effect that may be prevented by pre-treatment with tin salts. The severity of the effect depended on genetic characteristics of the subjects (not further specified) (Levine 1982, 1983 a and b, 1996)^{NEG106, NEG107, NEG108, NEG105}.

More studies are summarised in table 1.

Additional information

No new data were found.

3.2.4 Toxicity due to long-term exposure and carcinogenicity

Summary of the data in Arbete och Hälsa 2002:10 (part two)

The LOAEL in rats (Long Evans) exposed during their whole lifetime to SnCl₂ in drinking water was 0.4 mg Sn/kg bw. At this dose level (5 µg Sn/mL), which was the only dose tested in the experiment, fatty degenerative changes in liver and vacuolar changes in the renal tubules were observed (Schroeder 1967, 1968)^{NEG158, NEG160}.

Male and female F344 rats and B6C3F1 mice were exposed to 1000 and 2000 mg/kg food (20-40 and 35-89 mg Sn/kg bw for rats, 92-182 and 203-348 mg Sn/kg bw) as SnCl₂ and metallic tin for 105 weeks. Survival showed a dose dependency in male rats and female mice. C-cell adenomas and carcinomas of the thyroid gland occurred in male rats with a significant positive trend, i.e. in the dose groups a significantly higher tumour incidence compared to untreated controls was observed. In female mice hepatocellular adenomas and carcinomas (combined) exhibited a significant dose-related trend and the number of histiocytic lymphomas occurred with a significant positive trend. Total tumour incidence did not differ from historical control incidences. An association between treatment and the development of C-cell tumours of the thyroid gland in male rats was not fully excluded by the authors (NTP 1982)^{NEG124}.

More studies are summarised in table 1.

Additional information

No new data were found.

Table 1 Dose-effect relationships from animal repeated dose studies (adapted from Arbete och Hälsa 2002:10).

| Exposure regimen | Dose | Species | No animals/ group (controls) | Effect | Reference |
|--|--|------------------------------------|------------------------------------|--|--|
| SnCl ₂ for 28 days, 2 daily doses | 2.0 mg Sn/kg bw/day (oral) | Weanling male Wistar rats | 5 (5) | Decreased calcium content and decreased phosphatase activities in femoral bone. | Yamaguchi 1980 ^{NEG197} |
| SnCl ₂ for 5 days | 2 mg Sn/kg bw/day (oral) | Female rabbits | 5 (5) | No adverse effects on haem biosynthesis observed. | Zareba 1992 ^{NEG208} |
| SnCl ₂ for 1 month | 2 mg Sn/kg bw/day (oral) | Male rabbits | 5 (5) | Decreased zinc and copper concentrations in bone marrow, increased iron concentrations in liver and kidneys. | Zareba 1989 ^{NEG207} |
| SnCl ₂ for 4 months | 10 mg Sn/kg bw/day (oral) | Female rabbits | 6 | Transient anaemia, high s-iron, total iron binding capacity and saturation index. | Chmielnicka 1992 ^{NEG33} |
| 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) (oral) ~13-14 mg Sn/kg bw/day (200 mg Sn/kg diet, 15, 30 or 52 mg Zn/kg diet) (oral) ~39 mg Sn/kg bw/day (500 mg Sn/kg diet, 15 or 30 mg Zn/kg diet) (oral) ~142 mg Sn/kg bw/day (2000 mg Sn/kg diet, 15 mg Zn/kg diet) (oral) | Male rats, Sprague-Dawley | 7 (7) | ≥ 7 mg Sn/kg bw decreased calcium content of the tibias. ≥ 13-14 mg Sn/kg bw decrease in absorption of zinc. ≥ 39 mg Sn/kg bw decreased retention of zinc in tibia, kidney, liver and plasma, decreased copper levels in plasma, liver and kidney. | Johnson 1984, 1985 ^{NEG91, NEG92} |
| SnCl ₂ in diet for 4 weeks | 25 and 50 mg Sn/kg bw/day (250 and 500 mg Sn/kg diet) (oral) | 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. | Janssen 1985 ^{NEG88} |
| NaSn ₂ F ₅ by gavage for 30 days | 13.4 mg Sn/kg bw/day (20 mg NaSn ₂ F ₅ /kg bw/day) (oral) 67 mg Sn/kg bw/day (100 mg NaSn ₂ F ₅ /kg bw/day) (oral) 117 mg Sn/kg bw/day (175 mg NaSn ₂ F ₅ /kg bw/day) (oral) | Male and female Wistar rats | 20 (20) | No adverse effects noted. ≥ 67 mg/kg bw dose-dependent growth retardation. 15-20% of rats had degenerative changes in kidney tubular epithelium. | Conine 1976 ^{NEG36} |
| SnCl ₂ in drinking water for life | 0.34-0.38 mg Sn/kg bw/day (5µg/ml) (oral) | Long-Evans rats, males and females | 94 (82) | No significant change in tumour incidence. | Kanisawa 1969 ^{NEG95} |

3.2.5 *Mutagenicity and genotoxicity*

Summary of the data in Arbete och Hälsa 2002:10 (part two)

Only *in vitro* data are available. SnCl₂ was not mutagenic in the Ames test, while SnF₂ was slightly mutagenic in strain TA100 (Gocke 1981, Prival 1991)^{NEG72, NEG137}. SnCl₂ induced DNA damage in *E. coli* (Bernardo-Filho 1994, Dantas 1996, Silva 1994)^{NEG9, NEG42, NEG170}, CHO-cells (McLean 1983)^{NEG116} and human white blood cells (McLean 1983)^{NEG115}. The effects in CHO and human white blood cells were dose dependent. SnCl₄ induced chromosomal damage in human lymphocytes (Talukder 1989, Ganguly 1993)^{NEG179, NEG69}, but no DNA damage was induced in the SOS-chromotest (Hamasaki 1992)^{NEG75} and a test with CHO-cells (McLean 1983)^{NEG116}.

SnF₂ did not induce increases of micronucleated polychromatic erythrocytes in bone marrow from NMRI mice and did not induce sex-linked recessive mutations in *Drosophila* (Gocke 1981)^{NEG72}.

Additional information

SnCl₂ induced DNA damage in a comet assay and reduced viability (Trypan blue dye exclusion and flow-cytometry) in a K562 cell line derived from a chronic myelogenous human leukemia (with super-expression of reactive oxygen species detoxifying enzymes). Reduced viability was only found in cells incubated in TBS (tris buffered saline) but not in cells incubated with RPMI 1640 medium supplemented with FBS (fetal bovine serum). In earlier studies DNA damage by SnCl₂ was correlated with formation of reactive oxygen species (ROS) and direct binding to DNA. This study confirmed that direct binding to DNA plays a major part, although the author concluded that also a correlation with ROS-formation exists⁵.

3.2.6 *Reproductive and developmental toxicity*

Summary of the data in Arbete och Hälsa 2002:10 (part two)

Pregnant rats (Sprague-Dawley) were given 125-625 mg Sn/kg food as various tin salts. Foetal tin concentrations were significantly increased on day 20 of gestation compared to control values (Theuer 1971)^{NEG182}. Tin salts given in the diet of pregnant rats passed the placenta. Foetal tin values were found to be elevated when the maternal diet contained tin salts.

Additional information

No new data were found.

Hazard assessment

4.1 Assessment of health hazard

Tin (metal)

No information concerning the effects after acute and short-term exposure to tin (metal) is available. Therefore, DECOS is of the opinion that a short term occupational exposure limit for tin (metal) is not indicated.

In addition, no information concerning the effects after long-term exposure to tin (metal) is available in man or experimental animals. Therefore, DECOS conclude that a health based recommended occupational exposure limit for tin (metal) cannot be derived.

Soluble inorganic tin compounds

No human and animal data are available concerning the effects of soluble inorganic tin compounds after acute or short term *inhalatory* exposure and only limited information is available concerning the effects after oral exposure. In man, gastrointestinal illness follows acute ingestions of food containing high levels of tin chloride (~1.7-2.6 mg Sn/kg bw) Benoy *et al*, 1971^{NEG8}. In addition, orally administered SnCl₂ to volunteers (~ 0.7 mg/kg bw/day) for 20 days, may inter-

ferre with the excretions of zinc and selenium (Greger *et al*, 1981; Johnson *et al*, 1982a/b)^{NEG73, NEG89, NEG90}.

Positive patch tests to SnCl₂ have been reported. However, only one case of occupational allergic contact dermatitis has been described (Nielsen *et al*, 1998)^{NEG122}.

In rats, SnCl₂ administered for 28 days may interfere with the iron, copper and zinc status (Pekelharing *et al*, 1994)^{NEG134}.

Based on the available acute data, DECOS is of the opinion that a short term occupational exposure limit for inorganic tin compounds cannot be derived.

No data are available concerning the effects in man and experimental animals after longterm *inhalatory* exposure to soluble inorganic tin compounds.

In animals oral long-term exposure to soluble tin compounds (ie SnCl₂) decreased the calcium content in the bone (LOAEL ~ 0.6 mg/kg bw/day, Yamaguchi *et al*, 1980)^{NEG197}, and caused degenerative changes in liver and kidney (LOAEL ~0.4 mg/kg bw/day, Schroeder, 1967/1968)^{NEG158, NEG160}, growth retardation and anemia (NOAEL ~ 22 mg/kg bw/day, De Groot *et al*, 1973a/b)^{NEG45, NEG46}. The exact doses of exposure (in mg/kg bw/day) were difficult to estimate due to the study designs and the lack of information in the reports. The effects of tin on the status of other metals (especially zinc), enzyme levels, passage via the placenta and the immune system are insufficiently investigated.

The animal studies suggest that tinchloride is not carcinogenic after oral exposure with a possible exception of C-cell tumors of the thyroid in male rats. Nevertheless, DECOS is of the opinion that at present no conclusion on carcinogenic properties of SnCl₂ can be drawn.

In general, DECOS considers the toxicological data after long-term exposure limited and of low quality. The studies only reported particular end-points and as such do not provide complete toxicological information. Moreover, DECOS doubts the relevance of the oral studies for the risk assessment after inhalatory exposure.

Based on these considerations, DECOS concludes that the critical effect of long-term exposure to soluble inorganic tin compounds cannot be established based on the available information.

Insoluble inorganic tin compounds

No information concerning the effects after acute and short-term exposure (both inhalatory and oral) to insoluble inorganic tin compounds is available. Therefore, DECOS is of the opinion that a short term occupational exposure limit for these compounds is not indicated.

Long-term inhalatory exposure (3 to 50 years) to SnO₂-dust induces stannosis (abnormal findings in radiographs representing a pneumoconiosis) in man, but no signs of impaired lung functions (forced expiratory volume and airway resistance), were found (Robertson *et al*, 1955 and 1960)^{NEG149, NEG146}. However, systematic data concerning the exposure levels are not available. A few reports registered lung cancer cases in tin miners in China (Forman *et al* 1992; Qiao *et al*, 1989a/b; Taylor, 1989; Chen *et al*, 2001 and 2002)^{NEG63, NEG138, NEG139, NEG180,7,8}. However, exposure to tin could not be causally related to these cases.

No data concerning the effects of long-term inhalatory exposure of insoluble inorganic tin compounds in experimental animals are available.

Oral subchronic exposure to several insoluble inorganic tin compounds in animals may lead to growth retardation and anemia (De Groot *et al*, 1973a/b)^{NEG45, NEG46}. The effects of insoluble inorganic tin compounds on the status of other metals (in particular zinc), enzyme levels, passage via the placenta and the immune system are insufficiently investigated. In addition, no data are available regarding the carcinogenic properties of the insoluble inorganic tin compounds.

Again, DECOS considers the toxicological data after long-term exposure limited and of low quality and doubts the relevance of the oral studies for the risk assessment after inhalatory exposure.

Based on these considerations, DECOS concludes that the critical effect of long-term exposure to insoluble inorganic tin compounds cannot be established based on the available information.

4.2 Groups at risk

No groups at risk were identified.

4.3 Health-based recommended occupational exposure limit

DECOS concludes that at present the available data are insufficient as scientific basis for an occupational exposure limit for tin(metal), soluble and insoluble inorganic tin compounds.

4.4 Recommendations for research

The DECOS recommends:

- a study concerning the inhalatory effects of tin and tin compounds.
- more data on irritation and sensitisation are needed.
- investigations of effects of inorganic tin on the mineral status, enzymes and dose-effect relationships on the haematopoietic system, immune system, bone, liver and kidney are considered necessary.
- Since tin and inorganic tin compounds have the capacity to interfere with DNA, additional information is necessary to further elucidate possible mutagenic and carcinogenic properties.
- Measurements of occupational exposure levels of inorganic tin in air are needed in order to correlate these to blood or tissue levels measured in workers exposed to tin in their working environment. More detailed investigation of the lung effects reported is considered necessary.

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A Request for advice

B The committee

C Comments on the public review draft

D Abbreviations

Part 2 Arbete och Hälsa: Tin and inorganic tin compounds

Annexes

Request for advice

In a letter dated October 11, 1993, ref DGA/G/TOS/93/07732A, to, the State Secretary of Welfare, Health and Cultural Affairs, the Minister of Social Affairs and Employment wrote:

Some time ago a policy proposal has been formulated, as part of the simplification of the governmental advisory structure, to improve the integration of the development of recommendations for health based occupation standards and the development of comparable standards for the general population. A consequence of this policy proposal is the initiative to transfer the activities of the Dutch Expert Committee on Occupational Standards (DECOS) to the Health Council. DECOS has been established by ministerial decree of 2 June 1976. Its primary task is to recommend health based occupational exposure limits as the first step in the process of establishing Maximal Accepted Concentrations (MAC-values) for substances at the work place.

In an addendum, the Minister detailed his request to the Health Council as follows:

The Health Council should advise the Minister of Social Affairs and Employment on the hygienic aspects of his policy to protect workers against exposure to chemicals. Primarily, the Council should report on health based recommended exposure limits as a basis for (regulatory) exposure limits for air quality at the work place. This implies:

- A scientific evaluation of all relevant data on the health effects of exposure to substances using a criteria-document that will be made available to the Health Council as part of a specific request
-

for advice. If possible this evaluation should lead to a health based recommended exposure limit, or, in the case of genotoxic carcinogens, a 'exposure versus tumour incidence range' and a calculated concentration in air corresponding with reference tumour incidences of 10^{-4} and 10^{-6} per year.

- The evaluation of documents review the basis of occupational exposure limits that have been recently established in other countries.
- Recommending classifications for substances as part of the occupational hygiene policy of the government. In any case this regards the list of carcinogenic substances, for which the classification criteria of the Directive of the European Communities of 27 June 1967 (67/548/EEG) are used.
- Reporting on other subjects that will be specified at a later date.

In his letter of 14 December 1993, ref U 6102/WP/MK/459, to the Minister of Social Affairs and Employment the President of the Health Council agreed to establish DECOS as a Committee of the Health Council. The membership of the Committee is given in annex B.

The committee

Dutch expert committee on occupational standards

- GJ Mulder, *chairman*
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 - RB Beems
toxicologic pathologist; National Institute of Public Health and the Environment, Bilthoven
 - LJNGM Bloemen
epidemiologist; Environ Netherlands BV, Zeist
 - PJ Boogaard
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 - PJ Borm
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 - DJJ Heederik
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-

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The first part of the document was prepared by WMLG Gubbels-van Hal, from NOTOX BV, 's-Hertogenbosch, The Netherlands.

Secretarial assistance: F Smith.
Lay-out: M Javanmardi.

Comments on the public draft

A draft of the present report was released 2004 public review. The following organisations and persons have commented on the draft document:

- Dr E González-Hernández
Ministerio de Trabajo y Asuntos Sociales, Spain
- JHP Severens
Vereniging van Ondernemingen in de Galvano-technische Industrie

Abbreviations

| | |
|------------------------|---|
| <i>bp</i> | boiling point |
| <i>EC₅₀</i> | concentration at which a described effect is found in 50% of the exposed animals or at which the effect is decreased up to 50% of the control value |
| <i>HBR-OEL</i> | health based recommended occupational exposure limit |
| <i>h</i> | hour |
| <i>IC₅₀</i> | concentration at which inhibition of a certain function is found up to 50% of the control value |
| <i>LC₅₀</i> | lethal concentration for 50% of the exposed animals |
| <i>LC₁₀</i> | lowest lethal concentration |
| <i>LD₅₀</i> | lethal dose for 50% of the exposed animals |
| <i>LD₁₀</i> | lowest lethal dose |
| <i>LOAEL</i> | lowest observed adverse effect level |
| <i>MAC</i> | maximaal aanvaarde concentratie (maximal accepted concentration) |
| <i>MAEL</i> | minimal adverse effect level |
| <i>MAK</i> | Maximale Arbeitsplatz Konzentration |
| <i>MOAEL</i> | minimal observed adverse effect level |
| <i>MTD</i> | maximum tolerated dose |
| <i>NAEL</i> | no adverse effect level |
| <i>NEL</i> | no effect level |
| <i>NOAEL</i> | no observed adverse effect level |
| <i>OEL</i> | occupational exposure limit |
| <i>PEL</i> | permissible exposure limit |

| | |
|------------------------|---|
| <i>ppb</i> | parts per billion (v/v)10 ⁻⁹ |
| <i>ppm</i> | parts per million (v/v)10 ⁻⁶ |
| <i>RD₅₀</i> | concentration at which a 50% decrease of respiratory rate is observed |
| <i>REL</i> | recommended exposure limit |
| <i>STEL</i> | short term exposure limit |
| <i>tgg</i> | tijd gewogen gemiddelde |
| <i>TLV</i> | threshold limit value |
| <i>TWA</i> | time weighted average |
| <i>V_{max}</i> | maximal reaction velocity of an enzyme |

Organisations

| | |
|--------------|---|
| <i>ACGIH</i> | American Conference of Governmental Industrial Hygienists |
| <i>CEC</i> | Commission of the European Communities |
| <i>DECOS</i> | Dutch Expert Committee on Occupational Standards |
| <i>DFG</i> | Deutsche Forschungsgemeinschaft |
| <i>EPA</i> | Environmental Protection Agency (USA) |
| <i>FDA</i> | Food and Drug Administration (USA) |
| <i>HSE</i> | Health and Safety Executive (UK) |
| <i>IARC</i> | International Agency for Research on Cancer (WHO) |
| <i>INRS</i> | Institut National de Recherche et de Sécurité (France) |
| <i>NIOSH</i> | National Institute for Occupational Safety and Health (USA) |
| <i>NTP</i> | National Toxicology Programme (USA) |
| <i>OECD</i> | Organisation for Economic Cooperation and Development |
| <i>OSHA</i> | Occupational Safety and Health Administration (USA) |
| <i>RTECS</i> | Registry of Toxic Effects of Chemical Substances |
| <i>SER</i> | Social and Economic Council (Sociaal-Economische Raad NL) |
| <i>WATCH</i> | Working Group on the Assessment of Toxic Chemicals (UK) |
| <i>WHO</i> | World Health Organisation |

Toxicological terms

| | |
|-------------|---|
| <i>bid</i> | <i>bis in diem</i> (twice a day) |
| <i>bw</i> | body weight |
| <i>CARA</i> | chronic non-specific respiratory diseases |
| <i>CHD</i> | coronary heart disease |
| <i>CNS</i> | central nervous system |
| <i>ECG</i> | electrocardiogram |
| <i>EEG</i> | electro encephalogram |
| <i>FCA</i> | Freunds Complete Adjuvans |

| | |
|-------------|--------------------------------|
| <i>FEV</i> | forced expiratory volume |
| <i>FSH</i> | follicle stimulating hormone |
| <i>GD</i> | gestation day(s) |
| <i>GPMT</i> | Guinea pig maimisation test |
| <i>GSH</i> | glutathione |
| <i>HLiA</i> | hamster liver activated |
| <i>IHD</i> | ischaemic heart disease |
| <i>im</i> | intramuscular |
| <i>ip</i> | intraperitoneal |
| <i>ipl</i> | intrapleural |
| <i>it</i> | intratracheal |
| <i>iv</i> | intravenous |
| <i>LH</i> | lutheinsing hormone |
| <i>MAC</i> | minimal alveolar concentration |
| <i>MFO</i> | mixed function oxidase |
| <i>NA</i> | not activated |
| <i>PNS</i> | peripheral nervous system |
| <i>po</i> | <i>per os</i> (= oral) |
| <i>RBC</i> | red blood cells |
| <i>RLiA</i> | rat liver activated |
| <i>SCE</i> | sister chromatid exchange |
| <i>sc</i> | subcutaneous |
| <i>UDS</i> | unscheduled DNA-synthesis |

Statistical terms

| | |
|------------|--------------------------|
| <i>GM</i> | geometric mean |
| <i>OR</i> | Odds Ratio |
| <i>RR</i> | Relative Risk |
| <i>SD</i> | standard deviation |
| <i>SEM</i> | standard error of mean |
| <i>SMR</i> | standard mortality ratio |

Analytical methods

| | |
|-------------|--------------------------------------|
| <i>AAS</i> | atomic absorption spectroscopy |
| <i>BEEL</i> | biological equivalent exposure limit |
| <i>BEI</i> | biological exposure index |
| <i>BEM</i> | biological effect monitoring |
| <i>BM</i> | biological monitoring |

| | |
|-------------|--|
| <i>ECD</i> | electron capture detector |
| <i>EM</i> | environmental monitoring |
| <i>FID</i> | flame ionisation detector |
| <i>GC</i> | gas chromatography |
| <i>GLC</i> | gas liquid chromatography |
| <i>GSC</i> | gas solid chromatography |
| <i>HPLC</i> | high performance liquid chromatography |
| <i>IR</i> | infrared |
| <i>MS</i> | mass spectrometry |
| <i>NMR</i> | nuclear magnetic resonance |
| <i>PAS</i> | personal air sampling |
| <i>TLC</i> | thin layer chromatography |
| <i>UV</i> | ultraviolet |

Statistical terms

| | |
|------------|--------------------------|
| <i>GM</i> | geometric mean |
| <i>OR</i> | Odds Ratio |
| <i>RR</i> | Relative Risk |
| <i>SD</i> | standard deviation |
| <i>SEM</i> | standard error of mean |
| <i>SMR</i> | standard mortality ratio |

Part 2 Arbete och Hälsa: Tin and inorganic tin compounds

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and The Dutch Expert Committee on Occupational Standards

2002:10

Bente Westrum and Yugnar Thomassen

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130. Tin and inorganic tin compounds

Bente Westrum and Yngvar Thomassen



Nordic Council of Ministers

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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.

We acknowledge the Nordic Council of Ministers for its financial support of this project.

G.J. Mulder
Chairman
DECOS

G. Johanson
Chairman
NEG

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 |

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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 |

^aAvailable 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 ₂ P ₂ O 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 Sn²⁺/Sn⁴⁺ 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/m³ 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 (SnO₂). The other ores are complex sulphides, stannite (Cu₂FeSnS₄), and teallite (PbZnSnS₂) (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. SnCl₄ is used as a dehydrating agent in organic synthesis, a stabiliser for plastics, and as a chemical intermediate for other tin compounds. SnCl₂ serves as a reducing agent in manufacturing ceramics, glass and inks (85).

Dental amalgams contain varying proportions of tin (12-30%) (11). SnF₂ 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 SnF₂ 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, babbitt 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/m³) 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/m³ (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/m³.

| 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/m³). In Table 5, the branches and job functions with tin levels > 0.05 mg Sn/m³ are listed. If some samples contained > 0.05 mg Sn/m³, 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 SnO₂, the acid solution is centrifuged and the tin compounds in the supernatant are determined as above. The precipitate is then treated with alkali, rendering SnO₂ 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 (SnCl₄) occurs by passive diffusion. The absorption of SnCl₄ 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 $^{113}\text{Sn}(\text{II})$ or $^{113}\text{Sn}(\text{IV})$ 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 $\mu\text{g Sn/l}$ (19.4 nmol/l) after 24 hours. After 120 hours the concentration was 0.7 $\mu\text{g/l}$ (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 $^{113}\text{Sn}(\text{II})$ or $^{113}\text{Sn}(\text{IV})$ 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 radionuclide ^{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 SnF₂ or SnF₄, 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 \pm 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 μ g Sn/l (8.4 nmol/l) in serum and urine are reported (157, 189) and a 95th upper percentile of 20 μ g 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 SnCl₂ and SnCl₄ 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 ¹¹³Sn(II) or ¹¹³Sn(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 ¹¹³Sn(II) or ¹¹³Sn(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).

¹¹³Sn was given as SnCl₂ 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 ($0.3 \mu\text{Ci}/\text{rat}$) 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 $29 \pm 13 \mu\text{g}$ (mean \pm standard deviation) and $122 \pm 52 \mu\text{g}/\text{day}$, 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) synthetase 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 $\mu\text{mol/l}$ 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).

SnCl₂ 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 SnCl₂ (50 mg/kg body weight, daily for 2 days) induced the coumarin 7-hydroxylase in liver and kidney (58).

SnCl₂ (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). SnCl₂ orally (60 mg Sn/kg body weight/day for 3 days) in rats also suppressed insulin secretion and inhibited hepatic phosphorase activity (201, 202), active transport of calcium and mucosal alkaline phosphatase activity in the duodenum and increased bile calcium contents (195, 203).

SnCl₂ 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 SnCl₂ 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 SnCl₂ induced increase in calcium entry into the nerve terminals (79). SnCl₂ 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 SnCl₂ (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 SnCl₂ on nerve transmission is reported.

10. Effects in animals and in vitro studies

10.1 Irritation and sensitisation

Solutions of 1% or 2% SnCl₂ and 0.25% or 0.5% SnF₂ 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% SnCl₂ or 0.1% SnF₂ (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 SnCl₂ and SnCl₄ 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 SnCl₂ 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 SnCl₂/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 E₂ 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 SnCl₄ at 3000 mg/m³ for 10 minutes daily for "several months", only transient irritation of the eyes and nose developed (133).

10.2 Effects of single exposure

SnCl₂ (100 μmol/l) as well as SnO₂ (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 Sn²⁺ was combined with Cd²⁺ or Ni²⁺ (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 $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ 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 discolored 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 $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (~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 $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$. The cytochrome P-450 content was also significantly reduced (19).

Table 6. 24-hour LD₅₀-data in mice and rats treated with NaSn₂F₅ or SnCl₂·2H₂O (37).

| Species | Administration mode | LD ₅₀ (mg Sn/kg) |
|--|---------------------|--------------------------------|
| <i>NaSn₂F₅</i> | | |
| 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 |
| <i>SnCl₂·H₂O</i> | | |
| 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 SnO₂ or Sn particles at high doses. The species, doses, and times from dosing to examination were: rats 250-1000 mg SnO₂/kg, 200-800 mg Sn/kg, 4-26 months; rabbits 250 mg SnO₂/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 SnO₂. Severe growth retardation, decreased food efficiency, slight anaemia and slight histological changes in the liver were observed with $\geq 0.3\%$ SnCl₂, 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 zinc 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-protoporphyrins (208).

In rabbits, a daily oral dose of 10 mg Sn/kg body weight as $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ 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 zinc, 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 SnCl₂/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 SnCl₂ 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) SnCl₂/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, SnCl₂ 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 SnCl₂ 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 SnCl₂ 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 SnCl₂ 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 SnCl₂.

10.5 Mutagenicity and genotoxicity

In the Ames test using various *Salmonella* strains (TA 1535, TA 100, TA 1538, TA 98 and TA 1537), SnF₂ 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). SnCl₂ 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 (SnCl₂, SnCl₄ and SnSO₄) in the Rec-assay in *Bacillus subtilis*, but indicated a high toxic effect of SnCl₂ and SnCl₄ on

bacteria (94). SnCl₄ 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 SnCl₂ (5-75 µg/ml, corresponding to 26-395 µmol/l). The results indicate that SnCl₂ 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 SnCl₂ abolished the lethal effect and suggested the participation of reactive oxygen species in the toxicological effect of SnCl₂ (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 SnCl₂. Near-UV illumination inhibited the lethal effect of SnCl₂ 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 SnCl₂, but the interpretation was difficult because of a clear cytotoxic effect on the bacteria (128). SnCl₄ did not produce DNA-damage in the SOS chromotest (75).

SnCl₂ 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 SnCl₄ produced no such DNA damage. There was no loss in colony formation 6 days after either treatment (116).

Tin(II) as SnCl₂ (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 SnCl₄ 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).

SnCl₄ at 10 and 20 µg/ml (38-76 µmol/l) increased the frequency of chromosomal aberrations, micronuclei and sister chromatid 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 SnCl₄·5 H₂O/ml (5.7-11.4 µmol/l) for 70 hours. Both doses of SnCl₄ 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 $\mu\text{g/ml}$ (11.4 $\mu\text{mol/l}$, 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 suppresses 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 LD₅₀ values in ICR mice following intraperitoneal injections of salts of several metal ions including Sn(II) (as SnCl₂) subsequent to pretreatment with the same ion (93).

Intratracheally injected SnCl₂ 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, SnCl₂ (36 mg Sn) given with ⁶⁵ZnCl₂ solutions (0.5, 4 and 6 mg of Zn, respectively) or with turkey test meals (4 mg of ⁶⁵Zn) inhibited ⁶⁵Zn absorption, measured by whole body counting of the retention of ⁶⁵Zn 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 SnCl₂ (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% SnCl₂ 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 SnCl₂ at 1% were non-irritating. However, irritant reactions were frequent in patients tested with 10% and 5% SnCl₂ in petrolatum (44).

In 199 patients with suspected allergic reactions to metals, 13 had positive patch tests with 2% SnCl₂ 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% SnCl₂ 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 SnCl₂ 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 SnCl₂ 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 SnO₂ 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/m³ 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 SnO₂. 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 SnO₂. Total silica concentration in the aerosols did not exceed 3%. Total dust concentration in air varied between 3 and 70 mg/m³. 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/m³. No further details are given (87).

Symptoms like wheezing, cough, chest pain and dyspnoea on exertion reported in workers handling SnCl₄ were probably due to elevated levels of hydrogen chloride formed by the combination of SnCl₄ and water in the presence of heat (109).

11.2.3 Conclusion

Occupational exposure to SnO₂ 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

SnCl₂ 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 SnCl₄ (115, 116).

12.1.2 Animals

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

The LOEL for SnCl₂ 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 SnCl₂ orally with respect to interference with the status of iron, copper and zinc 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 susceptibility to bacterial infection was observed after a single intratracheal injection of SnCl₂ at a dose corresponding to 0.24 mg/kg body weight (78).

12.1.3 Humans

The NOEL of acute ingestion of SnCl₂ with respect to gastrointestinal illness is approximately 1.7-2.6 mg Sn/kg body weight (8).

The LOEL for SnCl₂ administered orally for 20 days with respect to interference with the excretion of zinc 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% SnCl₂ in petrolatum is irritant, whereas 1% SnCl₂ 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 SnCl₂ 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 SnCl₂ 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 SnCl₂ (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 | 6 (6) | Non-significant decrease in femoral epiphysis calcium content. | (197) |
| | 2.0 mg Sn/kg bw/day | Wistar rats | | 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) ~22-33 mg Sn/kg bw/day (0.1% of compound) ~70-100, ~220-330 mg Sn/kg bw/day (0.3, 1.0% of compound) | Male rats, Sprague-Dawley | 10 males, 10 females (10+10) | No adverse effects noted. No adverse effects noted. ≥ 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. | (46) |

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. | |
| SnCl ₂ in diet for 4 weeks | ~142 mg Sn/kg bw/day (2000 mg Sn/kg diet, 15 mg Zn/kg diet) | | | | |
| | 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 ₂ F ₅ by gavage for 30 days | 13.4 mg Sn/kg bw/day (20 mg NaSn ₂ F 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 ₂ F ₅ /kg bw/day) 117 mg Sn/kg bw/day (175 mg NaSn ₂ F ₅ /kg bw/day) | | | ≥ 67 mg/kg bw dose-dependent growth retardation. 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 SnO₂ 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 exposure limit of 2 mg/m³ in the interest of minimising the potential of stannosis (1, 123).

In the US Environmental Protection Agency Gene-Tox Program the overall evaluation placed SnCl₂ in the limited negative category for carcinogenicity (120).

SnCl₂ 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 SnF₂, 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 SnCl₄ and SnCl₂. 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).

SnCl₂ 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 SnCl₂ 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. SnCl₂ 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*. SnCl₂ is irritating to skin. Inhalation of SnO₂ 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, SnCl₂, 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.

Eksposering 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%. Absorbent 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. SnCl₂ 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*. SnCl₂ 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 eksposering i arbeidet.

Nøkkelord: bein, lever, magetarm sykdom, nyre, grenseverdi for eksposering i arbeid, SnCl₂, 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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