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Concise International Chemical Assessment Document 65

TIN AND INORGANIC TIN COMPOUNDS

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Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization, and produced within the framework of the Inter-Organization Programme for the Sound Management of Chemicals.



World Health Organization
Geneva, 2005

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

WHO Library Cataloguing-in-Publication Data

Tin and inorganic tin compounds.

(Concise international chemical assessment document ; 65)

1.Tin - adverse effects 2.Tin compounds - adverse effects
3.Risk assessment 4.Environmental exposure I.International
Programme on Chemical Safety II.Series.

ISBN 92 4 153065 0
ISSN 1020-6167

(LC/NLM Classification: QV 618)

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Risk assessment activities of the International Programme on Chemical Safety, including the production of Concise International Chemical Assessment Documents, are supported financially by the Department of Health and Department for Environment, Food & Rural Affairs, UK, Environmental Protection Agency, Food and Drug Administration, and National Institute of Environmental Health Sciences, USA, European Commission, German Federal Ministry of Environment, Nature Conservation and Nuclear Safety, Health Canada, Japanese Ministry of Health, Labour and Welfare, and Swiss Agency for Environment, Forests and Landscape.

Technically and linguistically edited by Marla Sheffer, Ottawa, Canada, and printed by Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Germany

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are published by the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs have been developed from the Environmental Health Criteria documents (EHCs), more than 200 of which have been published since 1976 as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are usually based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all

possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170.¹

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that

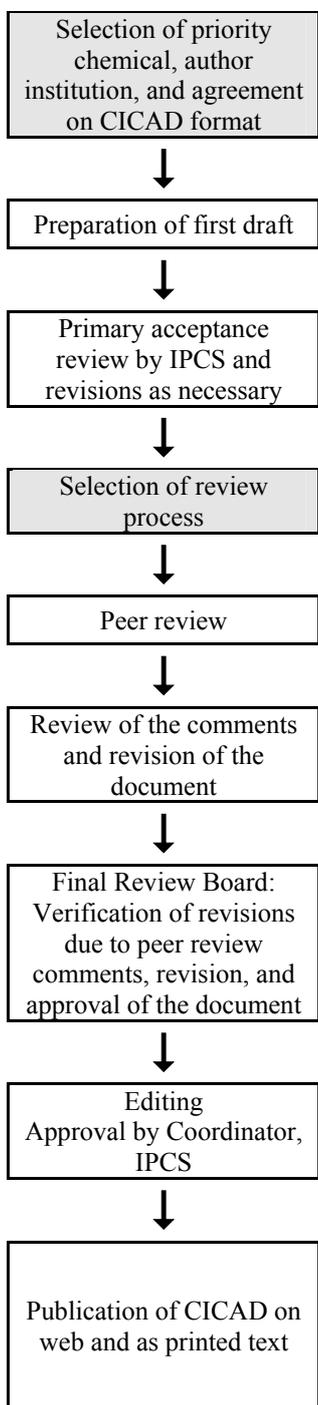
- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- it has high production volume;
- it has dispersive use.

The Steering Group will also advise IPCS on the appropriate form of the document (i.e. a standard CICAD or a *de novo* CICAD) and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is usually based on an existing national, regional, or international review. When no appropriate source document is available, a CICAD may be produced *de novo*. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The

¹ International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits*. Geneva, World Health Organization (Environmental Health Criteria 170) (also available at <http://www.who.int/pcs/>).

CICAD PREPARATION FLOW CHART



Advice from Risk Assessment Steering Group

Criteria of priority:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that

- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- the production volume is high;
- the use is dispersive.

Special emphasis is placed on avoiding duplication of effort by WHO and other international organizations.

A usual prerequisite of the production of a CICAD is the availability of a recent high-quality national/regional risk assessment document = source document. The source document and the CICAD may be produced in parallel. If the source document does not contain an environmental section, this may be produced *de novo*, provided it is not controversial. If no source document is available, IPCS may produce a *de novo* risk assessment document if the cost is justified.

Depending on the complexity and extent of controversy of the issues involved, the steering group may advise on different levels of peer review:

- standard IPCS Contact Points
- above + specialized experts
- above + consultative group

first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science. When a CICAD is prepared *de novo*, a consultative group is normally convened.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD¹ on tin and inorganic tin compounds was prepared jointly by Toxicology Advice & Consulting Ltd and the Centre for Ecology & Hydrology. The CICAD was based on three source documents. The first of these source documents was prepared by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards and considered the literature identified as of March 2002 (Westrum & Thomassen, 2002). The second source document was the monograph prepared by the 55th meeting of the Joint FAO/WHO Expert Committee on Food Additives, published in 2001 (JECFA, 2001). The third source document was the 2003 draft updated *Toxicological profile for tin and compounds*, produced by the US Agency for Toxic Substances and Disease Registry (ATSDR, 2003). In December 2003, Toxicology Advice & Consulting Ltd and the Centre for Ecology & Hydrology carried out comprehensive literature searches of online databases to identify any very recent references. Information on the nature of the peer review and the availability of the source documents is presented in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. This CICAD was approved as an international assessment at a meeting of the Final Review Board, held in Hanoi, Viet Nam, on 28 September – 1 October 2004. Participants at the Final Review Board meeting are listed in Appendix 4. The International Chemical Safety Cards for tin(II) chloride, tin(II) chloride dihydrate, tin(II) fluoride, tin(II) oxide, tin(IV) chloride, and tin(IV) oxide, produced by the International Programme on Chemical Safety (IPCS, 2004a–f), have also been reproduced in this document.

Tin is a grey-white metal. The most important inorganic tin compounds include the tin(II) and tin(IV) chlorides, tin(II) oxide, tin(II) fluoride, and the potassium and sodium stannates. The 2+ and 4+ oxidation states of tin, also known as tin(II) and tin(IV), are both fairly stable.

The annual world production of tin has been growing slowly in recent years and reached about 268 000 tonnes in 2003. About 10–15% of this figure is recovered metal. The major tin-producing countries are China, Indonesia, Peru, Bolivia, Brazil, and Australia, and significant quantities are also produced in Malaysia and Thailand. The main use of tin, accounting for about 34% of annual global production, is for solder alloys for electrical/electronic and general industrial applications. Tin also finds extensive use (about 25–30% of produc-

tion) as a protective coating for other metals, especially for food containers. Tin(II) chloride is commercially the most important inorganic compound and is used mainly as a reducing agent in organic and inorganic syntheses and in the manufacture of metallized glazing, glass, and pigments. Tin(IV) chloride is used in organic synthesis, in plastics, as an intermediate in organotin compound manufacture, and in the production of tin(IV) oxide films on glass. Tin(II) fluoride is broadly used in preventive dentistry.

Tin may be released to the atmosphere from both natural and anthropogenic sources. Tin is a component of many soils and may be released in dusts from wind storms, roads, and agricultural activities. Other less significant natural sources include forest fires and volcanic emissions. Gases, dusts, and fumes containing tin may be released from smelting and refining processes, industrial uses of tin, waste incineration, and burning of fossil fuels. The vapour pressure of elemental tin is negligible; tin and inorganic tin compounds are non-volatile under environmental conditions. Tin(II) chloride is soluble in water, whereas other tin compounds tend to be only slightly soluble. Tin compounds are likely to partition to soils and sediments. Inorganic tin may undergo oxidation–reduction, ligand exchange, and precipitation reactions in the environment. The biomethylation of inorganic tin has been demonstrated in pure bacterial cultures, sediments, and decaying plant material. Inorganic tin compounds may be bioconcentrated by organisms, but data are limited.

Average tin concentrations in air are generally below 0.1 $\mu\text{g}/\text{m}^3$ (ranging up to 0.8 $\mu\text{g}/\text{m}^3$), with higher concentrations near some industrial facilities. In general, tin occurs in trace amounts in natural waters. Higher inorganic tin concentrations are associated with industrial discharges and tributyltin use. In a survey of lakes and rivers, nearly 80% of samples were found to contain inorganic tin at concentrations below 1 $\mu\text{g}/\text{litre}$; higher levels of up to 37 $\mu\text{g}/\text{litre}$ were reported near pollution sources. Inorganic tin concentrations ranging from 0.001 to 0.01 $\mu\text{g}/\text{litre}$ have been reported for coastal waters, with levels of up to 8 $\mu\text{g}/\text{litre}$ near pollution sources. Inorganic tin concentrations in sediment ranged up to 8 mg/kg dry weight in coastal areas and up to 15.5 mg/kg in rivers and lakes. Tin concentrations in the Earth's crust are approximately 2–3 mg/kg. Total tin concentrations in soil can range from <1 to 200 mg/kg, but levels of 1000 mg/kg may occur in areas of high tin deposits. Certain ore deposits may contain up to 50 000 mg/kg as tin.

For the general population, the diet is the main source of exposure to inorganic tin. JECFA recently concluded that mean tin intakes in seven countries ranged from <1 up to 15 mg/day per person, but maximum daily intakes could reach 50–60 mg for certain

¹ For a list of abbreviations and acronyms used in this report, please refer to Appendix 1.

individuals who routinely consume canned fruits, vegetables, and juices from unlacquered cans. Drinking-water is not a significant source of inorganic tin and might contribute approximately 0.012–0.02 mg/day. Similarly, the low levels of inorganic tin in air mean that the amount of inhaled tin is very low, probably below approximately 0.01–0.02 mg/day.

In humans and laboratory mammals, absorption of inorganic tin from the gastrointestinal tract is low (generally less than 5%), but is influenced by dose, anion (compound solubility), and the presence of other substances. Unabsorbed ingested tin is mostly (95–99%) excreted in the faeces within 48 h. Absorbed tin distributes mainly to the bone, but also to the lungs, liver, and kidneys. Limited evidence suggests that inorganic tin does not readily cross the blood–brain barrier. Absorbed tin is mainly excreted in the urine, with some additional biliary excretion occurring. In mice, the biological half-life of absorbed inorganic tin was approximately 30 days.

Transient eye and nasal irritation occurred in guinea-pigs exposed to tin(IV) chloride by inhalation. Metallic tin is unlikely to have skin irritation potential, whereas tin(II) and tin(IV) chloride are skin irritants. In some studies, the inclusion of tin(II) chloride in the diet for 4–13 weeks produced gastrointestinal tissue changes indicative of local irritation. The early literature contains reports of gastrointestinal effects (nausea, abdominal cramps, vomiting, and diarrhoea) in humans following consumption of fruit or juice from unlacquered tin cans. The effects appear to result from local gastric irritation due to dissolved tin. This aspect is addressed further below. A small number of individuals have given skin reactions indicative of a local allergic response when patch-tested with tin or tin(II) chloride, but, given its widespread use, tin would not appear to be an important skin allergen.

In the early literature, there are a number of cases where occupational exposure to dust and fumes containing insoluble tin(IV) oxide led to a benign pneumoconiosis (stannosis). This condition is characterized by mottled shadows on the lungs, apparently caused by tin(IV) oxide deposits. Stannosis is not associated with fibrosis or loss of lung function.

In laboratory animals, the repeated ingestion of tin(II) chloride had adverse effects on the body status of copper, iron, zinc, and calcium. Tin salt-induced decreases in the calcium content of bone have led to reduced bone strength. Reductions in haemoglobin and effects on red blood cells, leading to anaemia, have been observed. Certain studies involving repeated administration of tin(II) chloride by the oral route have reported tissue effects in the liver, kidneys, testes, pancreas, and brain. In the most comprehensive of the available

lifetime oral studies, there were no microscopic changes in a wide range of tissues of rats or mice given tin at up to about 60 mg/kg body weight per day (rats) or 180–270 mg/kg body weight per day (mice) as tin(II) chloride in the diet. In this study, the NOAELs were 30 mg/kg body weight per day in rats and 130 mg/kg body weight per day in mice, with reduced survival seen at the higher doses.

Tin(II) chloride gave no clear evidence of carcinogenic activity when given in the diet to rats and mice for 2 years. More limited bioassays carried out on tin metal, tin(II) chloride, and a small number of other tin compounds also failed to detect carcinogenic activity. In short-term screening assays for genotoxicity potential, tin(II) chloride did not induce mutations in Ames bacterial tests, mutations or gene conversions in yeast, DNA damage in rat liver cells in culture, mutations in mouse lymphoma cells *in vitro*, or chromosome damage (micronuclei) *in vivo* in the bone marrow of mice treated by intraperitoneal injection. In bacterial rec assays (in which activity is an indirect indication of DNA damage), tin(II) chloride was active in *Escherichia coli* but (along with other tin salts) inactive in *Bacillus subtilis*. In culture, tin(II) chloride induced chromosome damage and SCEs in hamster ovary cells and DNA damage in human lymphocytes, hamster ovary cells, and plasmid DNA. Tin(IV) chloride tested *in vitro* did not damage DNA in hamster ovary cells but induced chromosome aberrations, micronuclei, and SCEs in human lymphocytes. Tin(II) fluoride caused DNA damage in cultures of human lymphocytes, but did not induce micronuclei formation in the bone marrow following injection into the peritoneum of mice; Ames tests on this compound gave no convincing evidence of activity. Limited evidence is consistent with the suggestion that tin-induced DNA damage might result from the production of reactive oxygen species. The mechanism underlying tin-induced chromosome damage in cultured mammalian cells is unclear, although it is known that certain inorganic compounds can yield positive results in such assays as a result of pH or ionic changes in the test medium.

Only limited data were identified on the potential of inorganic tin compounds to cause reproductive and developmental toxicity. No adverse effects were found in rats when tin (an uncharacterized form, produced by mixing aqueous tin(II) chloride with casein prior to dietary inclusion) was given in the diet for three generations or when tin(II) fluoride, sodium pentachlorostannite, or sodium pentafluorostannite were given in the diet throughout pregnancy. Similarly, repeated gavage treatment of pregnant rats, mice, and hamsters with tin(II) chloride was without adverse effect on the fetuses.

Limited data are available on the ability of ingested tin to adversely affect zinc absorption in humans. In one volunteer study, plasma appearance of zinc 1–4 h following a zinc dose was unaffected by concomitant ingestion of up to 100 mg tin (as tin(II) chloride). Another study reported that a single dose of 36 mg tin (again, as tin(II) chloride), taken with zinc, resulted in a lower zinc retention. Moderate disturbances in zinc excretion rates were reported in a third study in which the normal diet was supplemented with tin at 50 mg/day (as tin(II) chloride in fruit juice). Although a no-effect level for inhibition of zinc absorption has not been clearly established, the lowest dose reported to have this effect (36 mg) is about 2.5 to >36 times higher than the estimated mean population intakes as summarized by JECFA. However, those who routinely consume canned fruits, vegetables, and juices from unlacquered cans could have tin intakes (50–60 mg) that are similar to the acute (36 mg) or repeated (50 mg) dose levels reported in some studies to affect zinc absorption or balance. Whether this would have any clinical effect is likely to be critically dependent upon an adequate dietary supply of zinc.

The tin doses involved in the early reports of gastrointestinal effects following consumption of canned fruit or juice have been estimated (at 30–200 mg), but confidence in the accuracy of these figures is low. Two recent volunteer studies provide a better insight into effective doses and, perhaps more importantly, concentrations. The first study involved ingestion of tomato juice to which tin(II) chloride had been added to give tin concentrations of 161, 264, or 529 mg/kg (tin doses of about 40, 66, and 132 mg, respectively). At 161 mg/kg, one volunteer (of 18) reported mild gastrointestinal symptoms; typical acute symptoms were seen at 264 and 529 mg/kg. Serum levels of tin did not increase 0.5–4 h post-dosing at any dose, supporting the view that acute effects of tin ingestion are dependent upon concentration (resulting in local gastric irritation) rather than due to systemically absorbed tin. A second study involved ingestion of tomato soup containing tin that had migrated from unlacquered cans. The tin concentrations studied were <0.5, 201, and 267 mg/kg, providing acute tin doses of up to about 67 mg. No evidence of any acute effects was seen in this study. The low-effect or no-effect dose of approximately 67 mg tin in these studies is about 4.5 to >67 times higher than the JECFA estimates of mean population daily intakes and is similar to the estimated daily intake (50–60 mg) of individuals who routinely consume fruits, vegetables, and juices contained in unlacquered cans.

Under environmental speciation conditions, inorganic tin compounds have low toxicity in both aquatic and terrestrial organisms, largely due to their low solubility, poor absorption, low accumulation in tissues, and rapid excretion. Most laboratory testing with aquatic

organisms has been carried out with the soluble tin(II) chloride. The most sensitive microalgae are the marine diatoms *Skeletonema costatum* and *Thalassiosira guillardii*, with 72-h EC₅₀s of tin(II) cations, based on growth inhibition, of around 0.2 mg/litre. Acute LC/EC₅₀s of tin(II) for aquatic invertebrates range from 3.6 to 140 mg/litre, with a 21-day EC₅₀, based on reproductive success in daphnids, of 1.5 mg of tin(II) per litre. Fish toxicity tests clearly show that tin(IV) chloride is less toxic than the more soluble tin(II) chloride. Ninety-six-hour LC₅₀s for fish range from 35 mg of tin(II) per litre to >1000 mg of tin(IV) per litre. Embryolarval test results (i.e. 7- to 28-day LC₅₀s) for fish and amphibians range from 0.1 to 2.1 mg/litre for tin(II).

Concentrations showing toxicity to organisms are generally several orders of magnitude higher than those found in the environment. The most sensitive test results were 72-h exposures of diatoms and embryo-larval amphibian studies, with toxic effects seen at 0.1–0.2 mg of tin(II) per litre. Even at these concentrations, toxic effects caused by inorganic tin are unlikely, even near sources of local pollution. It should be noted that where concentrations are expressed as total tin, a percentage is likely to be in the form of organotins (e.g. tributyltin), which are more bioavailable and toxic. For more information on the environmental fate and toxicity of tributyltin, please refer to IPCS (1990, 1999).

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Tin (CAS No. 7440-31-5) has the atomic symbol Sn, the atomic number 50, and an atomic mass of 118.71. Tin occurs naturally as the stable isotopes ¹¹²Sn (0.97%), ¹¹⁴Sn (0.65%), ¹¹⁵Sn (0.36%), ¹¹⁶Sn (14.5%), ¹¹⁷Sn (7.7%), ¹¹⁸Sn (24.2%), ¹¹⁹Sn (8.6%), ¹²⁰Sn (32.6%), ¹²²Sn (4.6%), and ¹²⁴Sn (5.8%) (de Bièvre & Barnes, 1985). The most commercially significant inorganic tin compounds include tin(II) chloride, tin(IV) chloride, tin(IV) oxide, potassium and sodium stannates, tin(II) fluoride, tin(II) difluoroborate, and tin(II) pyrophosphate. Chemical formulae, synonyms, relative molecular masses, and CAS registry numbers of the important inorganic tin compounds covered in this CICAD are listed in Table 1. Table 2 contains other inorganic tin compounds that also feature in this CICAD.

Pure tin exists in two allotropic crystalline modifications: grey tin (alpha form) and white tin (beta form). At low temperatures (at about 18 °C and below), the grey tin changes to white tin. Physical and chemical properties of tin and some inorganic tin compounds are listed in Table 3.

Table 1: Chemical identification of tin and inorganic tin compounds reviewed in this CICAD.

Chemical name	Synonyms	Chemical formula	Relative molecular mass	CAS number
Tin		Sn	118.7	7440-31-5
Potassium stannate	Dipotassium tin trioxide	K ₂ SnO ₃	244.9	12142-33-5
Potassium stannate	Potassium stannate trihydrate	K ₂ Sn(OH) ₆	298.9	12125-03-0
Sodium stannate	Disodium tin trioxide	Na ₂ SnO ₃	212.7	12058-66-1
Sodium stannate	Sodium stannate trihydrate	Na ₂ Sn(OH) ₆	266.7	12027-70-2 12209-98-2 ^a
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 ₂ I ₂	443.4	13940-16-4
Tin(II) difluoroborate	Stannous fluoroborate	Sn(BF ₄) ₂	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(II) oxide	Tin oxide; stannous oxide	SnO	134.7	21651-19-4
Tin(IV) oxide	Tin dioxide; stannic oxide	SnO ₂	150.7	18282-10-5
Tin(II) pyrophosphate	Stannous pyrophosphate	Sn ₂ P ₂ O ₇	411.3	15578-26-4
Tin(II) sulfate	Stannous sulfate	SnSO ₄	214.8	7488-55-3
Tin(IV) sulfate	Stannic sulfate	Sn(SO ₄) ₂	310.9	19307-28-9

^a CAS number given in Westrum & Thomassen (2002).

The 2+ (stannous) and 4+ (stannic) oxidation states are both reasonably stable and interconverted by moderately active reagents. The Sn²⁺/Sn⁴⁺ potential is -0.15 V, and tin(II) can act as a mild reducing agent. Due to its amphoteric nature, tin reacts with strong acids and strong bases but remains relatively resistant to neutral solutions. A thin protective oxide film forms on tin exposed to oxygen or dry air at ordinary temperatures; heat accelerates this reaction. Tin is readily attacked by hydrogen iodide and hydrogen bromide and less readily by hydrogen chloride. Hot concentrated sulfuric acid reacts with tin to form tin(II) sulfate, whereas the diluted acid reacts only slowly with tin at room temperature. Reaction of tin with dilute nitric acid yields soluble tin nitrates; in concentrated nitric acid, tin is oxidized to insoluble hydrated tin dioxide. Organic acids such as lactic, citric, tartaric, and oxalic acid attack tin slowly in the presence of air and oxidizing substances (Gaver, 1997). Molten tin reacts with phosphorus, forming a phosphide. Stannates are produced by the action of strong potassium hydroxide or sodium hydroxide on tin (Mark, 1983). Tin(IV) chloride reacts with water to generate colloidal tin oxides (Wiberg et al., 2001).

3. ANALYTICAL METHODS

Tin is readily measured in multielement analyses of air, water, and solid waste samples by ICP-AES. For samples that are free of particulate matter, such as drinking-water, direct aspiration AAS, such as EPA Method 7870, may be used. Other samples, such as groundwater, industrial wastes, soils, sediments, sludges, and other solid wastes, require digestion prior to analysis to determine total and acid-leachable metal (US EPA, 1992). EPA Method 3050B, which describes acid digestion of sediments, sludges, and soils, does not list tin as an analyte; however, it states that other elements and matrices may be analysed by this method if performance is demonstrated for that analyte in that matrix at the concentrations of interest (US EPA, 1996).

The standard methods using either flame atomic absorption (Standard Method 3111B) or electrothermal atomic absorption (Standard Method 3113B) may be used for analysis of tin in water, depending on the sensitivity desired (APHA et al., 1998b,c). Although tin is not specifically listed as an analyte for the ICP-MS method (Standard Method 3125), this method may also be used in most cases and has lower detection limits (APHA et al., 1998a).

Table 2: Chemical identification of some further^a inorganic tin compounds featured briefly in this CICAD.

Chemical name	Synonyms	Chemical formula	Relative molecular mass	CAS number
Sodium pentachlorostannite	Sodium chlorostannite	NaSn ₂ Cl ₅	437.7	102696-35-5
Sodium hexachlorostannate	Sodium chlorostannate	Na ₂ SnCl ₆	3544.4	Not found
Sodium pentafluorostannite	Sodium fluorostannite	NaSn ₂ F ₅	236.7	22578-17-2
Stannane	Tin tetrahydride	SnH ₄	122.7	2406-52-2
Tin(II) orthophosphate	Tritin bis(orthophosphate); stannous phosphate	Sn ₃ (PO ₄) ₂	546.1	15578-32-2
Tin(IV) orthophosphate	Stannic phosphate	Sn ₃ (PO ₄) ₄	736.0	Not found
Tin(II) sulfide	Stannous sulfide; tin monosulfide	SnS	150.8	1314-95-0
Tin(IV) sulfide	Stannic sulfide; tin disulfide	SnS ₂	182.8	1315-01-1 12738-87-3
Tin(II) hydroxide	Stannous hydroxide; tin dihydroxide	Sn(OH) ₂	152.7	12026-24-3
Tin(IV) hydroxide	Stannic hydroxide; tin tetrahydroxide	Sn(OH) ₄	186.7	12054-72-7
Tin(II) chloride dihydrate	Stannous chloride dihydrate	SnCl ₂ ·2H ₂ O	225.6	10025-69-1
Tin(II) citrate	Stannous citrate; tritin dicitrate	Sn ₃ ((HO)C(COO)-(CH ₂ COO)) ₂	734.3	59178-29-9
Tin(IV) citrate	Stannic citrate	Not found	Not found	Not found
Sodium tin citrate	Not found	Not found	Not found	Not found
Tin(II) oxalate	Stannous oxalate	Sn(COO) ₂	206.7	814-94-8
Tin(II) tartrate	Stannous tartrate	Sn(OOC(CHOH) ₂ COO)	266.8	815-85-0 14844-29-2
Tin(II) nitrate	Stannous nitrate	Sn(NO ₃) ₂	242.7	Not found
Tin(IV) nitrate	Stannic nitrate	Sn(NO ₃) ₄	366.7	Not found
Tin(II) oleate	Stannous oleate	Sn(C ₁₇ H ₃₄ COO)	401.2	1912-84-1
Tin(II) 2-ethylhexanoate	Stannous bis(2-ethylhexanoate)	Sn(OOCCH(C ₂ H ₅)C ₄ H ₉) ₂	405.1	301-10-0
Tin(II) phytate	Stannous phytate	Not found	Not found	Not found

^a These were not the subject of the source documents and consequently were not included in the search updates. However, data on these are included when encountered, as they can provide insights into the effects of other inorganic tin compounds.

Table 3: Physical and chemical properties of tin and some inorganic tin compounds.^a

Compound (formula)	Melting point (°C)	Boiling point (°C)	Solubility in water
Sn	232	2602	Insoluble
SnBr ₄	31	205	Slightly soluble
SnCl ₂	247	Decomposes at 623–652	Soluble
SnCl ₄	-33	114	Slightly soluble (reacts with)
SnF ₂	213	850	Slightly soluble
SnI ₂	320	714	Slightly soluble
SnI ₄	143	365	Slightly soluble
SnO	1080	No data	Insoluble
SnO ₂	1630	1900	Insoluble
Sn ₂ P ₂ O ₇	Decomposes at 400	-	Insoluble
SnS	880	1210	Insoluble
SnSO ₄	Decomposes at >378	-	Reacts with

^a From Lide (1998–1999).

Table 4: Analytical methods.

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Acidify with nitric acid	ICP-MS	0.05–0.1 ng/g	103 ± 3%	Brzezinska-Paudyn & Van Loon (1988)
Water	Generate hydride with sodium borohydride or electrolytically, sweep into silica cell heated to 700 °C	AAS	0.02 µg/litre 0.5 µg/litre	No data	Rains (1982) Thompson & Thomerson (1974)
Water	Acidify with nitric acid	AAS (direct aspiration)	0.8 mg/litre	No data	USEPA (1986, 1992, 1996); APHA et al. (1998c)
Water	Acidify with nitric acid	AAS (furnace technique)	5 µg/litre	No data	APHA et al. (1998b)
Water ^a	Acidify with nitric acid	ICP-AES	No data	No data	APHA et al. (1998a)
Sediment	Digest in oxidizing acid	ICP-MS	25–50 ng/g		Brzezinska-Paudyn & Van Loon (1988)
Biological material	Digest in oxidizing acid	ICP-MS	25–50 ng/g		Brzezinska-Paudyn & Van Loon (1988)

^a Tin not listed specifically as an analyte, but can be determined by ICP-AES.

The method recommended by NIOSH for measuring airborne inorganic tin and its compounds, except oxides, is filter collection followed by acid digestion and AAS or ICP-AES (NIOSH, 1994a). If the aerosol phase is believed to contain tin(IV) oxide, the acid solution is centrifuged and the tin compounds in the supernatant are determined as above. The precipitate is then treated with alkali, rendering tin(IV) oxide to a soluble stannate, and the determination is made as above (Beliles, 1994). Other acid digestion procedures (aqua regia plus hydrogen fluoride) are available for simultaneous measurements of total tin and other elements by, for example, ICP-AES (Butler & Howe, 1999) or ICP-MS (Schramel et al., 1997). Radiochemical neutron activation analysis has been used for the measurement of tin in human biological materials at background levels (Versieck & Vanballenberghe, 1991). A field portable X-ray fluorescence spectrometer has been developed as a rapid, non-destructive, on-site alternative for analysis of membrane filters used in NIOSH Method No. 7300 (NIOSH, 1994a) for metals (Bernick & Campagna, 1995). An ICP-AES method with a limit of quantification of 30 µg/litre (which equated to 0.8 mg/kg product) has been used successfully to measure total tin in various foods (Perring & Basic-Dvorzak, 2002).

Although not specifically listed, tin can be quantified in water using ICP-MS, according to ISO 17294-2 (ISO, 2003a). ISO guidelines also exist to measure tin in canned milk (e.g. ISO, 2003b) and in fruit (ISO, 1998, 2004).

When selecting samplers for aerosol collection, their sampling characteristics should comply with internationally accepted sampling criteria, such as those outlined by

the ISO (2000). NIOSH (1994b) also offers internationally accepted sampling criteria.

Savolainen & Valkonen (1986) reported analysis of tin in tissue (brain and blood) samples down to a detection limit of 5 nmol/kg wet weight. Tissue samples were digested in a mixture of nitric, sulfuric, and perchloric acids (3:1:1 by volume), with a gradual increase in temperature to 275 °C. Tin was then converted to stannane using sodium borohydride and sodium hydroxide and, after argon purging, was analysed by AAS.

Analytical methods for total inorganic tin in water, sediment, and biological material are summarized in Table 4.

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

4.1 Natural and anthropogenic sources

Tin occurs naturally in the Earth's crust, with an average concentration of approximately 2–3 mg/kg (Budavari, 2001). Tin compounds are found in various environmental media in both inorganic and organic forms. Tin may be released to the environment from natural and anthropogenic sources. Tin is a component of many soils, and inorganic tin compounds may be released in dusts from wind storms, roads, and agricultural activities. Other less significant natural sources include forest fires and volcanic emissions. Releases of tin to environmental media may occur from

the production, use, disposal, and recovery of tin and tin compounds. Gases, dusts, and fumes containing tin may be released from smelting and refining processes, industrial uses of tin, waste incineration, and burning of fossil fuels (Lantzy & Mackenzie, 1979; IPCS, 1980; Byrd & Andreae, 1986; Senesi et al., 1999). Tin may be released to soil from landfilling of tin-containing wastes, including used cans (IPCS, 1980). The application of pretreated municipal sludge and urban refuse as soil amendments may also introduce tin to soils. Inorganic tin can be formed as a breakdown product of organotin degradation (Blunden & Chapman, 1982; Maguire et al., 1983; Maguire & Tkacz, 1985; Kawai et al., 1998).

Other point sources that might introduce tin to the soil include application of manure, corrosion of metal objects, and dispersion of metallic ores during transport (Senesi et al., 1999).

Total global emissions to the atmosphere from anthropogenic sources (industrial emissions and burning of fossil fuels) were estimated at 43 000 tonnes (~90% of total emissions) in the 1970s. Emissions from natural sources include continental dusts (~10% of total emissions), forest fires (<2% of total emissions), and volcanoes (<1% of total emissions) (Lantzy & Mackenzie, 1979). Worldwide emissions of tin to the atmosphere from coal and oil combustion, refuse incineration, and copper/nickel production facilities were estimated at 1470–10 810 tonnes in 1983 (Nriagu & Pacyna, 1988). No more recent data were identified.

4.2 Production and use

Tin is mined chiefly as cassiterite (SnO_2). The other ores are complex sulfides such as stannite ($\text{Cu}_2\text{FeSnS}_4$), teallite (PbSnS_2), canfieldite (Ag_3SnS_6), and cylinderite ($\text{PbSn}_4\text{FeSb}_2\text{S}_{14}$) (Beliles, 1994). Annual world production of tin was quite stable at approximately 210 000–230 000 tonnes for decades (Westrum & Thomassen, 2002) but is growing slowly and reached 268 000 tonnes in 2003 (K. Nimmo & S. Blunden, personal communication, 2004). Of this, about 10–15% is secondary metal recovered mainly from scrap waste and, to a much lesser degree, detinning (Westrum & Thomassen, 2002; K. Nimmo & S. Blunden, personal communication, 2004). More than 22 countries produce tin, but the 6 largest producers in 2001 were China (36%), Indonesia (23%), Peru (17%), Brazil (6%), Bolivia (6%), and Australia (4%) (ATSDR, 2003). Significant quantities are also produced from smelters in Malaysia and Thailand (Westrum & Thomassen, 2002; K. Nimmo & S. Blunden, personal communication, 2004). In Europe and North America (e.g. Belgium, Russian Federation, USA), the tin produced is mainly secondary; the USA (which is not a primary producer) is believed to be the world's largest producer of secondary tin. In 2002, about 13 000 tonnes of tin from old and

new scrap were recycled (ATSDR, 2003; Carlin, 2003a). Tin mining depends on the character of the deposit. About 20% of the primary deposits are embedded in underground granitic rock, and recovery methods are complex; the more important veins or lodes are secondary deposits (about 80%) in the form of an alluvial mud in the stream beds and placers, and the recovery is simpler (Gaver, 1997). The processing of tin ore following recovery involves smelting. 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 (Robertson, 1960, 1964). Smelted ore may be further refined by heat treatment or electrolytic processes (Gaver, 1997). Certain ore deposits may contain tin at up to 50 000 mg/kg (K. Nimmo & S. Blunden, personal communication, 2004).

Currently, the major use for tin is for solder alloys for electrical/electronic and general industrial applications; this use accounts for about 34% of the tin produced and is growing with the introduction of lead-free soldering technology. A further 25–30% of tin is used as a protective coating for other metals, especially for food containers (K. Nimmo & S. Blunden, personal communication, 2004). Altogether, about 25 000 million cans are produced and filled in Europe annually, about 20% of these having plain internal (unlacquered) tin-coated bodies. Globally, the total for food packaging is approximately 80 000 million cans (JECFA, 1989; Blunden & Wallace, 2003). Tin is also used in transportation applications (ATSDR, 2003; Carlin, 2003b).

An important property of tin is its ability to form alloys with other metals. Tin alloys cover a wide range of compositions and many applications. Common solder, an alloy of 63% tin and lead, is mainly used in the electrical industry; lead-free tin solders containing up to 5% silver or antimony are used at higher temperatures. A large number of tin alloys are widely employed, including those containing lead, antimony, silver, zinc, or indium; babbitt (containing mainly copper, antimony, tin, and lead; Wood's metal (50% bismuth, 25% lead, 12.5% tin, and 12.5% cadmium); brasses and bronzes (essentially tin–copper alloys); pewter (0–95% tin plus 1–8% bismuth and 0.5–3% copper); and dental amalgams (silver–tin–mercury alloys) (Bulten & Meinema, 1991). Tin alloys are important in the production of coatings by electroplating and hot tinning (the most important of these are tin–zinc, tin–nickel, tin–cobalt, and tin–copper) (Gaver, 1997; ATSDR, 2003). Among the newer alloys are niobium–tin and indium–tin alloys used in superconducting cables and magnets (Stewart & Lassiter, 2001) and indium–tin oxide for metallic photonic crystals (Giessen, 2004). Dental amalgam alloys have been used for centuries. Principally, three-compound (ternary) alloys of silver, tin, and copper with smaller amounts of other elements have been widely

used in dentistry. Today's dental alloys are composed of silver (40–70%), tin (12–30%), copper (12–30%), indium (0–4%), palladium (0.5%), and zinc (0.1%) (Berry et al., 1994). Tin coatings can be applied to most metal surfaces by electrodeposition, while in hot-dipping, 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 (Mark, 1983).

Tin(II) chloride is obtained by dissolving metallic tin in hydrochloric acid or by reducing a solution of tin(IV) chloride with metallic tin. The anhydrous salt is produced by the direct reaction of chlorine and molten tin or by heating tin with hydrogen chloride gas. It is an important industrial reducing agent, used in the preparation of glass and plastic for metallizing, metallized glazing, and electronic components on a plastic base, as a soldering flux, as a mordant in dyeing, and in the manufacture of tin chemicals, colour pigments, and sensitized paper (Graf, 1987; Gaver, 1997; ILO, 1998a; K. Nimmo & S. Blunden, personal communication, 2004). Tin(II) chloride is added to lyophilized kits to prepare ^{99m}Tc -labelled tracers (which account for about 80% of radiopharmaceuticals). It is important in nuclear medicine as an essential component in diagnostic agents used to visualize blood, heart, lung, kidney, and bone (Francis et al., 1981; Popescu et al., 1984; Rao et al., 1986). Tin(II) chloride is also used in certain countries as a food additive (as a preservative and colour retention agent) (ATSDR, 2003). Tin(IV) chloride is produced commercially by the direct chlorination of tin at 110–115 °C and is used as a dehydrating agent in organic synthesis, in the production of organotin compounds, in the production of tin(IV) oxide films on glass, as a mordant in the dyeing of silks, in the manufacture of blueprint and other sensitized paper, and as an antistatic agent in synthetic fibre (Graf, 1987; Gaver, 1997; K. Nimmo & S. Blunden, personal communication, 2004).

Tin(II) oxide is prepared from the precipitation of tin(II) chloride with alkali. It is used as a reducing agent, in the preparation of stannous salts, and in the preparation of gold–tin and copper–tin ruby glass (Graf, 1987; Gaver, 1997). Tin(IV) oxide is produced by the combustion of powdered tin or sprayed molten tin in a hot stream of air. It is used in the polishing of glass and enamels, in the manufacture of milk-coloured ruby and alabaster glass and enamels, as a mordant in printing and dyeing of fabrics, and in fingernail polish (Graf, 1987).

Tin(II) fluoride is produced commercially by the reaction of tin(II) oxide and aqueous hydrofluoric acid or by dissolving tin in anhydrous or aqueous hydrofluoric acid and is used primarily as an ingredient of caries-preventing toothpaste (Gaver, 1997). Sn^{2+} ions have a profound and long-lasting inhibiting effect on the oral

microflora *in vivo* (Attramadal & Svatun, 1984). Topical application of tin(II) fluoride appears to provide dentine with a layer of tin and fluoride, which might provide mechanical and chemical protection and be of clinical significance in restorative dentistry. Sn^{2+} ions possess antibacterial activity, whereas Sn^{4+} ions do not (Svatun et al., 1977; Ferretti et al., 1982; Rolla et al., 1983; Ellingsen & Rolla, 1987; Rykke et al., 1991). Tin(II) pyrophosphate is prepared from pyrophosphoric acid and tin(II) chloride and is used as an ingredient in caries-preventing toothpaste (Budavari, 2001).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

5.1 Environmental transport and distribution

5.1.1 Air

The vapour pressure of elemental tin is negligible (Cooper & Stranks, 1966), and the high boiling points of elemental tin and many inorganic tin compounds indicate that they are non-volatile under environmental conditions. However, the wind may carry airborne particles for long distances before deposition, depending on the type of emitting source, physical form and properties (e.g. size, density), physical or chemical changes that may occur during transport, adsorption processes, and meteorological conditions (Senesi et al., 1999).

5.1.2 Water

In the environment, tin compounds are generally only sparingly soluble in water and are likely to partition to soils and sediments. In water, inorganic tin may exist as either divalent (Sn^{2+}) or tetravalent (Sn^{4+}) cations under environmental conditions. Cations such as Sn^{2+} and Sn^{4+} will generally be adsorbed by soils to some extent, which reduces their mobility. Tin(II) dominates in reduced (oxygen-poor) water and will readily precipitate as tin(II) sulfide or as tin(II) hydroxide in alkaline water. Tin(IV) readily hydrolyses and can precipitate as tin(IV) hydroxide. The solubility product of tin(IV) hydroxide has been measured at approximately 10–56 g/litre at 25 °C. In general, tin(IV) would be expected to be the only stable ionic species in the weathering cycle (Wedepohl et al., 1978). Tin(II) can be hydrolysed into SnOH^+ , $\text{Sn}(\text{OH})_2^0$, and $\text{Sn}(\text{OH})_3^-$ at low concentrations, whereas the $\text{Sn}_2(\text{OH})_2^{2+}$ and $\text{Sn}(\text{OH})_4^{2+}$ polynuclear species predominate at higher concentrations (Seby et al., 2001). On release to estuaries, inorganic tin is principally converted to the insoluble hydroxide and is rapidly scavenged by particles, which are the largest sink

for the metal. Subsequent release of inorganic tin from benthic sediments is unlikely, except at highly anoxic sites (Byrd & Andreae, 1982; Andreae, 1983). Inorganic tin, as cassiterite, is usually the predominant form in sediments of estuaries associated with metal mining in south-west England (Bryan & Langston, 1992). In seawater, inorganic tin is most commonly present as $\text{SnO}(\text{OH}_3)^-$ (Bruland, 1983).

Tin is generally regarded as being relatively immobile in the environment (IPCS, 1980; Gerritse et al., 1982). However, tin may be transported in water if it partitions to suspended sediments (Cooney, 1988), but the significance of this mechanism has not been studied in detail. Analysis of inorganic tin from an enclosed harbour revealed that a large percentage (up to 93%) was present in particulate form (Langston et al., 1987).

5.1.3 Soils and sediments

From the information available, it appears likely that inorganic tin will partition to soils and sediments and will not volatilize from water (IPCS, 1980; Cooney, 1988). Transfer coefficients for tin in a soil-plant system were reported to be 0.01–0.1 (Kloke et al., 1984).

5.1.4 Biota

Marine plants are also important in the cycling of inorganic tin. Both live macroalgae and decaying plant material accumulate inorganic tin compounds and ultimately remove tin from water and release it to the atmosphere by the formation and release of tetramethyltins (Donard et al., 1987).

5.2 Environmental transformation

Inorganic tin may undergo oxidation-reduction, ligand exchange, and precipitation reactions in the environment (HSDB, 2003). The biomethylation of inorganic tin has been demonstrated in pure bacterial cultures, sediments, and decaying plant material, with a variety of products being detected, including mono-, di-, tri-, and tetramethyltins (Hallas et al., 1982; Tugrul et al., 1983; Gilmour et al., 1987; Falke & Weber, 1994). The net methylation rate was found to be independent of the inorganic tin content of the sediments (Tugrul et al., 1983). Methylation of tin in sediments was found to be positively correlated with increasing organic content in sediment and to follow predominately a biotic pathway (Hadjispyrou et al., 1998). Inorganic tin may also be converted to stannane in extremely anaerobic (oxygen-poor) conditions by decaying algal material (Donard & Weber, 1988). Conversely, methyltin compounds can also be demethylated sequentially to inorganic tin by photolysis (Blunden, 1983).

5.3 Bioaccumulation

Inorganic tin compounds may be bioconcentrated, but data are limited. It was estimated that the bioconcentration factors of inorganic tin were 100, 1000, and 3000 for marine and freshwater plants, invertebrates, and fish, respectively (Thompson et al., 1972). Marine macroalgae can bioconcentrate the Sn^{4+} ion by a factor of 1900 (Seidel et al., 1980). Donard et al. (1987) reported inorganic tin concentrations of up to 4.4 mg/kg dry weight in macroalgae. Tin-resistant bacteria contained tin at 3.7–7.7 g/kg dry weight (Maguire et al., 1984).

There is no information available on the potential transfer of inorganic tin compounds from lower trophic levels to higher levels.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

Ambient levels of tin in the environment are generally quite low, except in the vicinity of local pollution sources. Analytical results based on inorganic tin have been included where possible. However, many studies have analysed for total tin only; in these cases, the data are provided for information, while bearing in mind that the concentrations may include some organic tin compounds. The proportion of inorganic tin in total tin concentrations will vary depending on sampling time and site.

6.1.1 Air

Tin is detected in air infrequently and at low concentrations, except in the vicinity of industrial sources. Air concentrations of tin in US cities from several studies were as high as $0.8 \mu\text{g}/\text{m}^3$. Average concentrations are generally below $0.1 \mu\text{g}/\text{m}^3$, with higher concentrations near some industrial facilities (IPCS, 1980; US EPA, 1982). Average concentrations have been estimated to be 0.002 – $0.03 \mu\text{g}/\text{m}^3$ (Biégo et al., 1999), $0.001 \mu\text{g}/\text{m}^3$ in northern hemisphere air (Byrd & Andreae, 1982), and less than $0.3 \mu\text{g}/\text{m}^3$ (JECFA, 1989). Davison et al. (1974) reported that the total tin content of airborne fly ash from coal-burning power plants ranged from 7 mg/kg (particle diameter $>1.7 \mu\text{m}$) to 19 mg/kg (particle diameter 3.3 – $4.7 \mu\text{m}$).

Atmospheric tin is associated with particulate matter, and peak concentrations were found on smaller respirable particles (1 – $3 \mu\text{m}$) (IPCS, 1980). Samples of airborne inhalable particulate matter were collected in two urban/industrial areas in Illinois, USA (south-east

Chicago and East St. Louis) and a rural area in Bondville, also in Illinois, over a 2-year period. Average total tin concentrations in the coarse (2.5–10 µm) and fine (<2.5 µm) particulate fractions were <7 ng/m³ and 12 ng/m³, respectively, for East St. Louis; and <7 ng/m³ for both the fine and coarse fractions in samples from south-east Chicago as well as the rural site in Bondville (Sweet et al., 1993). The average total tin concentration in highway tunnel exhaust aerosol in the Elbtunnel in Hamburg, Germany, between August 1988 and January 1989 was 10.9 ng/m³ (Dannecker et al., 1990). Tin has been identified in air collected at 6 of the 214 current or former US EPA National Priorities List hazardous waste sites where it was detected in some environmental media (HazDat, 2003).

6.1.2 Water

Tin occurs in trace amounts in natural waters; however, it is seldom measured (NAS, 1977; IPCS, 1980). Higher inorganic tin concentrations are associated with industrial discharges and tributyltin use (IPCS, 1980; Maguire & Tkacz, 1985; Maguire et al., 1986). Inorganic tin concentrations of up to 0.003 µg/litre were reported for rainwater in the USA during 1981 (Tugrul et al., 1983). Tin has been identified in groundwater and surface water at 78 and 36 sites, respectively, of the 214 US EPA National Priorities List hazardous waste sites where it was detected in some environmental media (HazDat, 2003). In surface waters, tin was detected in only 3 of 59 samples from 15 US and Canadian rivers at concentrations ranging from 1.3 to 2.1 µg/litre, and it was not detected in 119 samples from 28 US rivers. A mean tin concentration of 0.038 µg/litre was reported for surface water in Maine, USA (NAS, 1977; IPCS, 1980). In a survey of Canadian waters, nearly 80% of samples were found to contain inorganic tin at concentrations below 1 µg/litre; higher levels of up to 37 µg/litre were reported near pollution sources (Maguire et al., 1986). Mean tin(IV) concentrations in Lake Michigan during 1978 ranged from 0.08 to 0.5 µg/litre (Hodge et al., 1979). Similarly, mean inorganic tin concentrations of 0.004 µg/litre were detected in the Lamas River, Turkey, between 1981 and 1983. Industrial pollution was found to increase inorganic tin levels in the river estuary to up to 0.7 µg/litre (Yemenicioglu et al., 1987).

Total tin is present in seawater at about 0.2–3 µg/litre (NAS, 1977; IPCS, 1980). Inorganic tin concentrations ranging from 0.001 to 0.01 µg/litre have been reported for coastal waters, with levels of up to 8 µg/litre near pollution sources (Tugrul et al., 1983; Valkirs et al., 1986). Tin(IV) concentrations ranging from 0.003 µg/litre for open seawater to 0.04 µg/litre in San Diego Bay, California, USA, have been reported (Hodge et al., 1979). Langston et al. (1987) found that concentrations of dissolved inorganic tin displayed extreme variability both temporally and spatially within

an enclosed harbour and were largely influenced by localized inputs. Concentrations generally ranged from <0.005 to 0.2 µg/litre; however, levels of up to 48.7 µg/litre were found near local pollution sources.

Tin concentrations in drinking-water, including the United Kingdom supply, have been reported to be below 10 µg/litre (Sherlock & Smart, 1984; JECFA, 2001). Tin concentrations in public water supplies ranged from 1.1 to 2.2 µg/litre in 42 US cities and from 0.8 to 30 µg/litre in 32 of 175 water supplies in Arizona, USA (NAS, 1977; IPCS, 1980). An average concentration of 6 µg/litre has been reported in US municipal drinking-water (Hadjimarkos, 1967).

Tin concentrations in fresh snow from the French Alps collected in 1998 at different altitudes ranged from 0.16 to 0.44 µg/litre (Veysseyre et al., 2001).

6.1.3 Sediment

Mean total tin concentrations in Antarctic sediment were 2.1 and 5.1 mg/kg dry weight for the <2 mm and <63 µm fractions, respectively (Giordano et al., 1999). Inorganic tin was detected in 100 of 235 sediment samples collected from Canadian waterways. Concentrations ranged up to 8 mg/kg dry weight in coastal areas and up to 15.5 mg/kg in rivers and lakes (Maguire et al., 1986). Sediment concentrations of inorganic tin in Toronto Harbour, Canada, during 1983 were found to be highest (up to 13.8 mg/kg) near areas of tributyltin contamination (Maguire & Tkacz, 1985). Sediment cores collected in January 1996 from Central Park Lake in New York City, New York, USA, contained average tin concentrations ranging from 4.0 mg/kg at a depth of 44–47 cm to 67 mg/kg at a depth of 22–24 cm. The average tin concentration in surface sediments (0- to 2-cm depth) in Central Park Lake was 32 mg/kg. The similarities between the history of municipal solid waste incineration in New York City and the accumulation of trace metals in the Central Park Lake sediments appear to be consistent with incineration being the major source of emissions of several metals to the New York City atmosphere (Chillrud et al., 1999). Total tin concentrations in sediments from the Wah Chang Ditch and the north-east corner of Swan Lake, an area that received runoff from a tin smelter in Texas, USA, during the 1940s and 1950s, were found to be as high as 8000 mg/kg (Park & Presley, 1997). Total tin concentrations up to 1000 mg/kg dry weight have been reported for metal-rich sediments in estuaries associated with metal mining in south-west England (Bryan & Langston, 1992).

6.1.4 Soil

Tin concentrations in soil are generally low, except in areas where tin-containing minerals are present

(Bulten & Meinema, 1991). Tin concentrations in the Earth's crust are approximately 2–3 mg/kg (Budavari, 2001). Crockett (1998) reported total tin concentrations in Antarctic soils ranging from 2.5 to 3.1 mg/kg. Total tin concentrations in soil can range from <1 to 200 mg/kg; however, in areas of high tin deposits, such as south-west England, levels of 1000 mg/kg may occur (IPCS, 1980; Schafer & Femfert, 1984). The mean background soil concentration in the USA is 0.89 mg/kg (Eckel & Langley, 1988).

Tin concentrations in topsoil (0–7.6 cm) from the western end of East St. Louis, Illinois, USA, ranged from <13 to 1130 mg/kg. The raised concentrations are thought to be the result of current or recent industrial facilities, including smelters of ferrous and non-ferrous metals, a coal-fired power plant, chemical producing companies, and petroleum refineries (Kaminski & Landsberger, 2000). Tin has been identified in soil at 120 sites and in sediment at 50 sites collected from 214 US EPA National Priorities List hazardous waste sites where it was detected in some environmental media (HazDat, 2003).

Concentrations of total tin in sewage sludges from countries in Europe and North America ranged from 40 to 700 mg/kg dry weight. Manure and poultry wastes contained tin at concentrations of 3.7–7.4 and 2.0–4.1 mg/kg dry weight, respectively (Senesi et al., 1999)

6.1.5 Biota

Total tin concentrations in marine macroalgae varied between 0.5 and 101 mg/kg dry weight and clearly demonstrated that most species of aquatic flora bioconcentrate tin from seawater (Eisler, 1989). Local and imported edible seaweeds obtained in British Columbia, Canada, were found to contain total tin concentrations ranging from <0.01 to 0.46 mg/kg dry weight (van Netten et al., 2000).

Total tin concentrations in muscle and liver samples of juvenile Japanese common squid (*Todarodes pacificus*) collected from three locations in and near Japanese coasts were 0.04–0.05 mg/kg wet weight and 0.08–0.13 mg/kg wet weight, respectively (Ichihashi et al., 2001). Inorganic tin concentrations in fish collected from the Great Lakes in North America (1982–1984) ranged up to 0.9 mg/kg wet weight (Maguire et al., 1986).

Mean total tin concentrations in the feathers of seabirds from the North Pacific and water birds from the coast of Namibia ranged from 0.2 to 15.2 mg/kg dry weight (Burger & Gochfeld, 2000, 2001; Burger et al., 2001).

Total tin concentrations in the kidneys of mink (*Mustela vison*) collected from the Kootenay River and lower Fraser River in British Columbia, Canada, were 6.25 and 5.5 µg/g dry weight, respectively. Tin concentrations in the livers of mink from the upper and lower Fraser River were 5.5 and 5.2 µg/g dry weight, respectively. Tin concentrations were <4 µg/g dry weight in the livers of otters (*Lontra canadensis*) collected from the Kootenay, lower and upper Columbia, and upper Fraser rivers and 2.7 µg/g in livers of otters from the lower Fraser River (Harding et al., 1998). Mean total tin concentrations in striped dolphins (*Stenella coeruleoalba*) from the Mediterranean Sea ranged from 0.4 mg/kg wet weight in lung tissue to 1.3 mg/kg in liver (Cardellicchio et al., 2002). Total tin concentrations in the livers of Antarctic fur seals (*Arctocephalus gazella*) were less than 0.4 mg/kg dry weight (<0.1 mg/kg wet weight) (Malcolm et al., 1994).

6.1.6 Food

Data presented in ATSDR (2003) indicate that organic tin accounts for only a small fraction of total tin in most foods. On that basis, in this section, tin figures are total tin, but essentially represent inorganic tin.

In most unprocessed foods, inorganic (and total) tin levels are generally less than 1 mg/kg. Higher concentrations can arise as tin(II) in canned foods due to dissolution of the tin coating or tin plate. Tin levels are usually below 25 mg/kg in lacquered food cans, but may exceed 100 mg/kg in unlacquered cans. Tin concentrations in canned foods increase with storage time and temperature. Once opened, the tin content in foods stored in metal cans increases more quickly over time, since tin can rapidly dissolve in the presence of oxygen. Acidic foods are more aggressive to the tin coating in metal cans, and canned acidic foods have higher tin contents. Oxidizing agents (nitrates, iron salts, copper salts, sulfur) accelerate detinning, whereas tin salts, sugars, and gelatin reduce the dissolution rate. Can size and the nature of the base steel might also affect the detinning rate (JECFA, 1989; Blunden & Wallace, 2003).

Tin concentrations of vegetables, fruits and fruit juices, nuts, dairy products, meat, fish, poultry, eggs, beverages, and other foods not packaged in metal cans are generally below 2 mg/kg. Tin concentrations in pastas and breads have been reported to range from <0.003 to 0.03 mg/kg. Mean tin concentrations ranging from <1 to 1000 mg/kg have been found in foods packaged in unlacquered or partially lacquered cans, whereas the average tin concentration in foods in lacquered cans has been reported to be up to 6.9 mg/kg (Biégo et al., 1999; Ysart et al., 1999; JECFA, 2001). Data from the Can Manufacturers Institute indicate that more than 90% of tin-lined cans used for food today are lacquered (CMI, 1988). Only light-coloured fruit and

fruit juices are packed in unlacquered cans, since tin helps maintain the colour of the fruit (JECFA, 2001).

Local and imported edible seaweeds obtained in British Columbia were found to contain tin in concentrations ranging from 0.01 to 0.46 mg/kg dry weight (van Netten et al., 2000). A study in Lithuania in 1990–1992 found an average of 0.22 mg/kg in raw milk (Ramonaityte, 2001). In a dietary tin intake study for adults in France, a range of fresh foods contained tin at concentrations of <0.003–0.2 mg/kg (average 0.03 mg/kg) (Biégo et al., 1999). Foods in lacquered cans contained tin at concentrations generally below 10 mg/kg and ranging from 0.5 mg/kg (in cherries) up to 13.4 mg/kg (in mushrooms) (Biégo et al., 1999). Tin concentrations ranged from 24 to 156 mg/kg in food from unlacquered cans, the highest concentration being detected in tomatoes (Biégo et al., 1999). Canned vegetables and fruit products were found to have mean tin concentrations of 44 and 17 mg/kg fresh weight, respectively, in a 1994 total diet study in the United Kingdom (Ysart et al., 1999). A study of metal concentrations in canned milk products in Lithuania in 1990–1992 found mean tin concentrations in evaporated sterilized milk, concentrated sterilized milk, and sweetened condensed milk of 85, 89, and 40 mg/kg, respectively. Tin concentrations in canned milk were shown to increase during storage (Ramonaityte, 2001).

Studies in the United Kingdom showed mean concentrations of tin in the diet of 1–2 mg/kg. The primary sources of tin were said to be canned goods (Evans & Sherlock, 1987). Tin density figures for selected diets in France, New Zealand, and the United Kingdom ranged from 1.2 to 4.4 mg/kg (JECFA, 2001).

6.1.7 Indoor dust

Analysis (using energy-dispersive X-ray fluorescence) of dust in eight US homes found tin at <10 mg/kg (the detection limit) in five cases and at 12, 14, and 73 mg/kg in the other three cases. These houses were selected because they were near the homes of men employed as electric cable splicers. Dust in the homes of these workers contained higher tin concentrations (45–242 mg/kg), and levels were higher in the laundry area (geometric mean 117 mg/kg) than in the rest of the house (66 mg/kg), suggesting that the tin source was occupational contamination of the clothing (Rinehart & Yanagisawa, 1993).

6.2 Human exposure: environmental

The major source of tin for the general population is food. Intake from the diet is highly dependent on the type and amount of canned food consumed (JECFA, 1989). For those consuming no canned food, intake might be approximately 3 mg/day (Sherlock & Smart,

1984). Individuals who routinely consume canned fruit, vegetables, and juices from unlacquered cans could ingest 50–60 mg tin daily, assuming about four servings per day (Johnson & Greger, 1982; Sherlock & Smart, 1984). An adult consuming 1 litre of juice with a tin content of 100 mg/litre (from unlacquered cans) daily would ingest 100 mg of tin per day from this source alone (JECFA, 1989). People with low incomes or living in institutions such as nursing homes, boarding schools, or prisons may routinely select or be served canned food and juices because of economic factors and ease of storage, and those who consume about four daily servings of food from open, unlacquered cans could consume about 200 mg of tin per day (Greger & Baier, 1981; Greger, 1988; JECFA, 2001).

JECFA has summarized data on estimates of mean dietary tin intakes for Australia, France, Japan, the Netherlands, New Zealand, the United Kingdom, and the USA. In Australia, results of a total diet study produced estimated mean tin intakes (for six sex–age groups) ranging from 0.4 to 5.2 mg/day, with the highest 95th percentile being 7.4 mg/day (Marro, 1996). Using the DIAMOND method of modelling nutrition data, the Australia New Zealand Food Authority estimated a mean intake of 1.9–2.4 mg/day for consumers aged 2–70 years, with a 95th percentile value of 10 mg/day (Baines, 2000). Australian surveys produced intake figures of 2.2–2.7 mg/day, with a 95th percentile of 12 mg/day (Baines, 2000). For French adults, it was estimated that the mean dietary intake of tin would be 0.05 mg/day from a fresh food diet, 0.34 mg/day from a diet with usual canned foods in lacquered cans, and 7.4 mg/day from a diet with usual canned foods in unlacquered cans (Biégo et al., 1999). In Japan, the average tin intake of 456 women in 22 cities and villages during the winters of 1990–1995 was estimated to be 0.64 mg/day (based on duplicate food samples and food composition databases), although this was probably an underestimate, because not all food types were included (Shimbo et al., 1996). Dutch total diet studies, based on the consumption by 18-year-old men of 221 food items within 23 food commodity groups, produced average tin intakes of 1.7 mg/day during 1976–1978 and 0.65 mg/day (maximum 1.8 mg/day) in 1984–1986 (van Dokkum et al., 1989). Based on analysis of selected foods in the 1997–1998 New Zealand total diet study, the estimated mean dietary intakes of tin ranged from 2.9 mg/day (for children aged 1–3 years) to 7.5 mg/day for adult female vegetarians. Canned spaghetti, baked beans, apricots, tomatoes, and peaches contributed 77% of the dietary exposure of men aged 19–24 years and of children aged 1–3 years (Vannoort et al., 2000). In the 1974–1975 New Zealand total diet study, it was estimated that young New Zealand men eating 3.5 kg of food per day might ingest a mean of 15 mg of tin per day (Dick et al., 1978). In the United Kingdom, results from total diet studies suggest that tin intake has been falling (mean

daily intakes were 4.4, 2.4, and 1.8 mg in 1976, 1994, and 1997, respectively), possibly due to use of an increasing proportion of lacquered cans (Ysart et al., 1999; UK MAFF, 2000; JECFA, 2001). However, a study in 35 female vegetarians in the United Kingdom (using a duplicate-diet sampling method) found a mean intake of 3.8 mg/day (range 0.03–16 mg/day), about twice as high as reported for the general population (UK MAFF, 2000). JECFA did not identify any reliable estimates for the US diet, noting that tin was not measured in the USA's total diet study, but small studies provided mean estimates of 1 mg/day from a diet without canned food (Schroeder et al., 1964) and 1.5–3.5 mg/day for (undefined) adults (Schroeder et al., 1964; Tipton et al., 1969). JECFA noted that a small, early study focusing on metabolism had claimed that a diet containing "substantial amounts of canned vegetables, fruit juices, and fish could supply as much as 38 mg/day" (Schroeder et al., 1964).

Drinking-water is not considered a significant source of tin. If it is assumed that concentrations of tin in drinking-water are 6–10 µg/litre (see section 6.1.2) and that adults consume 2 litres/day, these figures suggest an intake of 12–20 µg/day from this source (JECFA, 1989, 2001).

Inhaled air represents very low tin exposure. Based on tin levels in air of <0.3 µg/m³ (JECFA, 1989), an adult inhaling 20 m³ of air per day would in general inhale less than 6 µg/day. Air concentrations of tin in US cities ranging from below the detection limit to 0.8 µg/m³ (US EPA, 1982) imply an inhaled dose of up to about 16 µg/day. Based on estimated average tin concentrations of 0.002–0.03 µg/m³ (Biégo et al., 1999), an adult is unlikely to inhale more than 0.6 µg of tin per day. Exposures are presumably higher near emission sources such as waste incineration and non-ferrous metal production (Byrd & Andreae, 1982) (see section 6.1.1).

6.3 Human exposure: occupational

Most of the operations associated with the extraction of tin ore are wet processes, but tin and tin(IV) oxide dust and 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 (ILO, 1998a). Tin reclamation from tin-plated steel trimmings, rejects from companies manufacturing tin cans, rejected plating coils from the steel industry, tin drosses and sludges, solder drosses and sludges, used bronze and bronze rejects, and metal-type scrap also involve possible exposure to tin dusts and fumes (ILO, 1998b). Gases, dusts, and fumes containing tin may be released from smelting and refining processes, industrial

uses of tin, waste incineration, and burning of fossil fuels (IPCS, 1980; Senesi et al., 1999; ATSDR, 2003).

No systematic data on occupational exposure levels in tin production or processing were found by the authors of the Nordic/Dutch source document (Westrum & Thomassen, 2002). 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 desire of different enterprises to control their exposures and are likely to represent "worst-case measurements" (Rajan et al., 1997). Of the 3407 air filter samples (8-h personal monitoring) analysed for tin, 420 contained amounts above the detection limit (0.002 mg/m³). In Table 5, the branches and job functions with tin exposures above 0.05 mg/m³ are listed, together with the mean and range of concentrations.

Limited information on past occupational exposure to tin was found in the older literature. Analysis of dust samples collected in the vicinity of a worker grinding tin ore in a tin smelting works in Liverpool, United Kingdom, showed that the dust fraction with particle size <5 µm contained more than 33% metallic tin and no detectable silica. The tin ore handlers were said to be "exposed to considerable quantities of dust" (Robertson, 1960). In this smelting works, concentrations of total tin or tin(II) oxide were not measured, but particles <5 µm in diameter were collected using a Hexlet in "places where dust concentration was likely to be especially high." Preliminary figures for concentrations (in mg/m³) of tin as particles <5 µm in diameter in the workroom air were as follows: check sampling shed, 2.22; and dracco room (an area containing filters for furnace gases), 1.50. In addition, air samples were taken near workers: 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 (Robertson, 1964). 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 (Oyanguren et al., 1958).

In a review, Alessio et al. (1994) reported that tin concentrations in ambient air in three copper alloy industries ranged from 1 to 4 µg/m³. Atmospheric concentrations of tin of 16 and 0.2 µg/m³ were reported for manual metal arc mild steel welding and arc stainless steel high nickel welding, respectively. A tin concentration of 1 µg/m³ was found for silver brazing.

Tin concentrations in the particulate matter in the ambient air at art glass manufacturing plants measured by personal samples from oven charger and batch mixer workers ranged from 0.1 to 3.5 µg/m³ from three plants

Table 5: Branches and job functions in EXPO where tin concentrations of >0.05 mg/m³ air were detected.

Branch/job functions	Number of samples	Mean tin concentration (mg/m ³)	Tin concentration range (mg/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

that use arsenic as a fining agent (an agent that is added to disperse air bubbles in glass). Tin was not detected in the particulate matter in the air at three other plants that used antimony compounds instead of arsenic (Apostoli et al., 1998).

Tin production may also involve exposure to silica, lead, and arsenic in the mining of the sulfide ores of tin, as well as to bismuth and antimony in the roasting and smelting process. Exposure to these toxic metals might also occur during the preparation and use of tin alloys and solders. Tin mining might involve exposure to radon, thorium, and uranium (Fox et al., 1981; Qiao et al., 1989, 1997; Taylor et al., 1989; Hodgson & Jones, 1990; Oresgun & Babalola, 1990; Forman et al., 1992; Beliles, 1994).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

7.1 Absorption

Generally, absorption of tin from the gastrointestinal tract is low in humans and laboratory animals, including rats, mice, rabbits, cats, and dogs (JECFA, 2001; Stewart & Lassiter, 2001), but it may be influenced by aqueous solubility, dose, anion, and the presence of other substances. *In vitro* studies using rat small intestine suggested that absorption of tin occurs by passive diffusion (Kojima et al., 1978).

In a balance study in which eight healthy volunteers were given a control diet providing 0.11 mg of tin per day for 20 days, mean faecal excretion was 55% of the daily dose, suggesting a mean net absorption of 45% at this low dose (although the range was wide, varying from –4 to 71%). When the diet was supplemented (with tin(II) chloride) to provide an additional 50 mg of tin per day for 20 days, mean faecal excretion was 97% of the daily dose, suggesting a net absorption of 3% (range –7 to 9%) at this higher dose (Johnson & Greger, 1982).

Four human volunteers with tin blood levels of <2 ng/ml (<17 nmol/litre) each consumed 60 mg of tin in the form of fruit juice from an unlacquered can, and blood samples were taken after 2, 5, and 24 h. The two females had detectable tin blood levels (3 ng/ml) only in the 5-h samples. The two males had peak blood tin concentrations of 4.7 ng/ml after 2 h and 3.9 ng/ml after 24 h (Byrne & Kosta, 1979).

Anodic stripping voltammetry was used to study tin concentrations in the urine of 89 men and 85 women (aged 20 years or more) in the Japanese prefecture of Aichi over a 3-year period from 1986 to 1988. For 79 subjects, data were available for each year. Expressed as µg/g creatinine, the mean tin concentration was significantly higher in women (5.9 ± 3.0; range 1.9–16.0) than in men (3.7 ± 2.2; range 0.8–13.4; *P* < 0.001). Distributions of concentrations were lognormal in both sexes. Mean concentrations tended to increase with age in both men (3.3 ± 2.5 at 20–29 years, 4.7 ± 2.2 at >60 years) and women (5.1 ± 3.6 at 20–29 years, 7.3 ± 2.7 at >60 years). In men, mean concentrations increased significantly, in a dose-related manner, with frequency of fish consumption (2.9 ± 1.8, 3.5 ± 2.0, and 4.7 ± 2.9 for consumption on 1–2, 3–4, and 5–7 days per week, respectively). A similar dose-related increase was seen in females (5.3 ± 1.9, 5.8 ± 3.1, and 6.3 ± 3.2 for consumption on 1–2, 3–4, and 5–7 days per week, respectively), although the differences between groups were not statistically significant. Organotin contamination of fish was the suggested explanation for these findings. Urinary tin concentrations showed no relationship with the level of consumption of canned food (Hayashi et al., 1991).

Following single gavage administration of ¹¹³Sn(II) or ¹¹³Sn(IV) as the citrate or fluoride to rats, absorption was estimated to be 2.85% and 0.64% of the 20 mg/kg body weight dose for the 2+ and 4+ oxidation states, respectively, based on 48-h recovery of radioactivity in the urine and tissues. Absorption was lower when tin was given as the pyrophosphate, presumably due to this anion's greater tendency to form insoluble tin complexes (Hiles, 1974). These figures are in line with reports that absorption of tin(II) chloride is generally below 5% (Kutzner & Brod, 1971; Furchner & Drake, 1976;

Fritsch et al., 1977; Sullivan et al., 1984). In one case, rats reportedly absorbed 7.65% of a single oral dose of tin(IV) chloride (Kojima et al., 1978). The recovery of 99% of administered tin in the faeces and the lack of detectable urinary tin in the 24 h following ingestion of tin (7–20 mg/kg body weight) in orange juice by rats and cats indicate a very low gastrointestinal absorption of tin (Benoy et al., 1971). The presence of certain organic acids can increase tin absorption from the gastrointestinal tract (Kojima et al., 1978).

No increase in blood levels of tin was seen when male Wistar rats were given tin(II) chloride in the drinking-water at up to 250 mg/litre for 1–18 weeks (tin dose probably between 8 and 21 mg/kg body weight per day). At a tin(II) chloride concentration of 500 mg/litre, tin concentrations in blood rose in the first week and remained at 2–7 µg/litre (equivalent to 2–5 times control values) for the rest of the study. The data suggest that mucosal barriers are effective in preventing tin absorption at low doses but are overcome at higher doses (Savolainen & Valkonen, 1986).

Rabbits fed tin at 2 mg/kg body weight per day for 5 days (as tin(II) chloride) had blood tin concentrations of 2.3 µg/litre after 24 h and 0.7 µg/litre after 120 h. Tin was not detected (detection limit not stated in the source document) in the controls (Zareba & Chmielnicka, 1992).

Adequate data on uptake following inhalation or dermal exposure appear to be lacking (Westrum & Thomassen, 2002).

7.2 Distribution

Inorganic tin distributes mainly to bone, but also to the lungs, liver, kidneys, spleen, lymph nodes, tongue, and skin. Certain data indicate that tin may have a higher affinity for the thymus than for other organs. Laboratory animal data suggest that inorganic tin does not readily cross the blood–brain barrier (Hiles, 1974; Furchner & Drake, 1976; Hasset et al., 1984; Savolainen & Valkonen, 1986; JECFA, 2001).

Tin was seldom present in the lung tissue of newborn babies in the USA. In adults, the tin content in human lung tissue was higher in the USA than in Africa (Schroeder et al., 1964). These data suggest that tin levels in the human lung increase with age, and the likely source might be polluted air.

In an analysis of the tin content in tissue samples from adults who had died in accidents, the highest concentrations were found in the bone ash (4.1 mg/kg), followed by the lymph nodes, lungs, liver, and kidneys (1.5, 0.8, 0.4, and 0.2 mg/kg wet weight, respectively), whereas levels in muscle (0.07 mg/kg wet weight) and

brain (0.06 mg/kg wet weight) were lower (Hamilton et al., 1973). Autopsy samples from 78 deceased Spaniards contained mean tin concentrations of 0.47, 0.27, 0.25, 0.24, and 0.16 mg/kg in the bone, brain, kidneys, lungs, and liver, respectively (Garcia et al., 2001). Analysis of tissue samples from 20 deceased Spanish subjects (without known occupational tin exposure) found highest and lowest tin levels in bone (mean 6.2 mg/kg) and brain (mean 1 mg/kg), respectively (Llobet et al., 1998). Median tin concentrations (in mg/kg wet weight) in samples from adult US citizens were as follows: adrenal, 5.1; lung, 3.4; liver, 1.8; kidney, 1.5; spleen, 0.8; muscle, <0.4; and brain, 0.3 (Tipton & Cook, 1963). In healthy Japanese males, tin concentrations of 9.8 mg/kg dry weight in hilar lymph nodes and 1.5 mg/kg dry weight in lung tissue were reported (Teraoka, 1981). Analysis (using AAS) of several human organs from 11–13 adult males found mean concentrations (mg/kg dry weight) as follows: liver, 1.05; kidney cortex, 0.83; heart, 0.75; lung, 0.45; rib bone, 0.61; and testis, 2.08 (Chiba et al., 1991). The tin concentration in liver specimens from 11 US citizens ranged from 0.14 to 0.17 mg/kg wet weight (determined by neutron activation analysis), and the tin concentration in Japanese human liver specimens ($n = 23$) ranged from 0.08 to 1.12 mg/kg wet weight (determined by AAS) (Chiba et al., 1994). An average tin concentration of 12.8 mg/kg wet weight was reported in the thymus of two children (Sherman et al., 1985). Tin was detected at 4.6–15 mg/kg in adipose tissue samples from nine US subjects in a 1982 survey (Stanley, 1986).

In humans with no occupational exposure to tin compounds, blood tin concentrations of 2–9 µg/litre are reported (detection limit 2 µg/litre) (Hamilton et al., 1973; Kazantzis, 1994). Others reported normal tin concentrations of 11.6 ± 4.4 nmol/litre (mean \pm SD) in plasma and 21.7 ± 6.7 nmol/litre in red blood cells in 12 humans (8 women, 4 men, mean age 77.8 years) (Corrigan et al., 1992). Background tin concentrations of <1 µg/litre in serum and urine have been reported (Versieck & Vanballenberghe, 1991; Schramel et al., 1997), and a 95th upper percentile of 20 µg/litre in urine was calculated for a group of 496 US residents (Paschal et al., 1998).

Autopsy analysis of the internal organs of 7 Japanese metal industry workers and 12 Japanese males without occupational exposure found elevated concentrations of tin in the lungs, spleen, liver, and kidneys of chromate plating and chromate refining workers. In one chromate refining worker, marked concentrations of tin were found in the hilar lymph nodes (100 mg/kg dry weight) and lungs (100 mg/kg dry weight) (Teraoka, 1981).

Following a single gavage dose of 20 mg/kg body weight of radiolabelled $^{113}\text{Sn(II)}$ or $^{113}\text{Sn(IV)}$ as the

fluoride or citrate, the tissue distribution of tin in rats after 48 h as a percentage of the administered tin(II) or tin(IV), respectively, was as follows: skeleton, 1.0% and 0.24%; liver, 0.08% and 0.02%; and kidneys, 0.09% and 0.02%. When oral tin doses of 20 mg/kg body weight were given on 6 days/week for 4 weeks, only the bone contained higher tin concentrations after day 28 than after day 1. The half-time of tin in the femur was estimated to be 34–40 days. The investigator concluded that, of the soft tissues, 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 in the brain of rats 48 h following administration of $^{113}\text{Sn(II)}$ or $^{113}\text{Sn(IV)}$ as citrate or fluoride as a single oral dose (4 mg), as oral doses of 20 mg/kg body weight on 6 days/week for 4 weeks, or as a single intravenous dose (0.4 mg) (Hiles, 1974).

Studies on the retention of the radionuclide ^{113}Sn administered as tin(II) chloride intraperitoneally in rats showed that most of the tin retained in the body was deposited in the bone, followed by muscle, pelt, liver, and kidneys. In contrast to all other organs, the relative amount of tin in bone increased during the study (Furchner & Drake, 1976).

A study of the pharmacodynamics of several tin compounds in rabbits, using $^{113}\text{Sn(II)}$ chelates also labelled with $^{99\text{m}}\text{Tc}$ (meta-stable technetium-99), showed that free Sn^{2+} ions localize mainly in bone. The distribution of ^{113}Sn in bone was similar to that of calcium and other bone-seeking metal ions (Dewanjee & Wahner, 1979).

Tin concentrations of 0.1–0.29 mg/kg wet weight and 0.69 mg/kg dry weight have been reported in the bone tissue of unexposed mice (Chiba et al., 1991).

The concentrations of tin in the tibias of rats fed diets supplemented with tin(II) chloride (100–2000 mg of tin per kg of diet) were more than 5 times greater than the tin concentrations in the kidneys and nearly 20 times greater than the concentrations in the liver. No other organs were analysed. Tin accumulated in the tibia and kidneys in a dose-dependent manner (Johnson & Greger, 1985).

After lifelong administration of about 0.37 mg of tin per kg body weight per day as tin(II) chloride in the drinking-water of rats, mean tin concentrations were increased approximately 2- to 3-fold in the liver, heart, lungs, and spleen, but the differences were not statistically significant. Bone was not examined (Schroeder et al., 1968). In mice, a similar study (reported intake of about 0.37 mg/kg body weight per day) found tin levels of 1.2–4.5 mg/kg wet tissue in kidneys, liver, heart, lungs, spleen, and thyroid, compared with less than

0.5 mg/kg in tissues in the control group (Schroeder & Balassa, 1967).

A 2-year carcinogenesis study of tin(II) chloride administered at 1000 or 2000 mg/kg in the diet to F344 rats and B6C3F1 mice showed a dose-dependent difference in the concentration of tin in examined organs (i.e. bone, liver, and kidneys). For the low and high doses, tin levels in bone were, respectively, 9 and 38 mg/kg in male rats and 23 and 41 mg/kg in female mice. Tin concentrations in the kidneys were, respectively, 17 and 30 mg/kg in male rats and 0.7 and 0.9 mg/kg in female mice. In the liver, tin concentrations were, respectively, 0.2 and 0.4 mg/kg in male rats and 0.4 and 0.5 mg/kg in female mice. In both species, tissue levels tended to be higher in the females. Untreated rats and mice had tin concentrations that were below the detectable limits, which ranged from 0.01 to 0.1 mg/litre of “digested tissue” (NTP, 1982).

Some data indicate that the tin content is higher in the thymus than in other representative organs. In four young adult dogs, the tin concentration in thymus was about twice the concentrations in the spleen or muscle (Sherman & Cardarelli, 1988). Analysis of unexposed adult Lewis rats, adult COBS mice, and adult A/KI mice showed thymus tin concentrations of 20, 5.5, and 4.3 mg/kg, respectively. Tin concentrated in the thymus gland as the gland atrophied with age (Sherman et al., 1986).

The tin content of the brain (7–19 nmol/kg wet weight) of Wistar rats given tin(II) chloride dihydrate at 100 mg/litre in the drinking-water for 18 weeks was not significantly different from that in control rats (5–10 nmol/kg). At 250 mg/litre, brain tin was increased after 15 weeks (19 ± 8 nmol/kg) and 18 weeks (38 ± 8 nmol/kg). At 500 mg/litre, the tin content of the brain rose steadily throughout the 18 weeks to about 80 nmol/kg (Savolainen & Valkonen, 1986).

In pregnant rats fed tin at 20 mg/kg body weight per day as radioactive tin(II) or tin(IV) fluoride, no tin was found in fetal or placental tissues on day 10 of pregnancy. On day 21, fetuses of dams administered tin(II) fluoride apparently contained approximately 0.2% of the cumulative dose (Hiles, 1974). Fetal tin values were slightly elevated (0.8–1.3 mg/kg body weight) in Sprague-Dawley rats on day 20 of gestation when the maternal diets contained tin salts (tin(II) fluoride, sodium pentachlorostannite, or sodium pentafluorostannite) at 125–625 mg/kg in the feed (about 10–50 mg of tin per kg body weight per day). The increases were generally dose-related. Untreated rats had fetuses containing 0.64 mg of tin per kg body weight (Theuer et al., 1971). Others have reported briefly that “considerable” tin concentrations were noted in embryos of rats exposed to tin(II) chloride (Chmielnicka et al., 1981).

Data are very limited but suggest the possibility of a low level of transfer across the placenta (ATSDR, 2003).

7.3 Biotransformation

Few data on biotransformation are available. The difference in the relative affinity of the kidneys and liver for tin(II) and tin(IV) indicates a valence stability of the administered tin (Hiles, 1974). The difference observed between tin(II) and tin(IV) chloride in their effects on the immune response in C57BL/6J mice (see section 8.7) also suggests that these two oxidation states are not readily interconverted *in vivo* (Dimitrov et al., 1981). Together, these data suggest that tin cations are not rapidly oxidized or reduced during absorption and systemic transportation in mammals.

7.4 Excretion

Ingested tin is largely unabsorbed and excreted mainly in the faeces, with additional slow elimination of the absorbed fraction in the urine (JECFA, 2001).

In a mineral balance study, eight adult human males ate food providing 0.11 mg or 50 mg of tin per day (as tin(II) chloride) for 20-day periods. Their urinary excretion was 29 ± 13 $\mu\text{g/day}$ (mean \pm SD) and 122 ± 52 $\mu\text{g/day}$, respectively, representing 36% and 2.4% of the dose, respectively. Mean faecal excretion accounted for 55% and 97% at the low and high daily dose, respectively (Johnson & Greger, 1982). A review stated that, in humans, 20% of absorbed tin was cleared with a half-time of 4 days, a further 20% with a half-time of 25 days, and the remaining 60% with a longer half-time of 400 days. No further details were given (Magos, 1986). When nine healthy adults were given diets consisting of fresh foods (10 mg of tin per day), cold-stored canned foods (26 mg of tin per day), or warm-stored canned foods (163 mg of tin per day) for 24 days, faecal excretion accounted for the whole dose, and none was detected in the urine (Calloway & McMullen, 1966).

Rats and cats given (by stomach tube) orange juice supplying tin (derived from containers) at 7–20 mg/kg body weight excreted 99% of the dose in the faeces within 48 h (Benoy et al., 1971).

In laboratory animals, the small proportion of tin that is absorbed following ingestion is mainly excreted via the kidneys (Kutzner & Brod, 1971; Hiles, 1974; Furchner & Drake, 1976; IPCS, 1980; Widdowson, 1992).

In the 48 h following a single oral tin dose of 20 mg/kg body weight as $^{113}\text{Sn(II)}$ or $^{113}\text{Sn(IV)}$ fluoride or citrate, female rats excreted 95% of the radiolabel in the faeces and less than 1% in the urine. After a single intravenous dose of $^{113}\text{Sn(II)}$ or $^{113}\text{Sn(IV)}$ at 2 mg/kg

body weight, 35% and 40% of the doses, respectively, were excreted in the urine. Twelve per cent of the tin(II) appeared in the faeces, but only 3% of the tin(IV), indicating that the biliary route is more important for tin(II) than for tin(IV) compounds (Hiles, 1974).

Tin was given as $^{113}\text{Sn(II)}$ chloride orally, intraperitoneally, or intravenously to mice, rats, monkeys, and dogs. After parenteral administration, whole-body activities could be described by four-component exponential expressions, similar for all species studied. Following intravenous injection of tin(II) chloride into rats (11 kBq/rat), elimination proceeded with component half-times of 0.4, 4.9, 25, and 90 days (Furchner & Drake, 1976).

For rat liver and kidney, the biological half-life of tin(II) has been estimated to be 10–20 days. For bone, the half-life of tin(II) and tin(IV) is approximately 20–100 days (Hiles, 1974; Brown et al., 1977; Fritsch et al., 1977; Bulten & Meinema, 1991). A biological half-life of approximately 30 days was estimated for inorganic tin in mice, using a whole-body counting method (Brown et al., 1977).

7.5 Biological monitoring

Biological monitoring requires an understanding of the relationships between exposure, external dose, toxicokinetics, internal dose, and effects. Although adequate ultrasensitive analytical techniques (ICP-MS and radiochemical neutron activation) have been developed for the measurement of tin in tissues and urine (see section 3), relationships between tin dose and biological indicators have not yet been established for inorganic tin (Versieck & Vanballenberghe, 1991; Schramel et al., 1997).

7.6 PBPK models

The ICRP has developed a model for ingested tin, based on an empirical model developed by Furchner & Drake (1976). The fraction of ingested tin that is absorbed from the human gastrointestinal tract (uptake to blood) is assumed to be 0.02 (i.e. 2%). Absorbed tin is assumed to enter the blood, from where 50% is immediately transferred to excreta (specific routes not specified in the model), 35% is transferred to bone mineral, and 15% is uniformly distributed to all other tissues. Elimination of tin from any tissue or organ is assumed to occur in three phases, with individual half-times of 4, 25, and 400 days, respectively, during which periods some 20%, 20%, and 60% of tissue burdens, respectively, are eliminated (ICRP, 1981, 2001).

The ICRP has also developed a human model for inhaled tin (ICRP, 1994). Sulfides, oxides, hydroxides, halides, and nitrates of tin and tin(IV) orthophosphate

are classed as Type M; all other compounds of tin are classed as Type F. For Type F compounds, rapid 100% absorption is assumed to occur within 10 min of material deposition in the bronchi, bronchiole, and alveolar interstitial regions. Fifty per cent of each Type F compound deposited in the extrathoracic region transfers to the gastrointestinal tract. There is rapid absorption of approximately 25% of the tin deposited in the extrathoracic region during nose breathing and 50% absorption during mouth breathing. For Type M compounds, approximately 70% of the tin deposited in the alveolar interstitial regions is eventually transferred to blood, and there is rapid absorption of about 10% of the tin deposited in the bronchi and bronchiole regions and 5% of the tin deposited in the gastrointestinal tract. Approximately 2.5% of the deposit in the gastrointestinal tract is rapidly absorbed during nose breathing, and 5% is rapidly absorbed during mouth breathing (ICRP, 1994).

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

By the oral route, tin metal itself is described as practically innocuous (JECFA, 2001). In NTP studies, using groups of five animals per sex, the acute oral LD₅₀ for tin(II) chloride was in excess of 1.5 g/kg body weight (the highest dose tested) in rats. In the corresponding study in mice, the LD₅₀ was in excess of 1.2 g/kg body weight, but all mice died at 2.4 g/kg body weight (NTP, 1982). For tin(II) chloride, other studies report LD₅₀ values equivalent to 1.1–1.7 g of tin per kg body weight in rats. Sodium pentafluorostannite showed higher toxicity, with LD₅₀ values (again expressed as tin) of 0.15–0.38 and 0.40 g/kg body weight in rats and mice, respectively. Acute oral administration induced central nervous system effects, including ataxia, general depression, limb weakness, and flaccid paralysis. Both compounds induced pathology in the kidneys, characterized by swelling, discoloration, and tubular necrosis with subsequent regeneration (Conine et al., 1975; JECFA, 2001; Westrum & Thomassen, 2002). Oral LD₅₀ values have also been recorded in mice as 2.7 g/kg body weight for sodium tin citrate (Omori et al., 1973) and 0.25–1.2 g/kg body weight for tin(II) chloride (Pelikan et al., 1968). Necrosis in the liver and spleen were seen in mice treated orally with a single dose of tin(II) chloride (Pelikan et al., 1968). Tin(II) chloride disrupted haem synthesis when given orally to rabbits at 100 mg of tin per kg body weight, but not at 10 mg/kg body weight (Chmielnicka et al., 1992).

Changes (“widespread tiny densities”) were seen on X-ray examination of the lungs of rats 4 months after an

intratracheal instillation of 50 mg of metallic tin dust (in saline) from a tin smelting works (no further details on composition were given). These changes were said to be similar to those seen in workers exposed occupationally to the same material. Histologically, there was no fibrous response of any kind up to a year in the rats (Robertson, 1960).

Acute toxicity of inorganic tin compounds by intravenous and intraperitoneal injection is considerably higher than acute toxicity by the oral route. For example, an acute LD₅₀ value of 15 mg of tin per kg body weight has been reported in rats treated with tin(II) chloride by the intravenous route (Conine et al., 1975).

8.2 Short-term exposure

There were no effects on survival, growth, food utilization, blood or urine composition, serum biochemistry, organ weights, or the gross and microscopic appearance of a range of tissues and organs when groups of 10 male and 10 female Wistar rats were fed tin(II) chloride, tin(II) orthophosphate, tin(II) sulfate, tin(II) oxalate, or tin(II) tartrate at up to 0.1% in the diet for 4 weeks. At 0.3% and above, these compounds caused growth retardation, decreased food efficiency, mild anaemia, and slight histological changes in the liver. In similar studies, dietary concentrations of up to 1% tin(II) oleate, tin(II) sulfide, or tin(IV) oxide for 4 weeks were tolerated without adverse effect by rats (10 per sex per group). Overall, the NOEL of the tin salts studied was 0.1%, or 22–33 mg of tin per kg body weight per day in an unsupplemented diet containing “a liberal amount of iron and copper.” The investigators suggested that the NOEL might be lower in diets that are marginal in iron and copper. Dietary supplements of iron had a marked protective effect against tin-induced anaemia, whereas a decrease in dietary iron exacerbated this effect. The growth depression caused by tin was not alleviated by enriching the diet with iron and copper (de Groot, 1973).

The NTP has carried out studies in which tin(II) chloride was administered to F344/N rats and B6C3F1/N mice (five per sex per species per group) at 1900, 3800, 7500, 15 000, or 30 000 mg/kg in the diet for 2 weeks (up to about 950 and 2400 mg of tin per kg body weight per day in rats and mice, respectively). All animals survived treatment. The rats showed a dose-related decrease in growth and, at the top dose, lost weight and had roughened coats and distended abdomens. In mice, the only effect was reduced growth in the females at 15 000 mg/kg diet and above (NTP, 1982).

No significant toxicity was seen when Wistar rats (10 per sex per group) were given sodium pentafluorostannite at 20 mg/kg body weight per day for 30 days by stomach tube (equivalent to 13.4 mg of tin per kg body weight per day). At 100 mg/kg body weight per day

(67 mg of tin per kg body weight per day) and above, there was a dose-related reduction in growth. At the top dose (175 mg/kg body weight per day, equivalent to 117 mg of tin per kg body weight per day), degenerative changes were seen in the proximal tubular epithelium of the kidneys in 15–20% of the animals. At 15 days, a dose-related decrease in haemoglobin was found, although this was statistically significant only in males given 100 mg/kg body weight per day and above. Serum glucose levels were decreased, possibly related to reduced food intake (Conine et al., 1976).

Dose-related decreases in growth and haemoglobin level were noted in weanling Wistar rats given tin at 0, 250, or 500 mg/kg in the diet (as tin(II) chloride) for 4 weeks (about 0, 15, and 30 mg of tin per kg body weight per day, respectively). Crypt depth, villus length, and cell turnover were increased in parts of the intestine (Janssen et al., 1985).

Several studies report effects of tin administration on the bones. The calcium content of the femur (both epiphysis and diaphysis) was reduced in a dose-related manner in male Wistar rats given tin at 1, 3, 10, or 30 mg/kg body weight (as tin(II) chloride) every 12 h for 3 days. The effect was statistically significant at 6 mg/kg body weight per day and above. Serum calcium was decreased at 20 mg/kg body weight per day and above (Yamaguchi et al., 1980a). The distal epiphysis compressive strength decreased significantly in the femoral bone in Wistar rats administered 300 mg of tin (as tin(II) chloride) per litre drinking-water and laboratory chow contaminated with tin at 52.4 mg/kg for 4 weeks. This effect was not seen at 150 mg of tin per litre drinking-water. Feed and water intake were not reported (Ogoshi et al., 1981). The calcium content in the tibia of rats fed 100 mg of tin per kg in the diet as tin(II) chloride (approximately 7 mg of tin per kg body weight per day) for 28 days was decreased (Johnson & Greger, 1985). When gavage doses of 1 mg of tin per kg body weight (as tin(II) chloride) were given to male Wistar rats at 12-h intervals for 28–30 days (i.e. 2 mg of tin per kg body weight per day), there was an increase in the tin content of the femoral diaphysis and epiphysis, decreased calcium content in bone, and decreased acid and alkaline phosphatase activities in the femoral epiphysis (Yamaguchi & Okada, 1980; Yamaguchi et al., 1981a).

Other investigators have studied the effects of inorganic tin compounds on body balance of important minerals. Plasma and tissue (kidney, spleen, and tibia) concentrations of copper, iron, and zinc were unaffected in a group of seven Wistar rats fed diets containing 1 mg of tin per kg (as tin(II) chloride; about 0.07 mg of tin per kg body weight per day) for 28 days, but were slightly reduced at 10 mg of tin per kg in the diet (about 0.7 mg of tin per kg body weight per day). Greater effects were seen at 50 mg of tin per kg in the diet (about 3.5 mg of

tin per kg body weight per day) (Pekelharing et al., 1994). Copper metabolism was unaffected in Sprague-Dawley rats given up to 100 mg of tin per kg in the diet as tin(II) chloride (about 7 mg of tin per kg body weight per day) for 27 days; however, at 500 mg of tin per kg in the diet (about 39 mg of tin per kg body weight per day), copper levels were reduced in the plasma, liver, and kidneys, and zinc retention in the tibia, kidneys, liver, and plasma was decreased. Only small changes in iron metabolism were observed (Johnson & Greger, 1984, 1985). Administration of 100 mg of tin per kg in the diet for 4 weeks to weanling rats reduced copper levels in the duodenum, liver, kidneys, and femur and zinc levels in the kidneys and femur (Reicks & Rader, 1990; Rader et al., 1990). Oral administration of tin(II) chloride (2 mg of tin per kg body weight per day) to rabbits for 1 month decreased zinc and copper concentration in bone marrow and increased iron concentrations in liver and kidneys (Zareba & Chmielnicka, 1989). Iron status (tissue iron, haemoglobin, haematocrit, red blood cell count, plasma iron, total iron binding capacity, and transferrin saturation) in rabbits was not influenced by the inclusion of tin in the diet at <100 mg/kg (as tin(II) chloride) for 28 days, but these parameters were decreased at higher (not specified in the source document) dietary tin concentrations. Food intake and body weights were not reported (Beynen et al., 1992).

A study in Wistar rats fed on diets containing 1, 10, 50, 100, or 200 mg of tin per kg (as tin(II) chloride) for 28 days (1 mg/kg was equivalent to about 0.07 mg of tin per kg body weight per day) found that blood haemoglobin concentration and percentage transferrin saturation decreased in a linear manner with increasing dietary tin concentration (Pekelharing et al., 1994).

Gavage administration of tin at 1, 3, 10, or 30 mg/kg body weight (as tin(II) chloride) every 12 h for 3 days to male Wistar rats resulted in dose-related decreases in gastric acid secretion, duodenal alkaline phosphatase, and liver phosphorylase. These reductions were statistically significant only at 20 mg/kg body weight per day and above (Yamaguchi et al., 1980a).

Oral doses of 2 mg of tin per kg body weight per day for 5 days (as tin(II) chloride) did not affect haem biosynthesis in a group of five rabbits, based on examination of 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, urinary ALA, and co-protoporphyrins (Zareba & Chmielnicka, 1992).

8.3 Medium-term exposure

In NTP studies, food grade purity (98.5%) tin(II) chloride was given to F344/N rats (groups of 10 per sex) at 0, 500, 1000, 1900, 3800, or 7500 mg/kg in the diet

for 13 weeks. An equivalent study in B6C3F1/N mice was carried out using dietary concentrations of 0, 1900, 3800, 7500, 15 000, and 30 000 mg of tin(II) chloride per kg. A wide range of tissues and organs from the control and top-dose animals were examined microscopically. All rodents survived treatment. No effects were seen in either species at up to 1900 mg/kg diet, equivalent to about 170, 400, and 600 mg/kg body weight per day in rats (both sexes), male mice, and female mice, respectively. Both species showed gross distension of the caecum and reddened gastric mucosa at 3800 mg/kg diet (about 330, 900, and 1200 mg/kg body weight per day in rats, male mice, and female mice, respectively) and above. Growth was reduced at the top dose in each species. Microscopically, the tissues were normal (NTP, 1982).

There were no effects on survival, growth, food utilization, blood or urine composition, serum biochemistry, organ weights, or the gross and microscopic appearance of a range of tissues and organs when Wistar rats (10 per sex per group) were given up to 1% tin(II) oxide or 0.1% tin(II) chloride in the diet for 13 weeks. Growth retardation, decreased food efficiency, slight anaemia, and minor liver tissue changes were seen when tin(II) chloride was given at 0.3% in the diet and above. At 1% tin(II) chloride (about 315 mg of tin per kg body weight per day), marked growth retardation and some deaths occurred. This group showed moderate testicular degeneration, severe pancreatic atrophy, spongy white matter in the brain, acute bronchopneumonia, enteritis, distended intestine, and distinct changes in the liver cytoplasm, with mild proliferation in the bile duct epithelium. The NOEL of tin salts examined was 0.1% or 22–33 mg of tin per kg body weight per day in an unsupplemented diet containing “a liberal amount of iron and copper.” The investigators suggested that the NOEL might have been lower in diets that are marginal in iron and copper. Dietary supplements of iron had a marked protective effect against tin-induced anaemia, whereas a decrease in dietary iron exacerbated the effect. The growth depression caused by tin was not alleviated by enriching the diet with iron and copper (de Groot et al., 1973).

Slower growth, mild anaemia, increased relative liver and kidney weights, irritation of the gastrointestinal tract, “mild” histological changes in the liver, and pancreatic damage (ranging from necrosis of individual acinar cells to complete destruction of the pancreas) were observed in Wistar rats fed tin(II) chloride for 13 weeks (gradually increased from 163 mg of tin per kg body weight per day in weeks 0–4 to 310 mg of tin per kg body weight per day in weeks 8–13) (der Meulen et al., 1974).

In a study of the effect of tin(II) chloride on biochemical and bone indices in groups of 5–6 Wistar

rats, oral doses of 0.6, 2, or 6 mg of tin per kg body weight per day were given (in two daily doses, 12 h apart) for 90 days. The 6 mg/kg body weight per day dose level caused significant decreases in femur weight, lactate dehydrogenase and alkaline phosphatase activities in serum, succinate dehydrogenase activity in the liver, and calcium content and acid phosphatase activity in the femur. The 2 mg/kg body weight per day dose produced significant reductions in succinate dehydrogenase activity in the liver and in the calcium content and acid phosphatase activity in the femur. At 0.6 mg/kg body weight per day, a slight non-significant decrease in calcium content in the femoral epiphysis was observed. The results suggested a LOEL for inorganic tin orally administered of 0.6 mg/kg body weight per day (Yamaguchi & Okada, 1980; Yamaguchi et al., 1980b). In a study in which tin(II) chloride was added to the diet of male Wistar rats at 0, 10, 50, 100, or 250 mg of tin per kg for 90 days (approximately 0, 0.5, 2.5, 5, and 12.5 mg of tin per kg body weight per day), serum calcium and calcium content of the femoral epiphysis were significantly reduced at 2.5 mg/kg body weight per day and above. At 5 mg/kg body weight per day and above, there were additionally decreases in serum inorganic phosphate, femur diaphysis calcium, and femur epiphysis acid phosphatase. No effects were seen at 0.5 mg/kg body weight per day (Yamaguchi et al., 1981b).

Fatty degeneration with lymphocytic infiltration and atrophy of the exocrine tissue of the pancreas was seen when groups of 10 male Sprague-Dawley CD rats were given tin(II) chloride in the diet at 4000 mg/kg (equivalent to 240 mg/kg body weight per day) for 6 months (Fritsch et al., 1978).

In rabbits, oral administration of 10 mg of tin per kg body weight per day (as tin(II) chloride) for 4 months caused transient anaemia during weeks 6–10. A transient high serum iron concentration and a high total iron binding capacity and saturation index were also observed (Chmielnicka et al., 1993).

8.4 Long-term exposure and carcinogenicity

In the most comprehensive carcinogenicity study available, F344/N rats and B6C3F1/N mice (groups of 50 males and 50 females per species per dose group) were given food grade purity (98.5%) tin(II) chloride at 0, 1000, or 2000 mg/kg in the diet for 104–106 weeks. A wide range of tissues and organs were examined microscopically. Based on food intake and body weight data given in the original report, estimated average intakes (expressed as mg of tin per kg body weight per day) for the control, 1000, and 2000 mg/kg groups are approximately 0, 30, and 60 for male and female rats, 0, 90, and 180 for male mice, and 0, 130, and 270 for female mice, respectively. Westrum & Thomassen (2002) presented

estimated tin doses for male rats and female mice at selected weeks, and these are reproduced in Table 6. Treatment had no effect on food consumption or growth, but survival of the male rats and female mice was somewhat lower in the high-dose group. No evidence of carcinogenic activity was seen in the female rats or male mice. In the male rats, there were apparent increases in thyroid C-cell adenomas and C-cell adenomas/carcinomas combined (see Table 7). However, when compared with the laboratory's historical control rate (32/288; mean 11.1%, maximum 20%) of thyroid C-cell tumours, only the incidence in the low-dose group was significantly ($P < 0.01$) raised. The incidence of C-cell hyperplasia did not differ between control and treated groups. The male rats also showed an apparent increase in lung adenomas, with a statistically significant positive trend with dose (see Table 6). However, individual comparisons between the high-dose group and the low-dose or control groups were not statistically significant, the 6% incidence in the high-dose group was within the laboratory's historical control range (6/289; overall mean 2.1%, range 0–6%), and results of statistical tests on incidences of combined lung adenomas and carcinomas were not significant. In the female mice, statistical trend analysis suggested increases in hepatocellular adenoma/carcinoma combined and in histiocytic malignant lymphoma (see Table 8). However, when the incidences of total lymphomas or lymphomas/leukaemias were considered, statistical significance no longer remained, and the incidence of liver tumours in the high-dose group did not differ significantly from the laboratory's historical control incidence (24/297; mean 8%, range 4–18%). Overall, the NTP experts judged tin(II) chloride not to be carcinogenic in this study, but cautioned that the thyroid C-cell tumours in male rats might possibly have been associated with the test chemical (NTP, 1982). (In this study, the incidence of retinal degeneration was considerably increased in the high-dose male rats and low-dose female rats [60–74%] compared with the other groups [4–16%]. This was believed to be due to proximity to fluorescent lighting and may reflect poor group distribution of cage locations [NTP, 1982].)

Table 6: Calculated doses in the NTP 105-week study.^a

Species/sex	Study week	Tin concentration (mg/kg body weight per day)	
		Low dose	High dose
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

^a From NTP (1982).

Table 7: Key primary tumours in male rats in the NTP 105-week study.^a

Tumours	Control group	Low-dose group	High-dose group
C-cell adenoma (thyroid)	2/50	9/49 ^b	5/50
C-cell adenoma/carcinoma combined (thyroid)	2/50	13/49 ^b	8/50 ^b
Lung adenoma ^c	0/50	0/50	3/50

^a From NTP (1982).

^b $P < 0.05$, Fisher's exact test.

^c $P < 0.05$, Cochran-Armitage trend test.

Table 8: Key primary tumours in female mice in the NTP 105-week study.^a

Tumours	Control group	Low-dose group	High-dose group
Hepatic adenoma/carcinoma combined ^b	3/49	4/49	8/49 ^c
Histiocytic malignant lymphoma ^d	0/50	0/49	4/49

^a From NTP (1982).

^b $P < 0.05$, life table and incidental tumour trend tests; $P = 0.067$, Cochran-Armitage trend test.

^c $P = 0.038$ life table pairwise test, comparison with control group.

^d $P < 0.05$, Cochran-Armitage trend test.

Survival, growth, serum chemistry, and urinalysis were normal when groups of 30 male and 30 female Cpb:WU rats were given tin(II) chloride at 0, 20, 40, or 80 mg/kg in the diet for 115 weeks. Haemoglobin and haematocrit values were decreased in all tin groups at weeks 4 and 13, but values during the second year of the study were similar to controls. A complete autopsy was performed, and the principal organs and tissues were examined microscopically. Spleen weight was increased (apparently at the top two dose levels), but the organ was microscopically normal. There was no evidence of carcinogenic activity (Sinkeldam et al., 1981).

In a very limited study, groups of 56 male and 56 female Long-Evans rats were given drinking-water containing tin(II) chloride (at 5 mg of tin per litre, equivalent to about 0.37 mg of tin per kg body weight per day) from weaning until natural death. The control rats (possibly 56 males and 76 females) were given drinking-water without added tin. The control diet contained 0.28 mg of tin per kg, which would probably have supplied about 0.014 mg of tin per kg body weight per day. In the tin group, survival was reduced in the females, and (at 18 months) males had lower body weight. Serum biochemistry and urine composition appeared to be unaffected. Tin-treated rats had a higher incidence of fatty degeneration of the liver and of

vacuolar changes in the renal tubules. No evidence of carcinogenicity was seen, but the low dose administered means that the sensitivity of the study is limited (Schroeder et al., 1968; Kanisawa & Schroeder, 1969). It is worth noting that no such liver and kidney changes were found in F344 rats given much higher tin(II) chloride doses (up to 60 mg of tin per kg body weight per day) in the NTP study (NTP, 1982).

In another very limited study, 54 male and 54 female Charles River mice were given tin(II) chloride in the drinking-water (at 5 mg of tin per litre, equivalent to about 0.37 mg of tin per kg body weight per day) from weaning until natural death. Controls (34 males, 46 females) received drinking-water without added tin. For both groups, an additional dose of about 0.02 mg of tin per kg body weight per day was supplied by background levels of tin in the diet. Tin treatment had no adverse effect on growth, survival, or the gross and microscopic appearance of an unspecified range of tissues. There was no evidence of carcinogenicity, but the low dose administered means that the sensitivity of the study is limited (Schroeder & Balassa, 1967).

No significant difference was seen in the development of lung tumours when groups of 20 strain A mice (a strain susceptible to lung tumour development) were given multiple intraperitoneal injections of tin(II) chloride over 30 weeks. Total doses given were 240, 600, and 1200 mg/kg body weight, and the ratios of numbers of surviving animals to initial numbers were 18/20, 12/20, and 4/20, respectively (Stoner et al., 1976).

Several other limited carcinogenicity studies are available. No evidence of carcinogenic activity was seen in mice given 1000 or 5000 mg of tin per litre as sodium hexachlorostannate in the drinking-water or 5000 mg of tin per kg as tin(II) oleate in the diet for 1 year (Walters & Roe, 1965). Similarly, there was no clear evidence of carcinogenicity when small groups (approximately 30) of rats were given sodium hexachlorostannate at 2000 mg/kg in the diet or tin(II) 2-ethylhexanoate at 500–1000 mg/kg in the diet for up to 18 months (Roe et al., 1965). In both the above studies, the small group sizes and/or short treatment duration would have limited the studies' ability to detect weak carcinogens. Following subcutaneous implantation of tin foil, Wistar rats did not develop tumours (Oppenheimer et al., 1956). Intracranial implantation of metallic tin cylinders in 33 male Marsh mice, of which only 10 mice survived beyond 10 months, resulted in local gliosis, but no local tumours developed (Bischoff & Bryson, 1976a). After intrathoracic injection of tin needles (4 mg) into 43 male Marsh mice, the implants were engulfed by giant cells with some adjacent nodular fibroplasia and a new network of capillaries. Survival (up to 19 months) was unaffected, and no increase in intrathoracic tumours was seen (Bischoff & Bryson, 1976b).

In summary, the available laboratory animal studies, mostly limited in nature, have not shown tin metal, tin(II) chloride, or a small number of other tin compounds to be carcinogenic. However, the most comprehensive study suggested that C-cell tumours of the thyroid gland in male rats might have been associated with the administration of tin(II) chloride. In this lifetime NTP study, a comprehensive tissue examination found no non-neoplastic changes in rats and mice given dietary tin at up to 60 or 270 mg/kg body weight per day, respectively (as tin(II) chloride). A more limited, earlier study reported increased incidences of fatty degeneration of the liver and possibly vacuolar changes in the renal tubules of rats (of a different strain) given tin at about 0.4 mg/kg body weight per day (as tin(II) chloride) in the drinking-water for a lifetime.

8.5 Genotoxicity and related end-points

In NTP studies, anhydrous tin(II) chloride and tin(II) chloride dihydrate were not mutagenic in Ames tests. Tin(II) chloride was tested at up to 0.33 mg/plate in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without metabolic activation fractions (S9) derived from the liver of rats or hamsters. A preincubation step was used, and the top dose was limited by either (not disclosed) solubility or toxicity (Mortelmans et al., 1986). Tin(II) chloride dihydrate was not mutagenic at up to 10 mg/plate (there was no preincubation step) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without S9 (Prival et al., 1991). Tin(IV) chloride gave no evidence of mutagenic potential in a more limited study using only *S. typhimurium* strains TA98 and TA100 (Hamasaki et al., 1993). Tin(II) fluoride gave no convincing evidence of mutagenic activity when tested in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. There was some evidence of a weak dose-response in strain TA100, but only in the presence of a metabolic activation system (S9 liver fraction from Aroclor-pretreated rats) and on one type of modified (high-citrate) medium (Gocke et al., 1981). Tin(II) chloride did not induce mutations in *Escherichia coli* strain WP2 (Prival et al., 1991).

Several tin compounds have failed to give evidence of an ability to induce DNA damage in *Bacillus subtilis*, as assessed by the relative survival of wild-type and DNA repair-deficient strains (rec assays) on exposure to tin. Using *B. subtilis* strains H17(rec⁺) and H45(rec⁻), four tin salts (tin(II) chloride, tin(IV) chloride, tin(II) sulfate, and sodium stannate) gave no evidence of an ability to cause DNA damage, although the investigators noted that the two chlorides were highly toxic to the bacteria, which would have reduced the sensitivity of the test (Kada et al., 1980). Tin(II) chloride, tin(IV) chloride, and sodium stannate were similarly inactive in this assay in the absence of any added metabolic activation

fraction (Nishioka, 1975). The literature contains another report of a rec assay test with *B. subtilis* in which tin(IV) chloride, when tested at up to 10 mg, gave no evidence of an ability to damage DNA (Hamasaki et al., 1992).

Indirect evidence of the ability of tin(II) chloride to damage bacterial DNA comes from studies of relative survival of treated wild-type and DNA repair-deficient strains of *E. coli*. When *E. coli* were incubated with tin(II) chloride at 0–75 µg/ml, there was a concentration-related decrease in survival. At all tested concentrations (5 µg/ml and above), survival of the wild strain (AB 1157) was higher than that of the strains that were deficient in DNA repair ability (AB 1886, AB 2463, AB 2494, AB 2480, and IC 204), suggesting that tin(II) chloride caused DNA damage (Silva et al., 1994, 2002). Other studies showed that tin(II) chloride (0–75 µg/ml) caused lysogenic induction of *E. coli* K-12 and microscopically visible *E. coli* B filamentation (Bernardo-Filho et al., 1994).

The SOS chromotest, a simple colorimetric assay of the induction of the bacterial gene *sfIA* in *E. coli*, indicated effects at 2–3 mmol of tin(II) chloride per litre, but the high degree of bacterial toxicity complicates interpretation of the data (Olivier & Marzin, 1987). Tin(IV) chloride did not produce DNA damage in an SOS chromotest (Hamasaki et al., 1992).

When incubated with tin(II) chloride, plasmid DNA (pUC9.9) showed a decrease in supercoiling, indicating the induction of single-strand DNA breaks (Silva et al., 2002). Plasmid DNA studies using varying doses of tin(II) chloride and oxygen suggested that the mechanism might involve reactive oxygen species (Dantas et al., 1999).

Tin(II) chloride did not induce mutations or gene conversions in strain D7 of the yeast *Saccharomyces cerevisiae* (Singh, 1983).

Tin(II) chloride gave no evidence of genotoxicity potential in sex-linked recessive lethal mutation assays in *Drosophila melanogaster*, conducted under the NTP. The protocols involved 3-day feeding of adult fruitflies at 6540 mg/kg in the diet or intraperitoneal injection at a concentration of 12 180 mg/litre and scoring of lethal mutations in three broods (Foureman et al., 1994). Tin(II) chloride was also non-mutagenic in a wing spot test in *D. melanogaster*. The protocol involved feeding the larvae for 48 h (Tripathy et al., 1990). Tin(II) fluoride was mutagenic in a sex-linked recessive lethal mutation assay in *D. melanogaster* when fed to the adult flies at 0–25% for 24 h. However, sodium fluoride was more potent than tin(II) fluoride, suggesting a role for the fluoride anion. Other tin salts were not tested (Mitchell & Gerdes, 1973). There was no induction of sex-linked recessive lethal mutations in three successive

broods produced by *D. melanogaster* fed 1.25 mmol of tin(II) fluoride per litre (described as “close to the LD₅₀”) in 5% saccharose (Gocke et al., 1981).

Tin(II) chloride at concentrations of 50, 150, 350, or 500 µmol/litre produced dose-related DNA damage, as detected by alkaline sucrose gradient analysis in Chinese hamster ovary cells. Treatment of cells with tin(IV) as tin(IV) chloride produced no such DNA damage. There was no loss in colony formation 6 days after either treatment (McLean et al., 1983a).

Tin(II) as tin(II) chloride (5, 10, 25, or 50 µmol/litre) was readily taken up by human white blood cells and caused a dose-dependent increase in DNA strand breaks that was more extensive than that caused by equimolar amounts of chromium(VI), a known carcinogen and DNA-damaging agent. Tin(IV) as tin(IV) chloride did not cause DNA damage and, in contrast to other studies, was not taken up by cells (McLean et al., 1983b). Tin(II) chloride, phytate, and fluoride all caused DNA damage (strand breaks) in human white blood cells, although this potential was not realized when the tin was chelated with EDTA (Swierenga & McLean, 1983). Others have reported DNA damage in human peripheral blood nuclear cells treated *in vitro* with 0.4 µmol of tin(II) chloride per litre (Dantas et al., 1999). In a comet assay (an assay that can detect DNA damage at the single cell level) using K562 human leukaemia cells, incubation with tin(II) chloride at 0.06–0.9 mmol/litre resulted in a concentration-dependent increase in DNA damage and a reduction in K562 cell viability. There was evidence that this DNA damage was repairable (Dantas et al., 2002a).

Tin(II) chloride did not induce unscheduled DNA synthesis in rat liver cells, but enhanced the ability of a known genotoxin to do so (Swierenga & McLean, 1983).

An NTP study found no evidence of mutagenic activity when tin(II) chloride (up to about 0.1 mg/ml; slightly toxic) was incubated with mouse lymphoma cells, with and without rat liver S9 (Myhr & Caspary, 1991).

In NTP studies, tin(II) chloride induced chromosome aberrations and SCEs in Chinese hamster ovary cells, both with and without rat liver S9 (Gulati et al., 1989).

According to a report published only as an abstract, tin(IV) chloride at 10 and 20 µg/ml induced concentration-dependent increases in the frequency of chromosome aberrations, micronuclei, and SCEs in human lymphocytes *in vitro* (Talukder et al., 1989). Incubation of human lymphocytes from 27 male donors with tin(IV) chloride at 2 or 4 µg/ml for 70 h resulted in 2- to 3-fold increases in the incidences of chromosome aberrations and SCEs (Ganguly et al., 1992). When human

lymphocytes from 52 donors were incubated with tin(IV) chloride at 4 µg/ml for 48 h, there were significant elevations of chromosome aberrations and micronuclei formation (Ganguly, 1993). Mitotic index and cell cycle kinetics (replicative index) were depressed in all three studies.

A comet assay found evidence of DNA damage in the peripheral blood cells of patients intravenously injected with a radiopharmaceutical containing tin(II) chloride and radiolabelled with ^{99m}Tc. DNA damage increased in the first 2 h following treatment but was not detectable at 24 h. The investigators concluded that damage could be ascribed to both tin(II) chloride and ^{99m}Tc. The tin(II) chloride “dose” was reported to range from 0.092 to 0.416 “µM” (Dantas et al., 2002b). This “dose” is in fact a concentration expressed in µmol/litre. If the units should have been reported as µmol, then the doses were only 20–80 µg per person.

Tin(II) chloride did not induce micronuclei in the bone marrow when given by intraperitoneal injection to groups of 4–5 male mice at 0, 26.3, 52.5, 105, or 210 mg/kg body weight per day for 3 days (Shelby et al., 1993). Two intraperitoneal doses of 0, 9.8, 19.6, or 39.5 mg of tin(II) fluoride per kg body weight given 24 h apart to NMRI mice (groups of two per sex per dose level) did not induce micronuclei in the bone marrow erythrocytes (Gocke et al., 1981).

To conclude, in short-term screening assays for genotoxicity potential, tin(II) chloride did not induce mutations in Ames bacterial tests, mutations or gene conversions in yeast, DNA damage in rat liver cells in culture, mutations in mouse lymphoma cells *in vitro*, or chromosome damage (micronuclei) *in vivo* in mice treated by intraperitoneal injection. In bacterial rec assays (in which activity is an indirect indication of DNA damage), tin(II) chloride was active in *E. coli* but (along with other tin salts) inactive in *B. subtilis*. In culture, tin(II) chloride induced chromosome damage and SCEs in hamster ovary cells and DNA damage in human lymphocytes, hamster ovary cells, and plasmid DNA. Tin(IV) chloride tested *in vitro* did not damage DNA in hamster ovary cells but induced chromosome aberrations, micronuclei, and SCEs in human lymphocytes. Tin(II) fluoride caused DNA damage in cultures of human lymphocytes, but did not induce micronuclei formation when injected intraperitoneally into mice; Ames tests on this compound gave no convincing evidence of activity. There is some evidence that tin-induced DNA damage may arise from a secondary mechanism involving reactive oxygen species. The mechanism underlying the induction of chromosome damage in mammalian cells in culture has not been determined, although it is recognized that such events can occur as a result of changes in ionic strength or pH in the medium.

8.6 Reproductive toxicity

8.6.1 Effects on fertility

In a multigeneration study, CPB:WU rats were given tin in the diet at 0, 200, 400, or 800 mg/kg for three generations. To simulate the “form of the tin likely to be found in canned food,” tin(II) chloride was allowed to react in aqueous medium with the casein content of the diet. The iron content was increased for the F₂ generation onwards. Tin did not affect growth of the parents, fertility, numbers of offspring per litter, or birth weight (Sinkeldam et al., 1979).

8.6.2 Developmental toxicity

In the multigeneration study in CPB:WU rats described above, tin did not affect numbers of offspring per litter or birth weight. Increased mortality of F₂ offspring during the first half of lactation was corrected by increasing the iron content of the mothers’ diet. Tin reduced offspring growth and haemoglobin levels during lactation but not thereafter. On pathological examination of rats from the F_{3b} and F_{3c} generations, the F_{3b} pups showed microscopic changes in the liver and spleen at weaning but not at 4 weeks of age (Sinkeldam et al., 1979).

Within this multigeneration study, a teratogenicity study was carried out using 20 F_{2b} females per dose level. On visceral and skeletal examination, there was no increase in the incidence of fetal malformations (Sinkeldam et al., 1979).

When groups of 9–10 female Sprague-Dawley rats were given diets containing tin at 0, 125, 156, 250, 312, 500, or 625 mg/kg (as tin(II) fluoride) throughout pregnancy (to day 20), there were no effects on the numbers of litters, resorptions, or live fetuses per litter. Mean placental and fetal weights were also unaffected (Theuer et al., 1971).

In the same series of studies, the numbers of litters, resorptions, and live fetuses per litter and the mean placental and fetal weights were unaffected by the inclusion of tin (as sodium pentachlorostannite) at 125, 250, or 500 mg/kg in the diet of groups of nine female Sprague-Dawley rats, throughout pregnancy (Theuer et al., 1971).

Other groups of nine female Sprague-Dawley rats were also given 125, 250, or 500 mg of tin per kg in the diet, but as sodium pentafluorostannite, throughout pregnancy. There were no effects on the numbers of litters or live fetuses or on placental and fetal weights. An apparent increase in resorptions was noted in the low- and high-dose groups, which was due to three rats (one low-dose, two high-dose) producing no live fetuses.

The observation was not considered toxicologically significant (Theuer et al., 1971).

Gavage administration of tin(II) chloride at 0, 0.5, 2.3, 11, or 50 mg/kg body weight per day to rats and mice (on days 6–15 of pregnancy) or hamsters (on days 6–10 of pregnancy) did not affect nidation, fetal survival, or the incidences of fetal malformations in soft and skeletal tissue (Food and Drug Research Laboratories, 1972).

8.7 Other toxicity

8.7.1 Local tissue irritation

Transient irritation of the eyes and nose was noted when guinea-pigs were exposed by inhalation to tin(IV) chloride at 3000 mg/m³ air, 10 min daily for “several months” (Pedley, 1927).

Application of aqueous solutions of 2% tin(II) chloride or 0.5% tin(II) fluoride on pieces of gauze to the intact skin of rabbits for 18 h produced no skin irritation. At abraded skin sites, 0.5% tin(II) chloride or 0.1% tin(II) fluoride caused polymorphonuclear leukocyte infiltration, whereas application of 1% tin(II) chloride or 0.25% tin(II) fluoride resulted in pustule development and complete destruction of the (abraded) epidermis (Stone & Willis, 1968).

Following uncovered application for 1 min (and histological examination 6 h later), a threshold concentration for skin irritation in rats of 5% was established for both tin(II) chloride and tin(IV) chloride (in ethanol). For the oral mucosa, equivalent threshold concentrations for irritation were 3% (tin(II) chloride) and 0.05% (tin(IV) chloride) (Larsson et al., 1990).

Diffusely reddened gastric and duodenal mucosa, as well as mucosal hypertrophy and hyperplasia in the entire small bowel, were seen at autopsy in a study in which Wistar rats were fed a diet containing tin(II) chloride for 13 weeks. The tin dose was gradually increased from 163 mg/kg body weight per day during weeks 0–4 up to 310 mg/kg body weight per day in weeks 8–13 (der Meulen et al., 1974). Ridge-like villi, increased migration of epithelial cells along the villus, increased villus length, a decreased number of villi per unit surface, and increased total length and weight of the small intestine were seen after feeding rats diets containing tin(II) chloride at 250 or 500 mg/kg for 4 weeks (Janssen et al., 1985).

8.7.2 Other toxic effects

Intraperitoneal or intravenous injections of metallic tin powder (200 mg in saline) produced a striking plasmacellular hyperplasia in the draining lymph nodes

and spleen of Lewis rats (Levine & Sowinski, 1982; Levine et al., 1983). Depending on the rat strain, the lymph node response to metallic tin varied from a very mild response to insoluble foreign particles to a marked granulomatous hyperplasia (August rats) and intense plasmacellular hyperplasia (Lewis rats and F₁ hybrids of Lewis rats) (Levine & Saltzman, 1996). Pretreatment with tin salts (including tin(II) chloride and tin(II) sulfate) in drinking-water prevented the plasmacellular response to subsequently injected metallic tin for up to 2 months after the pretreatment (Levine & Sowinski, 1983). The production of plasma cell hyperplasia by metallic tin and the prevention of such response by tin salts are apparently unique to this metal (Levine & Saltzman, 1991).

To study the potential of inorganic tin compounds to affect the immune system, male C57BL/6J mice were given tin(II) chloride and tin(IV) chloride at approximately 5 and 3.5 mg of tin per kg body weight, respectively, by intraperitoneal injection. Sheep red blood cells were given by the same route 72 h later, and immunotoxicity assays were carried out on days 5, 7, 10, and 13 following sheep red blood cell injection. In plaque-forming assays using spleen cells, on day 5, tin(IV) chloride significantly suppressed both IgM and IgG antibody production; tin(II) chloride also appeared to suppress (to a non-significant extent) IgM production, but to stimulate IgG production. By day 7, antibody production was unaffected by either compound. In an antigen rosette formation test (measuring agglutination of red blood cells around lymphocytes), the response was significantly stimulated by tin(II) chloride and suppressed by tin(IV) chloride; these effects had disappeared by day 13. Cellular immunity was assessed in a leukocyte adherence inhibition test (measuring a reduction in the proportion of spleen cells adhering to glass). Tin(IV) chloride had no obvious effect in this assay, but tin(II) chloride significantly increased the degree of inhibition, indicating immunostimulation (at days 7–13). Finally, neither compound demonstrated delayed-type hypersensitivity in an assay measuring footpad thickness 24 h following injection of sheep red blood cells into one footpad (Dimitrov et al., 1981).

Other data also suggest that tin chlorides might be able to affect the mouse immune response. For example, intraperitoneal injection of tin(II) chloride (about 20 mg of tin per kg body weight per day for 3 days) suppressed both primary and secondary immune response parameters in mice, 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 (Hayashi et al., 1984). In mice, the intratracheal instillation of tin(II) chloride (0.01 or 0.1 mg, approximately 6 or 60 µg tin, corresponding to 0.24 and 2.4 mg of tin per kg body weight, respectively) in saline increased the mortality induced by

subsequent bacterial infection (by aerosolized Group C *Streptococcus* sp.). A similar action was reported for intratracheal instillation of fly ash, carbon, bentonite, and a number of metal oxides and inhalation of "soluble metals" (Hatch et al., 1985).

Tin compounds can alter various enzyme activities. For example, tin(II) fluoride inhibited hepatic mixed-function oxidase enzyme activity in Charles River CD albino rats when given at 30 mg of tin per kg body weight by single intraperitoneal dose (Shargel & Masnyj, 1981). When fed to rats, diets containing tin(II) chloride (100 mg of tin per kg diet) for 4 weeks caused reduction in hepatocellular antioxidant metalloenzyme activities of superoxide dismutase and glutathione peroxidase. Impairment in hepatocellular antioxidant protection favours the peroxidation of fatty acids (Reicks & Rader, 1990). In mice, intravenous injection of tin(II) chloride resulted in significant inhibition of the P450 cytochrome-dependent hepatic drug metabolizing enzymes such as azo-reductase and aromatic hydroxylase (Burba, 1983). Pretreatment of mice with tin(II) chloride (50 mg/kg body weight per day for 2 days) induced coumarin 7-hydroxylase in liver and kidney (Emde et al., 1996).

Tin(II) tartrate (20 mg of tin per kg body weight, single intraperitoneal injection) caused a decrease in glutathione in partially hepatectomized Sprague-Dawley rats, allowing an increase in lipid peroxidation, which damaged the hepatocytic membranes (Dwivedi et al., 1984). The inhibitory effect of tin on sulfhydryl-containing enzymes, particularly hepatic glutathione reductase and glucose 6-phosphate dehydrogenase, may be caused by the sulfhydryl 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, through the formation of an unacceptable substrate complex for enzyme catalysis (Dwivedi et al., 1983).

Tin(II) compounds can adversely affect the erythrocytes (Chiba & Kikuchi, 1978; Chiba et al., 1980; Dwivedi et al., 1985b; Johnson & Greger, 1985; Zareba & Chmielnicka, 1985; see section 8.7). Tin(II) chloride (~3–30 mg of tin per kg body weight, single subcutaneous dose) and tin(II) tartrate (~9 mg of tin per kg body weight, single intraperitoneal dose) induced haem oxygenase in rat liver and kidney (Kappas & Maines, 1976; Maines & Kappas, 1977a; Kutty & Maines, 1984; Dwivedi et al., 1985b). The Sn^{2+} ion is more potent as an inducer of haem oxygenase-1 in rat cardiac tissue than is the Sn^{4+} ion, administered subcutaneously as tin(IV) citrate (single dose, 60 mg of tin per kg body weight) (Neil et al., 1995). Increased renal haem oxidase activity was observed (together with depleted renal cytochrome

P450) in rats given tin(II) chloride (63 mg/kg body weight, subcutaneously, twice weekly for 8–15 weeks) (Sacerdoti et al., 1989; Escalante et al., 1991; Laniado-Schwartzman et al., 1992). Haem is essential for cell respiration, energy generation, and oxidative biotransformation. Metal ions directly regulate cellular content of haem and haem proteins by controlling production of ALA synthetase and haem oxygenase. Thus, metal ions may impair the oxidative function of cells, particularly those dependent on cytochrome P450. As a result, the biological impact of chemicals that are detoxified or metabolically transformed by the P450 system is greatly altered (Maines & Kappas, 1977a; Dwivedi et al., 1985b). Chelation of the metal ion into the porphyrin ring is not necessary in order to regulate the enzymes of haem synthesis and oxidation (Maines & Kappas, 1977b). Tin(II) fluoride and other tin(II) halides form complexes with haemoproteins such as hepatic cytochrome P450 and haemoglobin (Dahl & Hodgson, 1977). Substitution of the central iron atom of haem by tin 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 (Drummond & Kappas, 1982; Sardana & Kappas, 1987).

The activity of ALAD in the erythrocytes of Harlan-Sprague-Dawley rats fed tin at 2000 mg/kg in the diet (as tin(II) chloride) for 21 days was reduced to 55% of the control value (Johnson & Greger, 1985). When tin(II) chloride was given at 2 mg/kg body weight to Wistar rats by subcutaneous, intraperitoneal, or intragastric routes every other day, ALAD activity was clearly decreased after two doses, whereas seven doses resulted in almost complete enzyme inhibition (Zareba & Chmielnicka, 1985). ALAD was inhibited by tin(II) chloride, but not by tin(IV) chloride. The inhibition was rapidly reversed (Chiba & Kikuchi, 1978; Chiba et al., 1980). ALA synthetase and ALAD were inhibited by tin(II) tartrate (Dwivedi et al., 1985b). Tin(II) concentrations of 1.5 $\mu\text{mol/litre}$ 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 (Despaux et al., 1977). A protective effect of zinc with respect to ALAD activity in blood and ALA levels in urine was observed after combined administration of tin(II) chloride and zinc sulfate in rabbits (Chmielnicka et al., 1992). One subunit of the ALAD enzyme contains one zinc atom and eight sulfhydryl groups (Tsukamoto et al., 1979). Tin presumably attacks one sulfhydryl group and binds weakly at the zinc-binding site of the enzyme (Chiba & Kikuchi, 1984). Intraperitoneal injection of selenium (as sodium selenite) simultaneously with tin(II) chloride in ICR mice completely prevents tin-induced ALAD inhibition. It has been suggested that selenium protects

essential thiol groups in ALAD that are otherwise blocked by tin (Chiba et al., 1985a, 1985b; Chiba & Shinohara, 1992).

Oral administration of tin(II) chloride (2 mg of tin per kg body weight per day) to rats had inhibitory effects on calcium content, acid and alkaline phosphatase activity, and collagen synthesis in femoral bone (Yamaguchi et al., 1980b, 1981a, 1982a, 1982b). When tin was given orally at 60 mg/kg body weight per day for 3 days (as tin(II) chloride), insulin secretion and hepatic phosphor-ylase activity were inhibited in rats (Yamaguchi et al., 1978a, 1978b), as were active transport of calcium and mucosal alkaline phosphatase activity in the duodenum, and bile calcium content was increased (Yamaguchi & Yamamoto, 1978; Yamaguchi et al., 1979). In rats, tin directly inhibits bone formation independently of calcium homeostasis. Administration of 1.0 mg of tin(II) chloride per kg body weight to weanling male rats at 12-h intervals for 28 days inhibited collagen synthesis prior to suppression of DNA synthesis in the femoral epiphysis (Yamaguchi et al., 1982b).

Slight but statistically significant increases in cerebral and muscle acetylcholinesterase activity were seen in groups of six male Wistar rats given 1.11 or 2.22 mmol of tin(II) chloride per litre in drinking-water (about 21 and 42 mg of tin per kg body weight per day, respectively) for 18 weeks, whereas no effect was seen at 0.44 mmol/litre (about 8 mg of tin per kg body weight per day) (Savolainen & Valkonen, 1986). Studies of frog neuromuscular transmission suggest that activation of the N-type calcium channel is involved in the tin(II) chloride-induced increase in calcium entry into the nerve terminals (Hattori & Maehashi, 1992). Tin(II) chloride itself may facilitate the transmitter release from nerve terminals in mammalian (mouse) as well as in amphibian (frog) species (Hattori & Maehashi, 1993). An intra-peritoneal dose of tin(II) chloride (5–30 mg of tin per kg body weight) suppressed gastric secretion in rats. 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 (Yamaguchi et al., 1976, 1978c). Injection of tin(II) chloride can stimulate or depress the central nervous system of rats (Silva et al., 2002).

8.8 Mode of action

Tin is ubiquitous in animal tissues. There is evidence that tin is essential for growth in rats (Schwarz et al., 1970; Schwarz, 1974a, 1974b; IPCS, 1980; Yokoi et al., 1990; ATSDR, 2003), but no essential function has been shown in other mammals, including humans (Schwarz et al., 1970; Hiles, 1974; IPCS, 1980; Alfrey, 1981; Nielsen, 1984; Dwivedi et al., 1985a; Sherman et al., 1986; Cardarelli, 1990; Tsangaris & Williams, 1992; ATSDR, 2003).

Studies in rats show that ingestion of inorganic tin (as tin(II) chloride) interferes with the body status and handling of copper, iron, and zinc. The mechanism is unknown, but possibly tin impairs absorption of these metals (Johnson & Greger, 1984; Beynen et al., 1992; Pekelharing et al., 1994; Yu & Beynen, 1995).

Limited data suggest a possible neurotoxic effect of tin(II) chloride. Cerebral and muscle acetylcholinesterase activities were slightly increased in rats given tin(II) chloride in the drinking-water for 18 weeks (Savolainen & Valkonen, 1986). The possible mechanism is unknown, but calcium, magnesium, and manganese cations also activate acetylcholinesterase (Tomlinson et al., 1981), suggesting a possible effect on the deacylation phase of enzyme–substrate reactions (Tomlinson et al., 1981; Savolainen & Valkonen, 1986). Studies of frog neuromuscular transmission suggest that activation of the N-type calcium channel is involved in the tin(II) chloride-induced increase in calcium entry into the nerve terminals (Hattori & Maehashi, 1992). Tin(II) chloride itself may facilitate the transmitter release from nerve terminals in mammalian (mouse) as well as in amphibian (frog) species (Hattori & Maehashi, 1993). Suppressed gastric secretion in rats given an intraperitoneal dose of tin(II) chloride (5–30 mg of tin per kg body weight) might be associated with inhibition of nerve transmission as well as reduction of gastrin release from G cells (Yamaguchi et al., 1976, 1978c).

9. EFFECTS ON HUMANS

No clearly irritant reactions were seen when 73 nickel-sensitive patients were patch-tested with metallic tin (Menné et al., 1987) or when other subjects were patch-tested with metallic tin or 1% tin(II) chloride in petrolatum (de Fine Olivarius et al., 1993). Irritant reactions were noted in patients patch-tested with 5% or 10% tin(II) chloride in petrolatum (de Fine Olivarius et al., 1993).

Patch tests with metallic tin in 73 nickel-sensitive patients revealed six positive allergic skin reactions (as well as four “doubtful” reactions) (Menné et al., 1987). Patch-testing with 1% tin(II) chloride in petrolatum and with a tin disc suggested that some patients are sensitized to tin (de Fine Olivarius et al., 1993). In 199 patients with suspected allergic reactions to metals, 13 had positive patch tests with 2% tin(II) chloride in petrolatum (Rammelsberg & Pevny, 1986). One out of 50 craftsmen in the ceramics industry had a positive reaction when patch-tested with 2.5% metallic tin dispersed in petrolatum (Gaddoni et al., 1993). A worker who produced metal patterns for body parts on trucks and was exposed to airborne dust from an alloy that

contained tin had dermatitis around the eyes, forehead, and wrists. He had a positive patch test to 1% tin(II) chloride in petrolatum (Nielsen & Skov, 1998). Considering its widespread use, it is unlikely that tin is an important contact allergen.

In groups of 10–11 humans, the acute ingestion of 36 mg tin (as tin(II) chloride) together with 0.5, 4, or 6 mg zinc (as $^{65}\text{ZnCl}_2$ solutions) or with 4 mg of ^{65}Zn (in a turkey-based meal) inhibited ^{65}Zn absorption, as measured by whole-body counting of the retention of ^{65}Zn after 7–10 days. According to the authors, the dose required to inhibit zinc absorption under the conditions in this study was well in excess of that supplied by the normal diet (Valberg et al., 1984). However, others were unable to demonstrate any clear inhibition of the plasma appearance of zinc after 1–4 h when human volunteers ingested a single dose of 25, 50, or 100 mg of tin (as tin(II) chloride) with 12.5 mg of zinc (Solomons et al., 1983). Moderate disturbances in zinc and selenium excretion rates were reported in eight adult males when the normal diet (supplying 0.11 mg of tin per day) was supplemented with 50 mg of tin per day (as tin(II) chloride in fruit juice) for 20 days, in a cross-over design study. Faecal and urinary excretion rates of copper, iron, manganese, magnesium, and calcium were unaffected, as were haematocrit and serum ferritin levels (Greger et al., 1982; Johnson & Greger, 1982; Johnson et al., 1982).

There are a number of reports of acute gastrointestinal illness following the intake of fruit or fruit juice from unlacquered tin cans, as well as a smaller number of controlled volunteer trials. These reports have been summarized comprehensively (JECFA, 2001; Blunden & Wallace, 2003). Corrosion of these containers had led to detinning, with tin concentrations reaching 200–2000 mg/kg in the food (Capar & Boyer, 1980; Greger & Baier, 1981). Ingested doses have been estimated as 30–200 mg (Warburton et al., 1962; Barker & Runte, 1972; Nehring, 1972; Svensson, 1975). Symptoms most frequently reported were nausea, abdominal cramps, vomiting, and diarrhoea. The median incubation period was 1 h (range 15 min to 14 h), and the median duration of symptoms was 12 h (Barker & Runte, 1972). Concentrations may be more critical than dose in causing these effects. JECFA has concluded that limited human data indicate that acute manifestations of gastric irritation may arise, in certain individuals, from the consumption of 150 mg of tin per litre in canned beverages or 250 mg of tin per kg in other canned foods. As some canned foods containing up to 700 mg of tin per kg produced no detectable effects, it may be that certain individuals are particularly sensitive or that the chemical form of tin is important (JECFA, 1989, 2001).

In a randomized, double-blind, cross-over study, a group of 18 healthy volunteers (males and females who

had fasted for at least 7 h) consumed 250 ml of tomato juice to which tin(II) chloride had been added to give tin concentrations of 161, 264, or 529 mg/kg. The control juice contained <0.5 mg of tin per kg. The only reaction in the 161 mg/kg group considered to be treatment-related was mild gastrointestinal symptoms in one volunteer (of 18). At 264 mg/kg, 3 of 18 subjects reported a total of 7 gastrointestinal symptoms, of which 2 were mild and 5 were moderate. Treatment at 529 mg/kg was discontinued, after 4 of 5 subjects reported a variety of mild and moderate gastrointestinal symptoms. Blood samples taken before dosing and at 0.5–4 h after dosing did not reveal increased serum levels of tin, supporting the view that effects are due to local irritation rather than to systemically absorbed tin (Boogaard et al., 2003).

In a second such study carried out at the same centre, another group of 23 healthy volunteers consumed 250 ml of tomato soup containing tin that had migrated from the unlacquered cans. Tin concentrations were <0.5 (controls), 201, and 267 mg/kg. The incidences of subjects reporting an adverse effect (3/23, 0/23, and 4/23 in the control, low-dose, and high-dose groups, respectively) bore no clear relationship with dose. The seven self-reported events were distributed among the classifications “gastrointestinal,” “central and peripheral system,” and “psychiatric,” and the study provided no evidence of significant toxicity from the acute ingestion of 267 mg of tin per kg in tomato soup (a tin dose of about 67 mg) (Boogaard et al., 2003).

The differences in toxicity seen in these studies might reflect differences in chemical speciation. In the soup study, 52% of the tin content was present in solid matter, whereas only 15% of the tin was found in solid matter in the freshly prepared mixture of juice and tin(II) chloride that was ingested by the volunteers. Low-molecular-weight species (<1000 daltons) in the supernatant accounted for about 59% and 32% of the tin content of the juice and soup, respectively. Within 24 h, the proportion of tin associated with solid matter in the juice/tin(II) chloride mixture increased from 15% to 35%, indicating gradual complexation. It was suggested that the concentration of low-molecular-weight tin species and the nature of the chemical species formed are important factors determining the extent of gastric irritation (Boogaard et al., 2003).

There are several case-reports of a benign pneumoconiosis called stannosis (identified by chest roentgenograms) in workers exposed to tin(IV) oxide dust and fumes for 3 years or more in tin smelting works, scrap metal recovery plants, and hearth tinning. In general, no information on exposure levels was available (Barták et al., 1948; Pendergrass & Pryde, 1948; Cutter et al., 1949; Dundon & Hughes, 1950; Spencer & Wycoff, 1954; Schuler et al., 1958; Cole & Davies, 1964; Sluis-Cremer et al., 1989). A chest roentgenogram revealed a

“peculiar widespread mottling of both lung fields by discrete shadows” in a man who had been employed in the tending of a detinning furnace for 18 years. The employment was terminated 8 years before chest examination. At autopsy 10 years later, the tin content of wet lung tissue was 1100 mg/kg (Dundon & Hughes, 1950).

In a health assessment of the employees, including ex-employee pensioners, from a United Kingdom tin smelting works, chest X-ray examinations provided radiological evidence of a benign pneumoconiosis in 121 out of 215 workers. The X-ray changes were either widespread, tiny, dense shadows or softer, larger, more nodular opacities and were found in workers handling raw ore, smelting furnace house workers, and refinery furnace men. Employment time ranged from 3 to 50 years. None of the affected men had any clinical symptoms or signs of pneumoconiosis, and there was no X-ray evidence of fibrosis or significant emphysema. Only men engaged in “dusty” work experienced X-ray changes. No significant X-ray changes were seen in fitters, joiners, or electricians, who were exposed only to the “general dustiness” of the works for up to 50 years, or in ingot casters, who worked with molten tin (Robertson & Whitaker, 1955; Robertson, 1960). Lung function measurements (forced expiratory volume and airway resistance) were normal. Mortality at the tin smelting works was lower than expected (observed 131, expected 166 deaths) in comparison with the male United Kingdom population for the period 1921–1955. The concentrations of tin (in mg/m³) associated with particle size <5 µm (Hexlet sampler) were given in section 6.3. The number of samples and strategy and methods of sampling and analysis were not described, and total airborne tin concentrations were not measured (Robertson, 1964).

Autopsy findings were given for seven tin 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 tin(IV) oxide. X-ray emission microanalysis identified tin in a minute particle of dust in lung phagocytes (Robertson et al., 1961). A survey carried out over a number of years of workers exposed to condensation aerosols formed during the smelting of tin and consisting mainly of tin(IV) oxide found that the total silica concentration in the aerosols did not exceed 3% and that the 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 were given (Hlebnikova, 1957).

Symptoms such as wheezing, cough, chest pain, and dyspnoea on exertion, reported in workers handling tin(IV) chloride, were probably due to elevated levels of hydrogen chloride formed by the combination of tin(IV) chloride and water in the presence of heat (Levy et al., 1985).

The lung cancer experience of tin miners in China (principally in Yunnan province) and England has been assessed. In the English studies (covering 1939–1986), an increased mortality from cancer of the lung was seen in a cohort of Cornish tin miners, but the data indicated the main risk factors to be tobacco smoking and radon exposure (Fox et al., 1981; Hodgson & Jones, 1990). In the Chinese studies of workers at the Yunnan Tin Corporation, 1724 lung cancer cases were registered during the period 1954–1986, of whom 90% had a history of working underground. Tin was not considered a contributing factor; the major causes were believed to be radon, arsenic, tobacco, and diet (Qiao et al., 1989, 1997; Taylor et al., 1989; Forman et al., 1992). A nested case–control study of lung cancer in four Chinese tin mines revealed an increased risk of lung cancer; the main risk factors were smoking and arsenic exposure, along with cumulative exposure to dust containing crystalline silica (Chen & Chen, 2002).

Uraemic patients might be especially prone to accumulate trace elements from environmental sources, and elevated tin levels have been found in muscle, serum, liver, and kidney of such patients. As tin affects kidney enzyme activity in animals, it has been suggested that tin might be involved in a degenerative feedback effect in uraemic patients (Rudolph et al., 1973; Nunnolley et al., 1978). In a Belgian case–control study ($n = 272$ men and women), 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 reconstructed from self-reported occupational histories by three industrial hygienists independently (Nuyts et al., 1995).

Plasma and red blood cell tin concentrations were higher in patients with Alzheimer disease (plasma 21.6 nmol/litre and red blood cells 32 nmol/litre) than in those with multi-infarct dementia (12.4 and 19.9 nmol/litre) and controls (11.6 and 21.7 nmol/litre) (Corrigan et al., 1991, 1992). There were negative correlations between tin levels and the red blood cell polyunsaturated fatty acid levels in the Alzheimer disease patients (16 women, 8 men, mean age 77.4 years, SD 8.3 years), and the authors suggested that tin may be involved in lipid peroxidation in that illness

(Corrigan et al., 1991). Later studies involving the analysis of tin in hippocampal tissues obtained post-mortem from patients with Alzheimer disease and controls found no significant difference in tin concentrations in the tissues (Corrigan et al., 1993).

In summary, occupational exposure to tin(IV) oxide dust or fumes has induced stannosis, with no indication of fibrosis or apparent disability beyond chest X-ray opacities. In one case-control study, an increased risk of chronic renal failure was reported. Excretion rates of zinc and selenium were moderately changed in subjects who ingested about 0.7 mg of tin per kg body weight per day for 20 days.

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

Most laboratory testing with aquatic organisms has been carried out with the soluble tin(II) chloride, leading to a classification of moderately toxic to aquatic organisms. However, speciation under environmental conditions favours the tin oxide compounds, which have low toxicity in organisms largely due to their low solubility, poor absorption, low accumulation in tissues, and rapid excretion.

10.1 Aquatic environment

The toxicity of inorganic tin to aquatic organisms is summarized in Table 9. The most sensitive microalgae are the marine diatoms *Skeletonema costatum* and *Thalassiosira guillardii*, with 72-h EC₅₀s of tin(II), based on growth inhibition, of around 0.2 mg/litre. Acute LC/EC₅₀s of tin(II) for aquatic invertebrates range from 3.6 to 140 mg/litre, with a 21-day EC₅₀, based on reproductive success in daphnids, of 1.5 mg/litre. The fish toxicity tests clearly show that tin(IV) chloride is less toxic than the more soluble tin(II) chloride. Ninety-six-hour LC₅₀s for fish range from 35 mg/litre for tin(II) to >1000 mg/litre for tin(IV). Embryo-larval test results (7- to 28-day LC₅₀s) for fish and amphibians range from 0.1 to 2.1 mg/litre for tin(II).

The toxicity of tin(IV) chloride to three pure strains of sulfate-reducing marine bacteria isolated from a tributyltin-polluted sediment was determined. Adverse effects on suspended anaerobic cell cultures were reported at concentrations ranging from 130 mg of tin(IV) per litre (500 µmol/litre) to 156 mg/litre (600 µmol/litre) (Lascourreges et al., 2000).

Pawlik-Skowronska et al. (1997) found that tin(II) and tin(IV) salts inhibited the growth of planktonic cyanobacteria (*Synechocystis aquatilis*). Toxicity

increased with increasing tin concentrations, time of exposure, and pH value of the medium (in the pH range 7.0–9.8); tin(II) seemed to be more toxic than tin(IV). At the lowest tin(II) concentration of 1 mg/litre, there was a 36–40% decrease in growth and chlorophyll *a* content after 96 h at pH 9.8. The presence of humic acids reduced the toxicity of tin. At high pH values, anionic tin species such as SnO₃H⁻, SnO₃²⁻, or Sn(OH)₆²⁻ exist, whereas at neutral or acidic pH values, cationic or neutral tin species like Sn(OH)⁺, Sn(OH)₂²⁺, Sn(OH)₂, or SnO are present.

10.2 Terrestrial environment

Kick et al. (1971) found adverse effects on the yield of spring wheat (expressed as dry weight) at soil inorganic tin(II) concentrations of 125 mg/kg; however, the addition of sludge completely eliminated the toxic effect due to an increase in soil nutrient content and a decrease in soil acidity. *Sinapis alba* seeds showed low sensitivity to inorganic tin, with 72-h EC₅₀s, based on root growth inhibition, of 281 mg/litre for tin(II) (as tin(II) chloride) and 417 mg/litre for tin(IV) (as sodium stannate) (Fargasova, 1994).

Inorganic tin (as tin(II) chloride) had no significant effect on day-old chicks fed a diet containing 200 mg of tin per kg for 21 days (Howell & Hill, 1978). A significant increase in myopathy was reported in ducklings during a 4-week exposure to 1000 mg of tin per kg (as tin(II) chloride) in the diet (Van Vleet, 1982).

Tin(II) chloride was found to cause 60% repellency (percentage of mice refusing to eat more than 50% of wheat treated with 2.0% tin(II) chloride) in house mice (*Mus musculus*) (Schafer & Bowles, 1985).

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose-response assessment

Occupational inhalation of particles containing water-insoluble tin compounds has been associated with a benign pneumoconiosis (stannosis) observed as X-ray opacities. Where information was given, this effect was restricted to workers in particularly dusty work areas. This condition is not associated with fibrosis and appears not to be associated with any apparent lung dysfunction. The literature on long-term inhalation of inorganic tin consists mainly of case-reports in humans, with poor exposure assessment and old methods of examination. Reports on effects concerning microscopic pathology

Table 9: Toxicity of inorganic tin compounds to aquatic species.

Organism	End-point	Ion ^a	Tin concentration (mg/litre)	Reference
Microorganisms				
Bacterium (<i>Pseudomonas fluorescens</i>)	1-h EC ₅₀ (viability)	Sn ^{4+ b}	245	Han & Cooney (1995)
Bacterium (<i>Serratia</i> sp.)	1-h EC ₅₀ (viability)	Sn ^{4+ b}	287	Han & Cooney (1995)
Marine bacterium (<i>Vibrio harveyi</i>)	EC ₅₀ (bioluminescence)	Sn ²⁺	2.3	Thomulka & Lange (1996)
Cyanobacterium (<i>Anabaena flosaquae</i>)	4-h EC ₅₀ (primary productivity)	Sn ²⁺	>5	Wong et al. (1982)
	4-h EC ₅₀ (primary productivity)	Sn ^{4+ b}	>5	Wong et al. (1982)
Green alga (<i>Ankistrodesmus falcatus</i>)	8-day EC ₅₀ (growth inhibition) ^c	Sn ²⁺	12	Wong et al. (1982)
	4-h EC ₅₀ (primary productivity)	Sn ²⁺	14	Wong et al. (1982)
	8-day EC ₅₀ (growth inhibition) ^c	Sn ^{4+ b}	2	Wong et al. (1982)
	4-h EC ₅₀ (primary productivity)	Sn ^{4+ b}	12	Wong et al. (1982)
Green alga (<i>Scenedesmus quadricauda</i>)	4-h EC ₅₀ (primary productivity)	Sn ²⁺	>50	Wong et al. (1982)
	4-h EC ₅₀ (primary productivity)	Sn ^{4+ b}	>50	Wong et al. (1982)
Diatom (<i>Skeletonema costatum</i>)	72-h EC ₅₀ (growth inhibition) ^c	Sn ²⁺	0.2	Walsh et al. (1985)
Diatom (<i>Thalassiosira guillardii</i>)	72-h EC ₅₀ (growth inhibition) ^c	Sn ²⁺	0.2	Walsh et al. (1985)
Ciliate (<i>Tetrahymena pyriformis</i>)	3-h EC ₅₀ (growth inhibition)	Sn ^d	132	Sauvant et al. (1995)
	6-h EC ₅₀ (growth inhibition)	Sn ^d	80	Sauvant et al. (1995)
	9-h EC ₅₀ (growth inhibition)	Sn ^d	90	Sauvant et al. (1995)
Invertebrates				
Pulmonate snail (<i>Taphius glabratus</i>)	24-h NOEC (behaviour)	Sn ²⁺	10	Harry & Aldrich (1963)
Tubificid worm (<i>Tubifex tubifex</i>)	48-h EC ₅₀ (immobilization)	Sn ²⁺	140	Khangarot (1991)
	96-h EC ₅₀ (immobilization)	Sn ²⁺	21	Khangarot (1991)
	48-h LC ₅₀	Sn ²⁺	54.9	Fargasova (1994)
	96-h LC ₅₀	Sn ²⁺	30	Fargasova (1994)
	48-h LC ₅₀	Sn ^{4+ e}	33.1	Fargasova (1994)
	96-h LC ₅₀	Sn ^{4+ e}	27.5	Fargasova (1994)
Amphipod (<i>Crangonyx pseudogracilis</i>)	48-h LC ₅₀	Sn ²⁺	71.8	Martin & Holdich (1986)
	96-h LC ₅₀	Sn ²⁺	50.1	Martin & Holdich (1986)
Water flea (<i>Daphnia magna</i>)	24-h LC ₅₀	Sn ²⁺	37	Khangarot et al. (1987)
	48-h LC ₅₀	Sn ²⁺	19.5	Khangarot et al. (1987)
	48-h LC ₅₀	Sn ²⁺	55	Biesinger & Christensen (1972)
	21-day LC ₅₀	Sn ²⁺	42	Biesinger & Christensen (1972)
	21-day EC ₅₀ (reproductive inhibition)	Sn ²⁺	1.5	Biesinger & Christensen (1972)
	48-h LC ₅₀	Sn ⁴⁺	32.9	Cabejszek & Stasiak (1960)
	48-h EC ₅₀ (immobilization)	Sn ⁴⁺	21.6	Khangarot & Ray (1989)
Midge (<i>Chironomus plumosus</i>)	48-h LC ₅₀	Sn ²⁺	8.3	Fargasova (1994)
	96-h LC ₅₀	Sn ²⁺	3.6	Fargasova (1994)
	48-h LC ₅₀	Sn ^{4+ e}	8.3	Fargasova (1994)
	96-h LC ₅₀	Sn ^{4+ e}	3	Fargasova (1994)
Fish				
Goldfish (<i>Carassius auratus</i>)	7-day LC ₅₀ (embryo-larval test)	Sn ²⁺	2.1	Birge (1978)
Carp (<i>Cyprinus carpio</i>)	96-h EC ₅₀ (hatching success)	Sn ²⁺	295	Kapur & Yadav (1982)
Mud dab (<i>Limanda limanda</i>)	96-h LC ₅₀	Sn ²⁺	35 ^f	Taylor et al. (1985)
Largemouth bass (<i>Micropterus salmoides</i>)	8-day LC ₅₀ (embryo-larval test)	Sn ²⁺	1.9	Birge et al. (1978)

Table 9 (Contd)

Organism	End-point	Ion ^a	Tin concentration (mg/litre)	Reference
Rainbow trout (<i>Oncorhynchus mykiss</i>)	28-day LC ₅₀ (embryo-larval test)	Sn ²⁺	0.4	Birge (1978); Birge et al. (1978)
Killifish (<i>Oryzias latipes</i>)	48-h LC ₅₀	Sn ^{4+ b}	480 ^g	Tsuji et al. (1986)
Zebra fish (<i>Brachydanio rerio</i>)	96-h LC ₅₀ ^h	Sn ^{4+ b}	>1000	Hoechst AG (1995)
Amphibians				
Marbled salamander (<i>Ambystoma opacum</i>)	8-day LC ₅₀ (embryo-larval test)	Sn ²⁺	0.9	Birge et al. (1978)
Eastern narrow-mouthed toad (<i>Gastrophryne carolinensis</i>)	7-day LC ₅₀ (embryo-larval test)	Sn ²⁺	0.1	Birge (1978)

^a Tin(II) chloride unless otherwise stated.

^b Tin(IV) chloride.

^c Based on cell yield.

^d Salt not stated.

^e Sodium stannate (Na₂SnO₃).

^f 24- to 96-h LC₅₀s all 35 mg/litre.

^g 24- and 48-h LC₅₀s at 10 °C, 20 °C, and 30 °C all 480 mg/litre; precipitated in the test solution.

^h OECD Guideline 203 (fish, acute toxicity test).

and cell toxicity in the respiratory system are scarce. The information is insufficient to assess the health risk to the lungs.

Tin metal is not a skin irritant, but tin(II) chloride was irritating to human skin, and tin(II) and tin(IV) chlorides were irritating to the skin and oral mucosa of rats.

Occasional cases of allergic contact dermatitis in humans have been reported. However, the scarcity of reported reactions, despite its widespread use, suggests that tin is not an important contact allergen.

On acute ingestion, tin salts (e.g. tin(II) chloride) can cause gastrointestinal irritation, nausea, vomiting, abdominal cramps, and diarrhoea in humans.

Tin absorbed from the gut may interfere with the status of other important metallic minerals (e.g. zinc). On repeated ingestion, the critical effect of absorbed tin might be the decrease of calcium content in bone. Interference with the status of minerals has been observed at similar oral doses (0.6–0.7 mg of tin per kg body weight per day) in humans and laboratory animals. In laboratory animals, repeated ingestion has led to changes in enzyme levels in blood, liver, kidney, and bone and degenerative changes in liver and kidney. In an old lifetime study, degenerative changes were reported in the liver and kidneys of rats ingesting about 0.4 mg of tin per kg body weight per day from the drinking-water, but such effects were not seen in a later 2-year study, in which rats and mice ingested tin at much higher (at least 100-fold) doses from the diet. In certain studies, exact daily doses are difficult to estimate due to the study designs and lack of information in the reports. The most

comprehensive long-term study of reasonable quality involved continuous administration of tin(II) chloride in the diet of rats and mice at 0, 1000, or 2000 mg/kg for 2 years. Food consumption, growth, survival, and the gross and microscopic appearance of a wide range of tissues and organs were evaluated. In rats, the NOAEL was 1000 mg/kg diet, equivalent to 30 mg/kg body weight per day; at the higher dose, survival was decreased in the males. The male mice showed no effects (NOAEL 180 mg/kg body weight per day). Female mice were normal at 1000 mg/kg diet (NOAEL 130 mg/kg body weight per day), but survival was reduced at 270 mg/kg body weight per day (NTP, 1982).

Good-quality carcinogenicity studies are available on rats and mice administered tin(II) chloride in the diet for 2 years. Other, more limited, investigations of carcinogenicity potential have been carried out, notably on tin metal, tin(II) chloride, and tin(II) 2-ethylhexanoate. None of these studies gave any clear evidence of carcinogenicity, although there is some doubt regarding the C-cell tumours in the thyroid gland in male rats in the best available study.

Investigation of the genotoxicity potential of tin compounds *in vivo* is limited, but has not revealed any evidence of activity. Several *in vitro* studies also gave negative results, but inorganic tin compounds have induced DNA damage in human white blood cells, hamster ovary cells, and *E. coli* bacteria, as well as chromosome damage in hamster ovary cells. Some evidence suggests that the DNA damage may be a secondary effect associated with reactive oxygen species. The mechanism resulting in chromosome damage has not been determined, although it is known that certain inorganic salts can give positive results in

such assays as the result of changes in the ionic strength or pH of the test medium.

11.1.2 *Criteria for setting tolerable intakes/concentrations*

The very limited information on the levels of exposure in the worker populations where cases of stannosis have been diagnosed does not allow the setting of tolerable concentrations for inhaled tin compounds.

Limited data are available on the ability of ingested tin to adversely affect zinc absorption in humans. In one volunteer study, plasma appearance of zinc 1–4 h following a zinc dose of 12.5 mg was unaffected by concomitant ingestion of up to 100 mg tin (as tin(II) chloride) (Solomons et al., 1983). However, others reported that a single dose of 36 mg tin (again, as tin(II) chloride), taken with up to 6 mg zinc (as radiolabelled zinc dichloride), resulted in a lower zinc retention (whole-body counting) 7–10 days later (Valberg et al., 1984). Moderate disturbances in zinc excretion rates were reported when the normal diet (supplying 0.11 mg of tin per day) of eight men was supplemented with 50 mg of tin per day (as tin(II) chloride in fruit juice) (Greger et al., 1982; Johnson & Greger, 1982; Johnson et al., 1982).

Early literature contains a number of reports of gastrointestinal effects (notably nausea, abdominal cramps, vomiting, and diarrhoea) following the intake of fruit or juice from unlacquered tin cans. Although the tin doses involved have been estimated (at 30–200 mg), confidence in the accuracy of these figures is low.

Two recent volunteer studies provided a better insight into effective doses and, perhaps more importantly, concentrations. The first study involved ingestion of 250 ml of tomato juice to which tin(II) chloride had been added to give tin concentrations of 161, 264, or 529 mg/kg. The control juice contained tin at <0.5 mg/kg. One volunteer experienced mild gastrointestinal symptoms at 161 mg/kg (a dose of about 40 mg tin); typical tin-induced acute symptoms were seen at 264 and 529 mg/kg (about 66 and 132 mg tin). Serum levels of tin did not increase at 0.5–4 h post-dosing at any dose, supporting the view that acute effects of tin ingestion are dependent upon concentration (resulting in local gastric irritation) rather than due to systemically absorbed tin (Boogaard et al., 2003). A second study, published by the same investigators, involved ingestion of tomato soup containing tin that had migrated from unlacquered cans; consequently, the tin species involved might be a better match for those that arise in canned food. The volunteers ingested 250 ml of tomato soup containing migrated tin at <0.5, 201, or 267 mg/kg. There was no evidence that consumption at these

concentrations (up to about 67 mg tin) produced any acute effects (Boogaard et al., 2003).

11.1.3 *Sample risk characterization*

11.1.3.1 *Exposure of the sample population*

For the general population, the major source of tin is the diet. By comparison, drinking-water and inhaled air contribute insignificant amounts.

From data on mean tin intake from food for the populations of seven countries (Australia, France, Japan, Netherlands, New Zealand, the United Kingdom, and the USA), JECFA (2001) concluded that tin intakes ranged from <1 up to 15 mg/person per day.

Certain individuals who routinely consume canned fruits, vegetables, and juices from unlacquered cans could ingest 50–60 mg of tin daily (Johnson & Greger, 1982; Sherlock & Smart, 1984; JECFA, 2001).

Those who consume about four servings of food stored in open unlacquered cans, on a daily basis, might consume in the region of 200 mg of tin per day (Greger & Baier, 1981; JECFA, 2001).

11.1.3.2 *Health risks in the sample population*

Although a no-effect level for inhibition of zinc absorption has not been clearly established, the lowest dose reported to have this effect (36 mg) is about 2.5 to >36 times higher than the estimated mean population intakes as summarized by JECFA. However, those who routinely consume canned fruits, vegetables, and juices from unlacquered cans could have tin intakes (50–60 mg) that are similar to the acute (36 mg) or repeated (50 mg) dose levels reported in some studies to affect zinc absorption or balance. Whether this would have any clinical effect is likely to be critically dependent upon an adequate dietary supply of zinc.

Of the two recent studies on the acute gastrointestinal effects of tin, one showed a LOAEL of approximately 66 mg of tin (264 mg/kg food). The other, which may be more relevant, found no evidence of effects at a similar dose of 67 mg of tin (267 mg/kg food). This dose is approximately 4.5 to >67 times higher than the values reported in JECFA (2001) as estimates of mean population dietary intakes for seven countries, but similar to the estimated daily intake (50–60 mg) of those individuals who routinely consume canned fruits, vegetables, and juices from unlacquered cans.

11.1.4 Uncertainties in the evaluation of health risks

Data on possible effects by inhalation exposure are rare. It is unclear whether occupational exposure to tin poses any extra risk to workers with existing renal disease.

Consumers with a high proportion of the diet consisting of foods or beverages from unlacquered cans may have higher than average exposure, especially with regard to canned acid fruits, juice, tomatoes, and tomato products. These may include people on low incomes, the elderly, and institutionalized individuals.

Chronic tin consumption might affect mineral balance in humans. It is unclear to what extent those individuals whose zinc status is marginal may be at extra risk due to consumption of tin in food. Such populations might include those with only low levels of zinc or those who are in a marginal nutritional status regarding zinc (e.g. the elderly, children, and pregnant women).

The possible significance of the increase in thyroid tumours that developed in rats fed tin(II) chloride in the diet for 2 years has not been firmly established.

Tin compounds have been subjected to only limited testing for genotoxicity potential. There is uncertainty over the mechanism by which some tin compounds apparently induce DNA damage and chromosome damage in mammalian cells in culture.

11.2 Evaluation of environmental effects

Ambient levels of tin in the environment are generally quite low, except in the vicinity of local pollution sources. Most monitoring studies have analysed only for total tin, and in these cases the proportion of inorganic tin will vary depending on sampling time and site. Therefore, in order to compare environmental concentrations with toxicity, only analytical results based on inorganic tin have been considered in the evaluation.

Tin may be transported in the atmosphere following the release of particulate matter derived from the combustion of fossil fuels and solid wastes. Inorganic tin compounds are non-volatile under environmental conditions. Average tin concentrations in air are generally below $0.1 \mu\text{g}/\text{m}^3$, with higher concentrations near some industrial facilities.

In general, tin occurs in trace amounts in natural waters; higher inorganic tin concentrations are associated with industrial discharges and tributyltin use (tributyltin degrades ultimately to inorganic tin). In a survey of lakes and rivers, nearly 80% of samples were

found to contain inorganic tin at concentrations below $1 \mu\text{g}/\text{litre}$; higher levels of up to $37 \mu\text{g}/\text{litre}$ were reported near local pollution sources. Inorganic tin concentrations ranging from 0.001 to $0.01 \mu\text{g}/\text{litre}$ have been reported for coastal waters, with levels of up to $8 \mu\text{g}/\text{litre}$ near anthropogenic sources. Concentrations of inorganic tin displayed extreme variability both temporally and spatially within enclosed harbours and were largely influenced by localized inputs. Concentrations generally ranged from <0.005 to $0.2 \mu\text{g}/\text{litre}$; however, levels of up to $48.7 \mu\text{g}/\text{litre}$ were found near local discharges and significant tributyltin usage.

In the environment, tin compounds are generally only sparingly soluble in water and are likely to partition to soils and sediments. Inorganic tin concentrations in sediment ranged up to $8 \text{mg}/\text{kg}$ dry weight in coastal areas and up to $15.5 \text{mg}/\text{kg}$ in rivers and lakes. Total tin concentrations in soil can range from <1 to $200 \text{mg}/\text{kg}$, but levels of $1000 \text{mg}/\text{kg}$ may occur in areas of high tin deposits.

Inorganic tin may undergo oxidation–reduction, ligand exchange, and precipitation reactions in the environment. The biomethylation of inorganic tin has been demonstrated in pure bacterial cultures, sediments, and decaying plant material. Inorganic tin compounds may be bioconcentrated by organisms, but data are limited.

Under environmental speciation conditions, inorganic tin compounds have low toxicity in both aquatic and terrestrial organisms, largely due to their low solubility, poor absorption, often low accumulation in tissues, and rapid excretion. Most laboratory testing with aquatic organisms has been carried out with the soluble tin(II) chloride. Figure 1 summarizes the toxicity of inorganic tin to a range of aquatic organisms (data from Table 8). The most sensitive microalgae are the marine diatoms, with 72-h EC_{50}s of tin(II), based on growth inhibition, of around $0.2 \text{mg}/\text{litre}$. Acute $\text{LC}/\text{EC}_{50}\text{s}$ of tin(II) for aquatic invertebrates range from 3.6 to $140 \text{mg}/\text{litre}$, with a 21-day EC_{50} , based on reproductive success in daphnids, of $1.5 \text{mg}/\text{litre}$. The fish toxicity tests clearly show that tin(IV) chloride is less toxic than the more soluble tin(II) chloride. Ninety-six-hour LC_{50}s for fish range from $35 \text{mg}/\text{litre}$ for tin(II) to $>1000 \text{mg}/\text{litre}$ for tin(IV). In longer-term embryo-larval tests (7- to 28-day LC_{50}s), results for fish and amphibians range from 0.1 to $2.1 \text{mg}/\text{litre}$ for tin(II).

In the environment, inorganic tin will partition to soil and sediment, and, as a consequence, bioavailability to organisms will tend to be low. Generally, as can be seen from Figure 1, the acute toxicity to aquatic organisms is low to moderate. Concentrations showing toxicity to organisms are generally several orders of magnitude higher than those found in the environment.

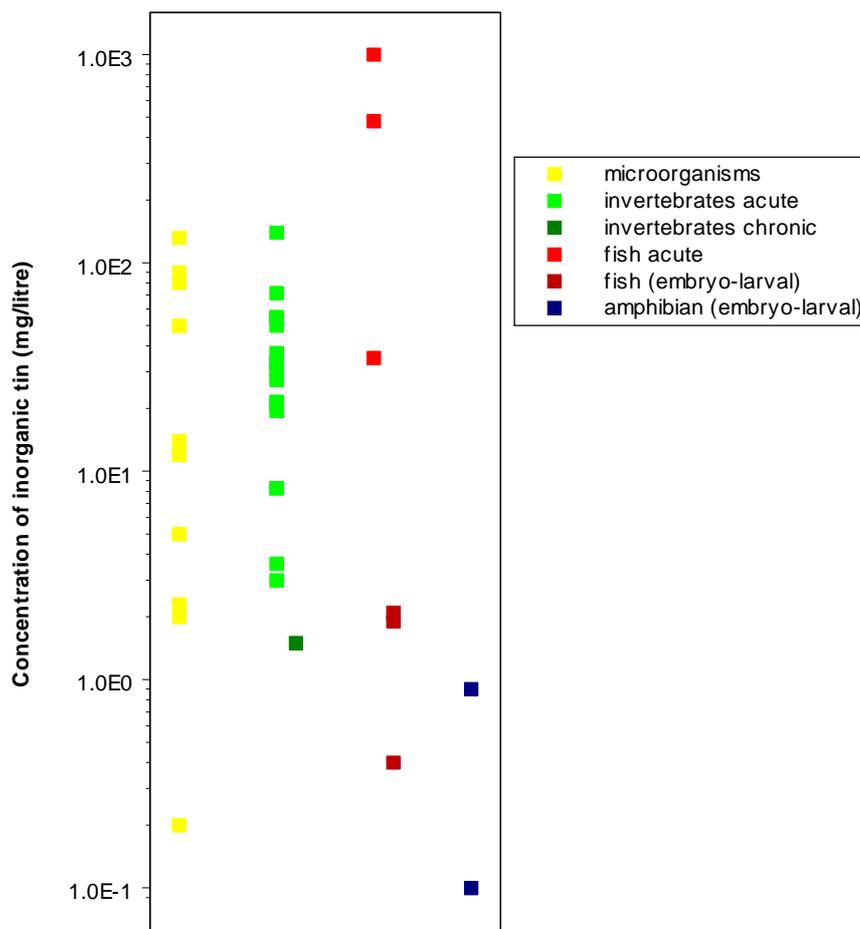


Figure 1: Toxicity of inorganic tin to aquatic organisms.

The most sensitive test results were 72-h exposures to diatoms and embryo-larval amphibian studies, with toxic effects seen at 0.1 to 0.2 mg/litre for tin(II). Even at these concentrations, toxic effects caused by inorganic tin are unlikely, even near sources of local pollution. It should be noted that where concentrations are expressed as total tin, a percentage is likely to be in the form of organotins, such as tributyltin, which are more bio-available and toxic. For more information on the environmental fate and toxicity of tributyltin, please refer to IPCS (1990, 1999).

12. PREVIOUS EVALUATIONS BY IOMC BODIES

JECFA has reviewed the toxicological literature on inorganic tin on a number of occasions (e.g. JECFA, 1989, 2001, 2005).¹

¹ At the 64th JECFA meeting in Rome in February 2005, the Committee concluded that the data available indicated that it is inappropriate to establish an acute reference dose for inorganic tin, since whether or not irritation of the gastrointestinal tract occurs after ingestion of a food containing tin depends on the concentration and nature of tin in the product, rather than on the dose ingested on a body weight basis. Therefore, the Committee concluded that the short-term intake estimates were not particularly relevant for the assessment, as they were estimated likely doses of total inorganic tin. The Committee reiterated its opinion, expressed at its 33rd and 55th meetings, that the available data for humans indicated that inorganic tin at concentrations of >150 mg/kg in canned beverages or

IARC has not evaluated the carcinogenic potential of tin compounds. IARC has evaluated inorganic fluorides, including tin(II) fluoride, and concluded that these are not classifiable as to their carcinogenicity to humans. Evidence for carcinogenicity of inorganic fluorides was considered inadequate for both humans and laboratory animals (IARC, 1987).

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>250 mg/kg in canned foods may produce acute manifestations of gastric irritation in certain individuals. Therefore, ingestion of reasonably sized portions containing inorganic tin at concentrations equal to the proposed standard for canned beverages (200 mg/kg) may lead to adverse reactions. No information was available as to whether there are subpopulations that are particularly sensitive for such adverse reactions. The Committee reiterated its advice that consumers should not store food and beverages in open tin-plated cans. In addition, the Committee noted that the basis for the PMTDI and PTWI established at its 26th and 33rd meetings was unclear and that these values may have been derived from intakes associated with acute effects. The Committee concluded that it was desirable to (re)assess the toxicokinetics and effects of inorganic tin after chronic exposure to dietary doses of inorganic tin at concentrations that did not elicit acute effects (JECFA, 2005).

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APPENDIX 1 — ABBREVIATIONS AND ACRONYMS

AAS	atomic absorption spectroscopy
AES	atomic emission spectroscopy
ALA	δ-aminolaevulinic acid
ALAD	δ-aminolaevulinic acid dehydratase
ATSDR	Agency for Toxic Substances and Disease Registry
CANCERLIT	Cancer Literature Online
CAS	Chemical Abstracts Service
CCRIS	Chemical Carcinogenesis Research Information System
CICAD	Concise International Chemical Assessment Document
DART	Developmental & Reproductive Toxicology
DNA	deoxyribonucleic acid
EC ₅₀	median effective concentration
EDTA	ethylenediaminetetraacetic acid
EHC	Environmental Health Criteria monographs
EPA	Environmental Protection Agency (USA)
ETIC	Environmental Teratology Information Center
FAO	Food and Agriculture Organization of the United Nations
GENE-TOX	Genetic Toxicology
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
ICP	inductively coupled plasma
ICRP	International Commission on Radiological Protection
Ig	immunoglobulin
ILO	International Labour Organization
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System (USA)
ISO	International Organization for Standardization
JECFA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
LC ₅₀	median lethal concentration
LD ₅₀	median lethal dose
LOAEL	lowest-observed-adverse-effect level
LOEL	lowest-observed-effect level
MS	mass spectrometry
NIOSH	National Institute for Occupational Safety and Health (USA)
NOAEL	no-observed-adverse-effect level
NOEC	no-observed-effect concentration
NOEL	no-observed-effect level
NTP	National Toxicology Program (USA)
OECD	Organisation for Economic Co-operation and Development
PIM	Poison Information Monograph
PMTDI	provisional maximum tolerable daily intake
PTWI	provisional tolerable weekly intake
RTECS	Registry of Toxic Effects of Chemical Substances
S ₉	metabolic activation fraction
SCE	sister chromatid exchange
SD	standard deviation
SIDS	Screening Information Data Set
TSCA	<i>Toxic Substances Control Act</i>
UNEP	United Nations Environment Programme
USA	United States of America
WHO	World Health Organization

APPENDIX 2 — SOURCE DOCUMENTS

Three publications served as source documents for this CICAD.

Westrum & Thomassen (2002)

The first source document was prepared by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards and considered the literature identified as of March 2002. This publication was a result of an agreement between the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards to write joint scientific criteria documents that can be used by the national regulatory authorities in both the Netherlands and the Nordic countries. The report (Arbete och Hälsa 2002:10) was authored by B. Westrum and Y. Thomassen and published on behalf of the Nordic Council of Ministers by the National Institute for Working Life (Arbetslivsinstitutet), Stockholm, Sweden. Hard copies are available from the institute. Electronic copies can be obtained at <http://www.arbetslivsinstitutet.se/>.

JECFA (2001)

The second source document was the monograph prepared by JECFA, published in 2001 following the 55th meeting held in 2000. The first draft of this monograph was prepared by Dr J.B. Greig, Food Standards Agency, London, United Kingdom, and Dr J.A. Pennington, Division of Nutrition Research Coordination, National Institutes of Health, Bethesda, Maryland, USA. The monograph was published in *Safety evaluation of certain food additives and contaminants* (WHO Food Additive Series 46). An electronic copy can be obtained at <http://www.inchem.org/documents/jecfa/jecmono/v46je01.htm>.

The list of experts at the 55th JECFA meeting follows:

Members

Ms J. Baines, Australia New Zealand Food Authority, Australia
Professor J.R. Bend, University of Western Ontario, Canada
Dr J. Chen, Chinese Academy of Preventive Medicine, China
Dr S.M. Dagher, American University of Beirut, Lebanon
Dr C.E. Fisher, Hatfield, Hertfordshire, England
Dr D.G. Hattan, Food and Drug Administration, USA
(*Rapporteur*)
Dr Y. Kawamura, National Institute of Health Sciences, Japan
Dr A.G.A.C. Knaap, National Institute of Public Health and the Environment, The Netherlands
Dr P.M. Kuznesof, Food and Drug Administration, USA (*Vice-Chairman*)
Dr J.C. Larsen, Ministry of Food, Agriculture and Fisheries, Denmark
Mrs I. Meyland, Ministry of Food, Agriculture and Fisheries, Denmark (*Rapporteur*)
Dr G. Pascal, National Institute for Agricultural Research, France
Dr A. Pintér, Director, National Institute of Environmental Health, Hungary
Professor R. Walker, University of Surrey, England (*Chairman*)

Secretariat

Dr P.J. Abbott, Australia New Zealand Food Authority, Australia
(*WHO Temporary Adviser*)
Dr L.M. Barraj, Novigen Sciences Inc., USA (*WHO Temporary Adviser*)
Dr David C. Bellinger, Boston Children's Hospital
Neuroepidemiology Unit, USA (*WHO Temporary Adviser*)
Dr M. Bolger, Food and Drug Administration, USA (*WHO Temporary Adviser*)
Ms M.L. Costarrica, FAO, Italy (*FAO Joint Secretary*)
Dr M. DiNovi, Food and Drug Administration, USA (*WHO Temporary Adviser*)
Dr R.L. Ellis, FAO, Italy
Dr R. Goyer, Chapel Hill, NC, USA (*WHO Temporary Adviser*)
Dr J. Greig, Food Standards Agency, England (*WHO Temporary Adviser*)
Mr E.F.F. Hecker, Ministry of Agriculture, Nature Management and Fisheries, The Netherlands (*WHO Temporary Adviser*)
Dr J.L. Herrman, WHO, Switzerland (*WHO Joint Secretary*)
Dr J.H. Hotchkiss, Cornell University, USA (*FAO Consultant*)
Dr F. Kayama, Jichi Medical School, Japan (*WHO Temporary Adviser*)
Dr A. Mattia, Food and Drug Administration, USA (*WHO Temporary Adviser*)
Dr G. Moy, WHO, Switzerland
Dr I.C. Munro, CanTox Health Sciences International, Canada
(*WHO Temporary Adviser*)
Dr A. Nishikawa, National Institute of Health Sciences, Japan
(*WHO Temporary Adviser*)
Dr J.A. Pennington, National Institutes of Health, USA (*FAO Consultant*)
Dr M.V. Rao, Dubai Food and Environment Laboratory, United Arab Emirates (*FAO Consultant*)
Professor A.G. Renwick, University of Southampton, England
(*WHO Temporary Adviser*)
Dr S. Resnik, Department of Industry, Argentina (*FAO Consultant*)
Dr H. Sakurai, Japan Industrial Safety and Health Association, Japan (*WHO Temporary Adviser*)
Professor I.G. Sipes, University of Arizona, USA (*WHO Temporary Adviser*)
Dr G.J.A. Speijers, National Institute of Public Health and Environmental Protection, The Netherlands (*WHO Temporary Adviser*)
Ms E. Vavasour, Health Canada, Canada (*WHO Temporary Adviser*)
Dr P.J.P. Verger, National Institute for Agricultural Research, France (*FAO Consultant*)
Mrs H. Wallin, National Food Administration, Finland (*FAO Consultant*)
Dr D.B. Whitehouse, Bowdon, Cheshire, England (*FAO Consultant*)

ATSDR (2003)

The third source document was the draft *Toxicological profile for tin and compounds (update)*, prepared by ATSDR through a contract with the Syracuse Research Corporation. Copies of the profile can be obtained from the ATSDR web site (<http://www.atsdr.cdc.gov/toxprofiles/>) or from:

Division of Toxicology
Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
US Department of Health and Human Services
1600 Clifton Road NE, Mailstop E-29
Atlanta, Georgia 30333
USA

A peer review panel was assembled for tin and compounds. The panel consisted of the following members:

Michael Aschner, PhD, Wake Forest University School of Medicine, Winston-Salem, North Carolina
 Olen Brown, PhD, University of Missouri-Columbia, Columbia, Missouri
 Bruce Jarnot, PhD, DABT, American Petroleum Institute, Washington, DC

These experts collectively have knowledge of tin and its compounds' physical and chemical properties, toxicokinetics, key health end-points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the *Comprehensive Environmental Response, Compensation, and Liability Act*, as amended. Scientists from the ATSDR reviewed the peer reviewers' comments and determined which comments would be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record. The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

In December 2003, a comprehensive literature search was conducted by Toxicology Advice & Consulting Ltd in order to identify critical data published since publication of the source documents. Databases searched included:

- ChemIDplus (The ChemIDplus system searches and/or identifies literature from a wide range of online databases and databanks, including ATSDR, CANCERLIT, CCRIS, DART/ETIC, GENE-TOX, HSDB, IRIS, MEDLINE, TOXLINE Core, TOXLINE Special, and TSCA)
- INCHEM (The INCHEM database consolidates information from a number of intergovernmental organizations, including JECFA Evaluations and Monographs, JMPR, IARC, EHC documents, and SIDS)
- RTECS, EPA Toxicological Profiles

Critical papers on mammalian toxicity were purchased, assessed, and included in the CICAD, where appropriate, by Toxicology Advice & Consulting Ltd.

APPENDIX 3 — CICAD PEER REVIEW

The draft CICAD on tin and inorganic tin compounds was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

- L. Alessio, Institute of Occupational Health, University of Brescia, Brescia, Italy
- M. Baril, Institut de recherche Robert Sauvé en santé et en sécurité du travail, Montreal, Canada
- R. Benson, US Environmental Protection Agency, Denver, CO, USA
- M. Berlin, University of Lund, Lund, Sweden
- S. Blunden, Tin Information Ltd, Uxbridge, United Kingdom
- R. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA
- I. Desi, Department of Public Health, Budapest, Hungary
- J. Donohue, US Environmental Protection Agency, Washington, DC, USA
- L. Fishbein, Fairfax, VA, USA
- P. Grandjean, University of Southern Denmark, Odense, Denmark
- S. Hahn, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany
- R. Hertel, Bundesinstitut für Risikobewertung, Berlin, Germany
- G. Koennecker, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany
- National Institute for Occupational Safety and Health, Cincinnati, OH, USA
- K. Nimmo, Tin Technology Ltd, St Albans, Hertfordshire, United Kingdom
- M. Nordberg, Karolinska Institute, Stockholm, Sweden
- H. Savolainen, Ministry of Social Affairs and Health, Tampere, Finland
- J. Stauber, CSIRO Energy Technology, Menai, New South Wales, Australia
- M.H. Sweeney, Hanoi, Viet Nam
- S. Tao, US Food & Drug Administration, College Park, MD, USA
- J.-P. Taverne, Association of European Producers of Steel for Packaging, Brussels, Belgium (on behalf of the Tin Inter-industry Working Group)
- M. Vojtisek, National Institute of Public Health, Prague, Czech Republic
- K. Ziegler-Skylakakis, European Commission, Luxembourg

APPENDIX 4 — CICAD FINAL REVIEW BOARD

**Hanoi, Viet Nam
28 September – 1 October 2004**

Members

Mr D.T. Bai, Centre of Environmental Protection & Chemical Safety, Institute of Industrial Chemistry, Hanoi, Viet Nam

Dr R. Chhabra, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

Mr P. Copestake, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Dr C. De Rosa, Agency for Toxic Substances and Disease Registry, Centres for Disease Control and Prevention, Atlanta, GA, USA

Dr S. Dobson, Centre for Ecology & Hydrology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr G. Dura, National Institute of Environmental Health of József Fodor Public Health Centre, Budapest, Hungary

Ms C.W. Fang, National Institute of Occupational Safety and Health Malaysia, Selangor, Malaysia

Dr L. Fishbein, Fairfax, VA, USA

Dr L. Fruchtingarten, Poison Control Center of Sao Paulo, Sao Paulo, Brazil

Dr C.L. Geraci, Document Development Branch, Centers for Disease Control and Prevention / National Institute for Occupational Safety and Health, Cincinnati, OH, USA

Dr H. Gibb, Sciences International, Alexandria, VA, USA

Dr R.F. Hertel, Federal Institute for Risk Assessment, Berlin, Germany

Mr P. Howe, Centre for Ecology & Hydrology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr S. Ishimitsu, Division of Safety Information on Drug, Food and Chemicals, National Institute of Health Sciences, Tokyo, Japan

Dr J. Kielhorn, Fraunhofer Institute for Toxicology and Experimental Medicine, Hanover, Germany

Dr S. Kunarattanapruke, Food & Drug Administration, Ministry of Public Health, Nonthaburi, Thailand

Dr Y. Liang, Department of Occupational Health, Fudan University School of Public Health, Shanghai, China

Ms B. Meek, Existing Substances Division, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Mr F.K. Muchiri, Directorate of Occupational Health and Safety Services, Nairobi, Kenya

Dr O. Sabzevari, Food and Drug Control Labs, Ministry of Health & Medical Education, Tehran, Islamic Republic of Iran

Dr J. Stauber, CSIRO Energy Technology, Menai, New South Wales, Australia

Dr M.H. Sweeney, US Embassy, Hanoi, Viet Nam

Mr P. Watts, Toxicology Advice & Consulting Ltd, Surrey, United Kingdom

Ms D. Willcocks, National Industrial Chemicals Notification and Assessment Scheme, Sydney, New South Wales, Australia

Dr K. Ziegler-Skylakakis, European Commission, Luxembourg

Secretariat

Dr A. Aitio, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

TIN (II) CHLORIDE DIHYDRATE**0738**
April 2004CAS No: 10025-69-1
RTECS No: XP8850000
UN No: 3260Stannous chloride dihydrate
SnCl₂ · 2H₂O
Molecular mass: 225.6

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			
EXPOSURE			
Inhalation	Cough. Sore throat.	Local exhaust or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin		Protective gloves.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Redness. Pain.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Diarrhoea. Nausea. Vomiting.	Do not eat, drink, or smoke during work.	Give plenty of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL

Sweep spilled substance into sealable containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place. Do NOT let this chemical enter the environment. Personal protection: P2 filter respirator for harmful particles.

PACKAGING & LABELLINGUN Hazard Class: 8
UN Pack Group: III**EMERGENCY RESPONSE**

Transport Emergency Card: TEC (R)-80GC2-II+III

STORAGE

Separated from strong oxidants. Keep in a well-ventilated room.

IMPORTANT DATA

Physical State; Appearance

COLOURLESS TO WHITE SOLID IN VARIOUS FORMS

Chemical dangers

Upon heating, toxic fumes are formed. The substance is a strong reducing agent and reacts violently with oxidants.

Occupational exposure limitsTLV: (as Sn, oxide and inorganic compounds, except tin hydride) 2 mg/m³ as TWA; (ACGIH 2004).
EU OEL: (tin inorganic compounds, as Sn) 2 mg/m³ as TWA; (EU 2004).**Routes of exposure**

The substance can be absorbed into the body by inhalation of its aerosol and by ingestion.

Inhalation risk

A harmful concentration of airborne particles can be reached quickly when dispersed.

Effects of short-term exposure

The substance is irritating to the eyes and the respiratory tract.

PHYSICAL PROPERTIES

Decomposes below boiling point at 652/C
Melting point: 38/CDensity: 2.71 g/cm³
Solubility in water: very good (>100 g/100 ml at 20/C)

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

NOTES

The apparent melting point caused by loss of crystal water is given.
Stannochlor is a trade name.

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible

TIN (II) FLUORIDE**0860**
April 2004CAS No: 7783-47-3
RTECS No: XQ3450000
UN No: 3288Stannous fluoride
Tin bifluoride
Tin difluoride
SnF₂
Molecular mass: 156.7

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings: all extinguishing agents allowed.
EXPLOSION			

EXPOSURE			
Inhalation	Cough. Sore throat.	Local exhaust or breathing protection.	Fresh air, rest.
Skin		Protective gloves.	Rinse skin with plenty of water or shower.
Eyes	Redness. Pain.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Burning sensation. Shock or collapse.	Do not eat, drink, or smoke during work.	Give plenty of water to drink. Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into covered containers. Personal protection: P2 filter respirator for harmful particles.	UN Hazard Class: 6.1 UN Pack Group: III Do not transport with food and feedstuffs.

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-61GT5-III	Separated from acids, chlorine and food and feedstuffs.

IMPORTANT DATA

Physical State; Appearance

WHITE CRYSTALLINE POWDER.

Chemical dangers

Reacts with acids to produce hydrogen fluoride. Reacts violently with chlorine causing fire hazard.

Occupational exposure limits

TLV: (as Sn, oxide and inorganic compounds, except tin hydride) 2 mg/m³ as TWA; (ACGIH 2004).

TLV: as F 2.5 mg/m³ as TWA; A4; (ACGIH 2004).

EU OEL: Tin inorganic compounds, as Sn 2 mg/m³ as TWA (EU 2004).

Routes of exposure

The substance can be absorbed into the body by inhalation of its aerosol and by ingestion.

Inhalation risk

A harmful concentration of airborne particles can be reached quickly when dispersed, especially if powdered.

Effects of short-term exposure

Corrosive on ingestion. The substance is irritating to the eyes.

Effects of long-term or repeated exposure

The substance may have effects on the teeth and bones (fluorosis).

PHYSICAL PROPERTIES

Boiling point: 850/C
Melting point: 213/C

Density: 4.57 g/cm³
Solubility in water, g/100 ml at 20/C: 30

ENVIRONMENTAL DATA

NOTES

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible

TIN(IV) CHLORIDE (ANHYDROUS)**0953**

October 2004

CAS No: 7646-78-8
 RTECS No: XP8750000
 UN No: 1827
 EC No: 050-001-00-5

Tin tetrachloride
 Stannic chloride
 SnCl₄
 Molecular mass: 260.5

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		NO hydrous agents. In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			

EXPOSURE		STRICT HYGIENE!	IN ALL CASES CONSULT A DOCTOR!
Inhalation	Cough. Sore throat. Burning sensation. Laboured breathing. Shortness of breath. Wheezing.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Half-upright position. Artificial respiration may be needed. Refer for medical attention.
Skin	Redness. Pain. Skin burns.	Protective gloves. Protective clothing.	Rinse skin with plenty of water or shower. Refer for medical attention.
Eyes	Redness. Pain. Severe deep burns.	Safety goggles, face shield, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Burning sensation. Shock or collapse.	Do not eat, drink, or smoke during work.	Do NOT induce vomiting. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Evacuate danger area! Ventilation. Cautiously neutralize spilled liquid with soda ash or lime then remove to safe place. Do NOT let this chemical enter the environment. Chemical protection suit including self-contained breathing apparatus.	<p>C Symbol R: 34-52/53 S: (1/2-)7/8-26-45-61 UN Hazard Class: 8 UN Pack Group: II</p> <p>Airtight. Unbreakable packaging; put breakable packaging into closed unbreakable container. Do not transport with food and feedstuffs.</p>

EMERGENCY RESPONSE	SAFE STORAGE
Transport Emergency Card: TEC (R)-80GCI-II-X NFPA Code: H3; F0; R1	Separated from food and feedstuffs. Dry. Well closed. Keep in a well-ventilated room.

IMPORTANT DATA

Physical State; Appearance

COLOURLESS OR SLIGHTLY YELLOW FUMING LIQUID, WITH PUNGENT ODOUR.

Physical dangers

The vapour is heavier than air.

Chemical dangers

Reacts violently with water or moist air to produce corrosive hydrogen chloride (see ICSC0163). Reacts with turpentine, alcohols and amines, causing fire and explosion hazard. Attacks many metal, some forms of plastic, rubber and coatings.

Occupational exposure limits

TLV: (as Sn, oxide and inorganic compounds, except tin hydride) 2 mg/m³ as TWA; (ACGIH 2004).

EU OEL: (Tin inorganic compounds, as Sn) 2 mg/m³ as TWA; (EU 2004).

Inhalation risk

A harmful contamination of the air can be reached very quickly on evaporation of this substance at 20/C.

Effects of short-term exposure

The substance is corrosive to the eyes, the skin and the respiratory tract. Corrosive on ingestion.

PHYSICAL PROPERTIES

Boiling point: 114/C

Melting point: -33/C

Relative density (water = 1): 2.26

Solubility in water: reaction

Vapour pressure, kPa at 20/C: 2.4

Relative vapour density (air = 1): 9.0

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

NOTES

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible

TIN(IV) OXIDE**0954**

October 2004

CAS No: 18282-10-5
RTECS No: XQ4000000Stannic oxide
Stannic anhydride
Tin dioxide
SnO₂
Molecular mass: 150.7

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible.		In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			

EXPOSURE		PREVENT DISPERSION OF DUST!	
Inhalation	Cough.	Local exhaust or breathing protection.	Fresh air, rest.
Skin		Protective gloves.	Rinse skin with plenty of water or shower.
Eyes		Safety goggles.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	Rinse mouth.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Personal protection: P2 filter respirator for harmful particles.	

EMERGENCY RESPONSE	SAFE STORAGE
	Separated from strong reducing agents.

IMPORTANT DATA

Physical State; Appearance

WHITE OR SLIGHTLY GREY POWDER

Chemical dangers

Reacts violently with strong reducing agents.

Occupational exposure limitsTLV: (as Sn, oxide and inorganic compounds, except tin hydride) 2 mg/m³ as TWA; (ACGIH 2004).EU OEL: (Tin inorganic compounds, as Sn) 2 mg/m³ as TWA; (EU 2004).**Inhalation risk**

A harmful concentration of airborne particles can be reached quickly when dispersed, especially if powdered.

Effects of short-term exposure

May cause mechanical irritation to the respiratory tract.

Effects of long-term or repeated exposure

Lungs may be affected by repeated or prolonged exposure to dust particles, resulting in a benign pneumoconiosis (stannosis).

PHYSICAL PROPERTIES

Sublimation point: 1800-1900/C

Melting point: 1630/C

Density: 6.95 g/cm³

Solubility in water: none

ENVIRONMENTAL DATA

Bioaccumulation of this chemical may occur in crustacea.

NOTES

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible

TIN (II) CHLORIDE (ANHYDROUS)**0955**
April 2004CAS No: 7772-99-8
RTECS No: XP8700000
UN No: 3260Tin dichloride
Tin protochloride
Stannous chloride
SnCl₂
Molecular mass: 189.6

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			In case of fire: keep drums, etc., cool by spraying with water.

EXPOSURE			
Inhalation	Cough. Sore throat.	Local exhaust or breathing protection.	Fresh air, rest.
Skin		Protective gloves.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Redness. Pain.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain. Diarrhoea. Nausea. Vomiting.	Do not eat, drink, or smoke during work.	Give plenty of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into covered containers. Carefully collect remainder. then remove to safe place. Do NOT let this chemical enter the environment. Personal protection: P2 filter respirator for harmful particles.	UN Hazard Class: 8 UN Pack Group: III Do not transport with food and feedstuffs.

EMERGENCY RESPONSE	STORAGE
Transport Emergency Card: TEC (R)-80GC2-II+III	Separated from incompatible materials, food and feedstuffs. Dry.

IMPORTANT DATA

Physical State; Appearance

COLOURLESS OR WHITE CRYSTALS

Chemical dangers

The substance decomposes on heating producing toxic and corrosive gases. The substance is a strong reducing agent and reacts with oxidants such as nitrates and peroxides, and bases.

Occupational exposure limits

TLV: (as Sn, Oxide and inorganic compounds, except tin hydride) 2 mg/m³ as TWA; (ACGIH 2004).
EU OEL: (tin inorganic compounds, as Sn) 2 mg/m³ as TWA; (EU 2004).

Routes of exposure

The substance can be absorbed into the body by inhalation of its aerosol and by ingestion.

Inhalation risk

A harmful concentration of airborne particles can be reached quickly when dispersed.

Effects of short-term exposure

The substance is irritating to the eyes and the respiratory tract.

PHYSICAL PROPERTIES

Boiling point (decomposes): 652/C
Melting point: 246.8/C

Density: 3.95 g/cm³
Solubility in water, g/100 ml at 20/C: 90

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

NOTES

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible

TIN(II) OXIDE**0956**

October 2004

CAS No: 21651-19-4
RTECS No: XQ3700000Tin monoxide
Stannous oxide
SnO
Molecular mass: 134.7

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Not combustible.		In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			

EXPOSURE		PREVENT DISPERSION OF DUST!	
Inhalation	Cough.	Local exhaust or breathing protection.	Fresh air, rest.
Skin		Protective gloves.	Rinse skin with plenty of water or shower.
Eyes		Safety goggles, or eye protection in combination with breathing protection if powder.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion		Do not eat, drink, or smoke during work.	Rinse mouth.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place. Personal protection: P2 filter respirator for harmful particles.	

EMERGENCY RESPONSE	SAFE STORAGE

IMPORTANT DATA

Physical State; Appearance

BLUE TO BLACK CRYSTALLINE POWDER

Chemical dangers

On heating at 300°C in air, oxidation to stannic oxide proceeds incandescently.

Occupational exposure limitsTLV: (as Sn, Oxide and inorganic compounds, except tin hydride) 2 mg/m³ as TWA; (ACGIH 2004).EU OEL: (Tin inorganic compounds, as Sn) 2 mg/m³ as TWA; (EU 2004).**Inhalation risk**

A harmful concentration of airborne particles can be reached quickly when dispersed, especially if powdered.

Effects of short-term exposure

May cause mechanical irritation to the respiratory tract.

Effects of long-term or repeated exposure

Lungs may be affected by repeated or prolonged exposure to dust particles, resulting in a benign pneumoconiosis (stannosis).

PHYSICAL PROPERTIES

Density: 6.45 g/cm³

Solubility in water: none

ENVIRONMENTAL DATA

Bioaccumulation of this chemical may occur in crustacea and in fish.

NOTES

ADDITIONAL INFORMATION

LEGAL NOTICE

Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible

RÉSUMÉ D'ORIENTATION

Ce CICAD¹ concernant l'étain et les composés inorganiques de l'étain a été préparé conjointement par Toxicology Advice & Consulting Ltd et le Centre for Ecology & Hydrology. Ce CICAD s'appuie sur trois documents bibliographiques. Le premier de ces documents source a été rédigé par le Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals ainsi que le Dutch Expert Committee on Occupational Standards et a tenu compte des publications identifiées jusqu'en mars 2002 (Westrum & Thomassen, 2002). Le deuxième de ces documents source est la monographie rédigée à l'occasion de la cinquante-cinquième réunion du Comité mixte FAO/OMS d'experts des Additifs alimentaires, publié en 2001 (JECFA, 2001). Le troisième document source est le projet remis à jour en 2003 de *Toxicological profile for tin and compounds*, élaboré par la Agency for Toxic Substances and Disease Registry des Etats-Unis d'Amérique (ATSDR, 2003). En décembre 2003, Toxicology Advice & Consulting Ltd et le Centre for Ecology & Hydrology ont procédé à une recherche bibliographique approfondie des bases de données en ligne pour identifier les dernières références bibliographiques. Des précisions sur l'examen par des pairs et l'existence de documents source figurent à l'Appendice 2. Concernant le présent CICAD, l'information sur l'examen par des pairs est fournie à l'Appendice 3. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Hanoï (Viet Nam) du 28 septembre au 1^{er} octobre 2004. La liste des participants à cette réunion figure à l'Appendice 4. La fiche d'information internationale sur la sécurité chimique (ICSC) établie pour le chlorure d'étain (II), le chlorure d'étain (II) à deux molécules d'eau, le fluorure d'étain (II), l'oxyde d'étain (II), le chlorure d'étain (IV) et l'oxyde d'étain (IV) par le Programme international sur la sécurité chimique (IPCS, 2004a-f) est également reproduite dans ce document.

L'étain est un métal gris-blanc. Les composés inorganiques de l'étain les plus importants sont notamment les chlorures d'étain (II) et (IV), l'oxyde d'étain (II) et le fluorure d'étain (II), ainsi que les stannates de potassium et de sodium. Les oxydes d'étain 2+ et 4+, connus également sous le nom d'étain (II) et étain (IV), sont tous deux relativement stables.

La production annuelle mondiale d'étain est en lente augmentation depuis quelques années et a atteint 268 000 tonnes en 2003. Environ 10-15 % de ce tonnage

représentent le métal extrait par récupération. Les pays producteurs d'étain les plus importants sont la Chine, l'Indonésie, le Pérou, la Bolivie, le Brésil et l'Australie; des quantités importantes sont également produites par la Malaisie et la Thaïlande. L'utilisation principale de l'étain, soit environ 34 % de la production mondiale annuelle, est la fabrication d'alliages utilisés pour la soudure avec des applications industrielles électriques/électroniques et générales. L'étain est également très utilisé (25-30 % de la production) comme revêtement protecteur d'autres métaux, en particulier dans les récipients alimentaires. Le chlorure d'étain (II) est le composé inorganique le plus important commercialement et est surtout utilisé comme agent réducteur en synthèse organique et inorganique ainsi que dans la fabrication des vernis, des verres et des pigments métallisés. Le chlorure d'étain (IV) est utilisé en synthèse organique dans les matières plastiques, comme intermédiaire dans la fabrication des organostanniques et pour la production de films d'oxyde d'étain (IV) sur le verre. Le fluorure d'étain (II) est largement utilisé en dentisterie préventive.

L'étain peut être libéré dans l'atmosphère à partir de sources naturelles ou anthropiques. On le trouve dans de nombreux sols et il peut se retrouver dans les poussières soulevées par le vent, la circulation routière et les activités agricoles. Il existe d'autres sources naturelles moins importantes, notamment les feux de forêt et les émissions volcaniques. Des gaz, des poussières et des fumées contenant de l'étain peuvent être émis pendant les processus de soudage et de raffinage, les usages industriels de l'étain, l'incinération des déchets et la combustion des combustibles fossiles. La tension de vapeur de l'étain élémentaire est négligeable; l'étain et les composés inorganiques de l'étain ne sont pas volatils dans les conditions environnementales. Le chlorure d'étain (II) est soluble dans l'eau, les autres composés stanniques n'étant que peu solubles. Les composés de l'étain sont susceptibles de se répartir dans les sols et les sédiments. L'étain inorganique peut subir une oxydo-réduction, un échange de ligand et des réactions de précipitation dans l'environnement. La biométhylation de l'étain inorganique a été mise en évidence dans des cultures bactériennes pures, dans des sédiments et des végétaux en décomposition. Les composés inorganiques de l'étain pourraient être bioconcentrés par les organismes vivants, mais les données sont limitées.

La concentration moyenne en étain dans l'air est généralement inférieure à 0,1 µg/m³ (jusqu'à 0,8 µg/m³), la concentration maximale s'observant à proximité de certains établissements industriels. En général, l'étain est présent à l'état de traces dans les eaux naturelles. Les concentrations plus élevées en étain inorganique sont liées à la présence de décharges industrielles et à l'utilisation du tributylétain. Au cours d'une campagne

¹ Voir liste des abréviations et des acronymes utilisés dans le rapport à l'Appendice 1.

de prélèvements dans des lacs et des rivières, près de 80 % des échantillons contenaient des concentrations d'étain inorganique inférieures à 1 µg/litre. Des concentrations atteignant 37 µg/litre ont été signalées près de sources de pollution. Dans les eaux côtières, on a signalé des concentrations en étain inorganique de 0,001 à 0,01 µg/litre, avec une concentration allant jusqu'à 8 µg/litre près des sources de pollution. La concentration en étain inorganique dans les sédiments allait jusqu'à 8 mg/kg de poids sec dans les zones côtières et jusqu'à 15,5 mg/kg dans les rivières et les lacs. La concentration en étain dans la croûte terrestre est d'environ 2-3 mg/kg. Dans le sol, la concentration totale en étain se situe entre des valeurs <1 et 200 mg/kg; des chiffres de 1000 mg/kg peuvent cependant être observés dans les gisements à haute teneur en étain. Dans certains gisements de minerai, elle peut s'élever jusqu'à 50 000 mg/kg.

Pour la population générale, c'est l'alimentation qui est la principale source d'exposition à l'étain inorganique. Le JECFA a conclu récemment que l'apport moyen en étain dans sept pays était de moins de 1 à 15 mg/jour par personne, mais que l'apport maximum journalier pouvait atteindre 50-60 mg chez certaines personnes qui consomment régulièrement des fruits, des légumes et des jus de fruits en boîte métallique non vernie. L'eau de boisson n'est pas une source importante d'étain inorganique et l'apport pourrait se situer au voisinage de 0,012-0,02 mg/jour. De même, la concentration en étain inorganique dans l'air étant faible, la quantité inhalée est très faible, probablement inférieure à 0,01-0,02 mg/jour environ.

Chez l'homme et les mammifères de laboratoire, l'absorption digestive de l'étain inorganique est faible (en général inférieure à 5 %) mais dépend de la dose, de la nature de l'anion lié à l'étain (solubilité du composé) et de la présence d'autres substances. L'essentiel de l'étain ingéré et non absorbé est essentiellement (95-99 %) excrété dans les fèces dans les 48 heures. La fraction absorbée est répartie entre les os, les poumons, le foie et les reins. D'après un certain nombre d'arguments, l'étain inorganique ne traverse pas facilement la barrière hémato-encéphalique. L'étain absorbé est surtout excrété dans l'urine, et en partie dans la bile. Chez la souris, la demi-vie biologique de l'étain inorganique absorbé est d'environ 30 jours.

Une irritation oculaire et nasale passagère a été observée chez le cobaye exposé au chlorure d'étain (IV) par inhalation. L'étain métal ne provoque probablement pas d'irritation cutanée, tandis que le chlorure d'étain (II) et le chlorure d'étain (IV) sont des irritants cutanés. Dans certaines études, l'inclusion de chlorure d'étain (II) dans l'alimentation pendant 4-13 semaines a provoqué des lésions des tissus digestifs indiquant une irritation locale. Les publications anciennes contiennent des observations

faisant état d'effets gastro-intestinaux (nausées, crampes abdominales, vomissements et diarrhée) chez l'homme après consommation de fruits ou de jus de fruit en boîte de métal non vernie. Les effets semblent résulter d'une irritation gastrique locale due à l'étain en solution. Cette question est traitée plus loin. Un petit nombre de personnes ont eu des réactions cutanées indiquant une réponse allergique locale avec un test cutané de provocation à l'étain et au chlorure d'étain (II), mais, bien que très répandu, l'étain ne semble pas être un allergène cutané important.

On trouve décrit dans la littérature ancienne un certain nombre de cas d'exposition professionnelle à des poussières et à des fumées contenant de l'oxyde d'étain (IV) insoluble ayant entraîné une pneumoconiose bénigne (stannose). L'affection est caractérisée par des opacités micronodulaires des poumons, provoquée apparemment par les dépôts d'oxyde d'étain (IV). La stannose n'est associée ni à une fibrose, ni à la diminution de la fonction pulmonaire.

Chez les animaux de laboratoire, l'ingestion répétée de chlorure d'étain (II) a montré des effets indésirables sur le bilan organique du cuivre, du fer, du zinc et du calcium. Une diminution de la teneur des os en calcium induite par les sels d'étain a entraîné une plus faible résistance des os. On a observé une diminution de la concentration de l'hémoglobine et un effet sur les hématies, entraînant une anémie. Certaines études comportant l'administration per os répétée de chlorure d'étain (II) ont signalé un effet sur les tissus du foie, des reins, des testicules, du pancréas et du cerveau. Dans l'étude la plus complète parmi les études connues d'administration per os sur la vie entière, aucune modification microscopique n'a été observée dans une grande variété de tissus chez le rat et la souris ayant reçu des doses d'étain sous forme de chlorure d'étain (II) dans l'alimentation allant jusqu'à près de 60 mg/kg de poids corporel par jour (rat) et 180-270 mg/kg de poids corporel par jour (souris). Dans cette étude, les NOAEL (dose sans effet nocif observé) étaient de 30 mg/kg de poids corporel par jour pour le rat et de 130 mg/kg de poids corporel par jour pour la souris, avec une diminution de la survie aux doses les plus élevées.

Aucune activité cancérogène du chlorure d'étain (II) n'est apparue clairement lorsqu'il est administré dans l'alimentation à des rats et des souris pendant 2 ans. Des essais biologiques plus limités sur l'étain métal, le chlorure d'étain (II) et un petit nombre d'autres composés stanniques n'ont eux non plus pas montré d'activité cancérogène. Dans des essais à court terme sur la génotoxicité, le chlorure d'étain (II) n'a pas induit de mutations dans les tests de Ames sur les bactéries, ni de mutations ou de conversions géniques chez les levures, ni de lésions de l'ADN dans les cultures cellulaires

d'hépatocytes de rats, ni de mutations chez les cellules de lymphome murin cultivées *in vitro*, ni de lésions chromosomiques (micronoyaux) *in vivo* dans la moelle osseuse de souris traitées par injection intrapéritonéale. Dans les « rec-assays » sur les bactéries (dans lesquelles l'activité est un indicateur indirect des lésions de l'ADN), le chlorure d'étain (II) était actif chez *Escherichia coli*, mais (comme un certain nombre d'autres sels d'étain) inactif sur *Bacillus subtilis*. En culture, le chlorure d'étain (II) a provoqué des lésions chromosomiques et des échanges entre chromatides soeurs dans les cellules ovariennes de hamster ainsi que des lésions de l'ADN de lymphocytes humains, de cellules ovariennes de hamster et de plasmides. Le chlorure d'étain (IV) testé *in vitro* n'a pas provoqué de lésion de l'ADN dans les cellules ovariennes de hamster mais des aberrations chromosomiques et la formation de micronoyaux ainsi que des échanges de chromatides soeurs dans les lymphocytes humains. Le fluorure d'étain (II) a provoqué des lésions de l'ADN dans des cultures de lymphocytes humains, mais n'a pas induit chez la souris la formation de micronoyaux dans la moelle osseuse après injection intrapéritonéale; les tests de Ames réalisés avec ces composés n'ont pas donné de signe convaincant de leur activité. D'après certaines observations, les lésions de l'ADN induites par l'étain pourraient résulter de la formation de radicaux libres. Le mécanisme à l'origine des lésions chromosomiques provoquées par l'étain dans les cellules de mammifères en culture n'est pas clair, même si l'on sait que certains composés inorganiques peuvent donner des résultats positifs dans ces essais par suite d'une modification des ions, ou du pH du milieu.

On n'a pu identifier que des données limitées concernant l'effet toxique potentiel des composés inorganiques de l'étain sur la reproduction et le développement. Aucun effet indésirable n'a été observé chez le rat lorsque l'étain (sous une forme non caractérisée, obtenue en mélangeant du chlorure d'étain (II) en solution aqueuse et de la caséine avant l'introduction dans l'alimentation) a été donné dans l'alimentation pendant trois générations ou lorsque du fluorure d'étain (II), du pentachlorostannite de sodium ou du pentafluorostannite de sodium ont été administrés dans l'alimentation tout au long de la gestation. De même, le traitement répété par gavage de femelles gestantes, rats, souris et hamsters, par le chlorure d'étain (II) n'a pas eu d'effet indésirable sur les foetus.

Les données disponibles sur les troubles chez l'homme de l'absorption du zinc dus à l'étain ingéré sont limitées. Dans une étude chez des volontaires, l'apparition du zinc dans le plasma 1 à 4 heures après l'administration d'une dose de zinc n'a pas été modifiée par l'ingestion concomitante d'étain jusqu'à la dose de 100 mg (sous forme de chlorure d'étain (II)). Une autre

étude a signalé qu'une dose unique de 36 mg d'étain (également sous forme de chlorure d'étain (II)), administrée avec du zinc, a entraîné une plus faible rétention du zinc. Une perturbation modérée de l'excrétion du zinc a été notée dans une troisième étude au cours de laquelle l'alimentation normale était supplémentée par une dose de 50 mg d'étain/jour (sous forme de chlorure d'étain (II) dans le jus de fruit). S'il n'a pas été nettement fixé de dose sans effet sur l'inhibition de l'absorption du zinc, la dose minimale signalée comme ayant cet effet (36 mg) est environ 2,5 à >36 fois plus élevée que l'apport moyen estimé pour la population comme l'a indiqué le JECFA. Toutefois, les personnes qui consomment habituellement des fruits, des légumes et des jus de fruits en boîte métallique non laquée peuvent avoir un apport en étain (50-60 mg) comparable aux doses aiguës (36 mg) ou répétées (50 mg) qui dans certaines études modifient l'absorption du zinc ou son bilan. La présence ou non d'un effet clinique pourrait dépendre fortement de l'apport alimentaire en zinc.

Les doses d'étain en cause dans les anciennes observations de troubles gastro-intestinaux après consommation de fruits ou de jus de fruits en boîte ont été estimées (30-200 mg), mais ces chiffres ne peuvent pas être considérés comme parfaitement fiables. Deux études récentes sur des volontaires donnent une meilleure idée des doses efficaces et, ce qui est peut-être plus important, des concentrations. La première étude comportait l'ingestion de jus de tomate dans lequel du chlorure d'étain (II) avait été ajouté pour obtenir une concentration en étain de 161, 264 et 529 mg/kg (doses d'étain de 40, 66 et 132 mg respectivement). A la dose de 161 mg/kg, l'un des volontaires (sur 18) a signalé des symptômes gastro-intestinaux bénins; des symptômes aigus typiques ont été observés aux doses de 264 et 529 mg/kg. La quantité d'étain présent dans le sérum n'a pas augmenté entre 0,5 et 4 heures après l'administration, quelle que soit la dose, confortant l'hypothèse que les effets aigus après ingestion d'étain dépendent de la concentration (entraînant une irritation gastrique locale) plutôt que d'un effet généralisé dû à l'étain absorbé. Une deuxième étude comportait l'ingestion de soupe à la tomate contenant de l'étain provenant d'une boîte de conserve non vernie. Les concentrations étudiées en étain étaient <0,5, 201 et 267 mg/kg, correspondant à des doses aiguës d'étain allant jusqu'à 67 mg. Rien n'indiquait d'effet aigu dans cette étude. La dose faible effet ou la dose sans effet d'environ 67 mg d'étain dans ces études est de 4,5 à >67 fois plus grande que les estimations du JECFA pour l'apport moyen journalier estimé pour la population et est comparable à l'apport journalier estimé (50-60 mg) chez les personnes qui consomment habituellement des fruits, des légumes et des jus de fruits conservés dans des boîtes métalliques non vernies.

Dans les conditions de spéciation qui sont celles de l'environnement, les composés inorganiques de l'étain ont une faible toxicité pour les organismes aquatiques et terrestres, en raison principalement de leur faible solubilité, de leur mauvaise absorption, du faible taux d'accumulation dans les tissus et de leur excrétion rapide. La plupart des analyses de laboratoire avec les organismes aquatiques ont porté sur le chlorure d'étain (II) qui est soluble. Les microalgues les plus sensibles sont les diatomées marines *Skeletonema costatum* et *Thalassiosira guillardii*, avec une CE_{50} (72 heures) pour les cations liés à l'étain (II) sur la croissance d'environ 0,2 mg/litre. La CL/CE_{50} de l'étain (II) pour les invertébrés aquatiques est de 3,6 à 140 mg/litre avec une CE_{50} (21 jours) sur la reproduction des daphnies de 1,5 mg d'étain (II) par litre. Les tests de toxicité chez les poissons montrent clairement que le chlorure d'étain (IV) est moins toxique que le chlorure d'étain (II), lequel est plus soluble. La CL_{50S} (96 heures) chez les poissons va de 35 mg d'étain (II) par litre à plus de 1000 mg d'étain (IV) par litre. Les résultats des tests chez les larves et les embryons (CL_{50} 7 à 28 jours) pour les poissons et les amphibiens sont de 0,1 à 2,1 mg/litre pour l'étain (II).

Les concentrations qui se révèlent toxiques pour les organismes sont en général plusieurs fois supérieures à celles qui s'observent dans l'environnement. Les tests les plus sensibles étaient l'exposition des diatomées pendant 72 heures et les études sur les larves et les embryons d'amphibiens, avec l'observation d'un effet toxique à 0,1-0,2 mg d'étain (II) par litre. Même à de telles concentrations, les effets toxiques provoqués par l'étain inorganique sont improbables, y compris à proximité des sources de pollution locales. On remarquera que lorsque les concentrations sont exprimées en étain total, une fraction de celui-ci a des chances de se trouver sous forme d'étain organique (tributylétain par exemple), dont la toxicité et la biodisponibilité sont plus grandes. Pour plus d'informations sur le devenir et la toxicité du tributylétain dans l'environnement, on se reportera aux publications de l'IPCS (1990, 1999).

RESUMEN DE ORIENTACIÓN

Este CICAD¹ sobre el estaño y sus compuestos inorgánicos fue preparado por Toxicology Advice & Consulting Ltd y el Centro de Ecología e Hidrología. Este CICAD se basó en tres documentos originales. El primero de dichos documentos, preparado por el Grupo Nórdico de Expertos para la documentación de criterios sobre los riesgos de los productos químicos para la salud y el Comité de Expertos Neerlandeses en Normas del Trabajo, comprendía la bibliografía identificada hasta marzo de 2002 (Westrum & Thomassen, 2002). El segundo documento original era la monografía preparada por la 55ª reunión del Comité Mixto FAO/OMS de Expertos en Aditivos Alimentarios, publicada en 2001 (JECFA, 2001). El tercer documento original era el proyecto de *Perfil toxicológico del estaño y sus compuestos*, actualizado en 2003, preparado por la Agencia para el Registro de Sustancias Tóxicas y Enfermedades de los Estados Unidos (ATSDR, 2003). En diciembre de 2003, Toxicology Advice & Consulting Ltd y el Centro de Ecología e Hidrología llevaron a cabo una búsqueda bibliográfica amplia de las bases de datos en línea para localizar las referencias más recientes. La información sobre el carácter del examen colegiado y la disponibilidad de los documentos originales se presenta en el apéndice 2. La información sobre el examen colegiado de este CICAD figura en el apéndice 3. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Hanoi (Viet Nam) del 28 de septiembre al 1º de octubre de 2004. La lista de participantes en esta reunión figura en el apéndice 4. También se reproducen en este documento las Fichas internacionales de seguridad química para el cloruro de estaño (II), el cloruro de estaño (II) dihidrato, el fluoruro de estaño (II), el óxido de estaño (II), el cloruro de estaño (IV) y el óxido de estaño (IV), preparadas por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 2004a-f).

El estaño es un metal blanco grisáceo. Los compuestos de estaño inorgánico más importantes son los cloruros de estaño (II) y (IV), el óxido de estaño (II), el fluoruro de estaño (II) y los estannatos de potasio y de sodio. Los estados de oxidación del estaño 2+ y 4+, conocidos también como estaño (II) y estaño (IV), son bastante estables.

La producción mundial anual de estaño ha ido creciendo lentamente en los últimos años, alcanzando un volumen de unas 268 000 toneladas en 2003. Alrededor del 10-15% de esta cifra es metal recuperado. Los principales países productores son China, Indonesia, Perú, Bolivia, Brasil y Australia y también se producen

¹ La lista de las abreviaturas y siglas utilizadas en este informe figura en el apéndice 1.

cantidades importantes en Malasia y Tailandia. La principal aplicación del estaño, que absorbe alrededor del 34% de la producción mundial anual, son las aleaciones para soldadura eléctrica/electrónica y las aplicaciones industriales en general. El estaño también se utiliza mucho (alrededor del 25-30% de la producción) como revestimiento protector de otros metales, en particular para recipientes de alimentos. El cloruro de estaño (II) es el compuesto inorgánico más importante desde el punto de vista comercial y se usa sobre todo como agente reductor en síntesis orgánicas e inorgánicas y en la manufactura de vidrio metalizado, vidrio y pigmentos. El cloruro de estaño (IV) se utiliza en procesos de síntesis orgánica, en plásticos, como intermediario en la fabricación de compuestos de estaño orgánico y en la producción de películas de óxido de estaño (IV) sobre vidrio. El fluoruro de estaño (II) se utiliza ampliamente en la odontología preventiva.

El estaño se puede liberar en la atmósfera a partir de fuentes naturales y antropogénicas. Es un componente de muchos suelos y se puede liberar en el polvo de los vendavales, los caminos y las actividades agrícolas. Otras fuentes naturales menos significativas son los incendios forestales y las emisiones volcánicas. Puede haber emisiones de gases, polvo y humo que contienen estaño procedentes de procesos de fusión y refinado, de usos industriales del estaño, de la incineración de desechos y de la quema de combustibles fósiles. La presión de vapor del estaño elemental es insignificante; el estaño y sus compuestos inorgánicos no son volátiles en las condiciones del medio ambiente. El cloruro de estaño (II) es soluble en agua, mientras que otros compuestos suelen ser sólo ligeramente solubles. Los compuestos de estaño probablemente se reparten entre el suelo y los sedimentos. El estaño inorgánico puede sufrir procesos de oxidación-reducción, intercambio de ligandos y reacciones de precipitación en el medio ambiente. Se ha demostrado la biometilación del estaño inorgánico en cultivos bacterianos puros, sedimentos y material vegetal en descomposición. Los compuestos inorgánicos de estaño pueden experimentar procesos de bioconcentración en los microorganismos, pero los datos son limitados.

Las concentraciones medias de estaño en el aire se suelen mantener por debajo de $0,1 \mu\text{g}/\text{m}^3$ (alcanzando valores de hasta $0,8 \mu\text{g}/\text{m}^3$), con concentraciones más altas cerca de algunas instalaciones industriales. En general, el estaño se encuentra en cantidades insignificantes en las aguas naturales. Las concentraciones más elevadas de estaño inorgánico están asociadas con descargas industriales y con el empleo de tributilestaño. En un estudio de lagos y ríos se encontró que casi el 80% de las muestras contenían estaño inorgánico en concentraciones inferiores a $1 \mu\text{g}/\text{l}$; se notificaron concentraciones más elevadas, de hasta $37 \mu\text{g}/\text{l}$, cerca de fuentes de contaminación. Se ha informado de concentraciones

de estaño inorgánico de $0,001$ a $0,01 \mu\text{g}/\text{l}$ en las aguas costeras, con niveles de hasta $8 \mu\text{g}/\text{l}$ cerca de fuentes de contaminación. Las concentraciones de estaño inorgánico en los sedimentos oscilaban entre $8 \text{ mg}/\text{kg}$ de peso seco en zonas costeras y hasta $15,5 \text{ mg}/\text{kg}$ en ríos y lagos. La concentración de estaño en la corteza terrestre es aproximadamente de $2-3 \text{ mg}/\text{kg}$. La concentración total de estaño en el suelo varía entre <1 y $200 \text{ mg}/\text{kg}$, pero se pueden encontrar niveles de $1000 \text{ mg}/\text{kg}$ en zonas con depósitos elevados de estaño. Algunos depósitos minerales pueden contener hasta $50\,000 \text{ mg}/\text{kg}$ como estaño.

Los alimentos son la fuente principal de exposición al estaño inorgánico para la población general. El JECFA ha llegado recientemente a la conclusión de que la ingesta media de estaño en siete países se situaba entre <1 y $15 \text{ mg}/\text{día}$ por persona, pero determinadas personas que habitualmente consumían frutas y hortalizas enlatadas o zumos procedentes de latas no barnizadas podían alcanzar valores máximos diarios de $50-60 \text{ mg}$. El agua de bebida no es una fuente importante de estaño inorgánico y podría contribuir con alrededor de $0,012-0,02 \text{ mg}/\text{día}$. Igualmente, los bajos niveles de estaño inorgánico en el aire indican que la cantidad inhalada de estaño es muy baja, probablemente inferior a unos $0,01-0,02 \text{ mg}/\text{día}$.

La absorción de estaño inorgánico a partir del tracto gastrointestinal es baja en las personas y los mamíferos de laboratorio (en general menos del 5%), pero depende de la dosis, los aniones (solubilidad del compuesto) y la presencia de otras sustancias. El estaño ingerido que no se absorbe se excreta fundamentalmente (95-99%) en las heces en un plazo de 48 h. El estaño absorbido se distribuye sobre todo en los huesos, pero también en los pulmones, el hígado y los riñones. Hay pruebas limitadas que parecen indicar que el estaño inorgánico no atraviesa la barrera hematoencefálica. El estaño absorbido se excreta básicamente en la orina, con alguna excreción biliar adicional. En ratones, la semivida biológica del estaño inorgánico absorbido fue de unos 30 días.

En cobayas expuestos a cloruro de estaño (IV) por inhalación se observó irritación ocular y nasal transitoria. Es poco probable que el estaño metálico pueda provocar irritación cutánea, mientras que los cloruros de estaño (II) y (IV) sí tienen esta propiedad. En algunos estudios, la inclusión de cloruro de estaño (II) en la alimentación durante 4-13 semanas produjo cambios en el tejido gastrointestinal indicativos de irritación local. Las primeras referencias bibliográficas contienen informes de efectos gastrointestinales (náuseas, calambres abdominales, vómitos y diarrea) en las personas tras el consumo de fruta o zumo de latas sin barnizar. Los efectos parecen ser el resultado de la irritación gástrica local debida al estaño disuelto. Este aspecto se examina con más detenimiento más adelante. Un pequeño número

de personas sufrieron reacciones cutáneas indicativas de una respuesta alérgica local cuando se sometieron a pruebas con parches de estaño o cloruro de estaño (II), pero, dado su empleo generalizado, no parece que el estaño sea un alérgeno cutáneo importante.

En las primeras referencias bibliográficas hay algunos casos de exposición ocupacional a polvo y humo que contenían óxido de estaño (IV) insoluble que indujo una pneumoconiosis benigna (estannosis). Este trastorno se caracteriza por sombras moteadas en los pulmones, al parecer debidas a depósitos de óxido de estaño (IV). La estannosis no está asociada con fibrosis o pérdida de función pulmonar.

En animales de laboratorio, la ingestión repetida de cloruro de estaño (II) tuvo efectos adversos en la presencia de cobre, hierro, zinc y calcio en el organismo. La disminución del contenido de calcio de los huesos inducida por las sales de estaño provocó una reducción de su resistencia. Se han observado reducciones de la hemoglobina y efectos en los glóbulos rojos que dan lugar a anemia. En ciertos estudios con administración repetida de cloruro de estaño (II) por vía oral se han notificado efectos en el hígado, los riñones, los testículos, el páncreas y el cerebro. En el más amplio de los estudios disponibles por vía oral a lo largo de toda la vida, no se observaron cambios microscópicos en una gran variedad de tejidos de ratas o ratones a los que se administró estaño en los alimentos en concentraciones de hasta alrededor de 60 mg/kg de peso corporal al día (ratas) o 180–270 mg/kg de peso corporal al día (ratones) en forma de cloruro de estaño (II). En este estudio, las NOAEL fueron de 30 mg/kg de peso corporal al día en ratas y de 130 mg/kg de peso corporal al día en ratones, observándose una supervivencia reducida con las dosis más altas.

El cloruro de estaño (II) no dio pruebas claras de actividad carcinogénica cuando se administró durante dos años a ratas y ratones con los alimentos. En biovaloraciones más limitadas llevadas a cabo con estaño metálico, cloruro de estaño (II) y un pequeño número de otros compuestos de estaño tampoco se logró detectar actividad carcinogénica. En valoraciones breves de detección del potencial genotóxico, el cloruro de estaño (II) no indujo mutaciones en las pruebas bacterianas de Ames, mutaciones o conversiones de genes en levaduras, daños en el ADN de células de hígado de rata cultivadas, mutaciones en células de linfoma de ratón *in vitro* o daños cromosómicos (micronúcleos) *in vivo* en la médula ósea de ratones tratados por inyección intraperitoneal. En valoraciones de reparación por recombinación en bacterias (en las cuales la actividad es una indicación indirecta de daño en el ADN), el cloruro de estaño (II) fue activo en *Escherichia coli*, pero (junto con otras sales de estaño) inactivo en *Bacillus subtilis*. En cultivos, el cloruro de estaño (II) indujo daños

cromosómicos e intercambio de cromátidas hermanas en células de ovario de hámster y daños en el ADN de linfocitos humanos, células de ovario de hámster y ADN de plasmidios. El cloruro de estaño (IV) sometido a prueba *in vitro* no provocó daños en el ADN de células de ovario de hámster, pero indujo aberraciones cromosómicas, micronúcleos e intercambio de cromátidas hermanas en linfocitos humanos. El fluoruro de estaño (II) provocó daños en el ADN de linfocitos humanos cultivados, pero no indujo formación de micronúcleos en la médula ósea tras la inyección en el peritoneo de ratones; en las pruebas de Ames sobre este compuesto no se demostró de manera convincente que tuviera actividad. Hay pruebas limitadas que respaldan la idea de que el daño en el ADN inducido por el estaño podría ser consecuencia de la producción de especies de oxígeno reactivo. No está claro el mecanismo mediante el cual el estaño induce daños cromosómicos en células de mamífero cultivadas, aunque se sabe que ciertos compuestos inorgánicos pueden dar resultado positivo en dichas valoraciones debido a cambios en el pH o el estado iónico del medio de prueba.

Sólo se encontraron datos limitados sobre el potencial de los compuestos de estaño inorgánico para provocar toxicidad reproductiva y en el desarrollo. No se detectaron efectos adversos en ratas cuando se les administró estaño (una forma no caracterizada obtenida mezclando cloruro de estaño(II) acuoso con caseína antes de su inclusión en la alimentación) en los alimentos durante tres generaciones o cuando se les administró fluoruro de estaño (II), pentacloroestannito de sodio o pentafluoroestannito de sodio con los alimentos durante toda la gestación. Igualmente, el tratamiento repetido de ratas, ratones y hámsteres con cloruro de estaño (II) mediante sonda no dio lugar a efectos adversos en los fetos.

Son limitados los datos disponibles sobre la capacidad del estaño ingerido para afectar negativamente a la absorción del zinc en las personas. En un estudio con voluntarios se observó que la aparición de zinc en el plasma entre una y cuatro horas después de la administración de una dosis de zinc no se vio afectada por la ingestión simultánea de hasta 100 mg de estaño (en forma de cloruro de estaño (II)). En otro estudio se notificó que una dosis única de 36 mg de estaño (también en forma de cloruro de estaño (II)), ingerida con zinc había dado lugar a una menor retención del zinc. En un tercer estudio en el que la alimentación normal se complementó con 50 mg/día de estaño (en forma de cloruro de estaño (II) en zumo de fruta), se detectaron trastornos moderados de los índices de excreción del zinc. Aunque no se ha establecido claramente un nivel sin efectos para la inhibición de la absorción del zinc, la dosis más baja notificada con este efecto (36 mg) es alrededor de 2,5 a >36 veces superior a la ingesta media estimada de la población según el

JECFA. Sin embargo, quienes habitualmente consumen frutas y hortalizas enlatadas y zumos de latas no barnizadas podrían tener ingestas de estaño (50–60 mg) similares a los niveles de la dosis aguda (36 mg) o repetida (50 mg) que, según lo notificado en algunos estudios, afectan a la absorción o el equilibrio del zinc. El hecho de que tenga o no algún efecto clínico es probable que dependa básicamente de un suministro adecuado de zinc con los alimentos.

Se han estimado (en 30–200 mg) las dosis de estaño correspondientes a los primeros informes de los efectos gastrointestinales tras el consumo de fruta o zumo enlatados, pero la confianza en la exactitud de estas cifras es escasa. Dos estudios recientes con voluntarios proporcionan un análisis mejor de las dosis efectivas y, lo que tal vez sea más importante, las concentraciones. El primer estudio consistía en la ingestión de zumo de tomate al que se había añadido cloruro de estaño (II) con objeto de obtener concentraciones de estaño de 161, 264 ó 529 mg/kg (dosis de estaño de unos 40, 66 y 132 mg, respectivamente). Con 161 mg/kg, un voluntario (de 18) informó de síntomas gastrointestinales ligeros; se observaron síntomas agudos característicos con 264 y 529 mg/kg. Los niveles de estaño en el suero no aumentaron con ninguna de las dosis en el intervalo de 0,5–4 h después de la administración, lo que respalda la opinión de que los efectos agudos de la ingestión de estaño dependen más de la concentración (que produce irritación gástrica local) que de la absorción sistémica de estaño. Un segundo estudio consistió en la ingestión de sopa de tomate con estaño que se había desplazado desde latas no barnizadas. Las concentraciones de estaño estudiadas fueron <0,5, 201 y 267 mg/kg, que proporcionaron dosis agudas de estaño de hasta unos 67 mg. No hay pruebas de que se hayan observado efectos agudos en este estudio. La dosis con efectos escasos o nulos en estos estudios, de unos 67 mg de estaño, es de alrededor de 4,5 a >67 veces superior a las estimaciones del JECFA para la ingesta diaria media de la población y similar a la ingesta diaria estimada (50–60 mg) de las personas que consumen habitualmente fruta, hortalizas y zumos contenidos en latas sin barnizar.

En condiciones de especiación en el medio ambiente, los compuestos de estaño inorgánico tienen una toxicidad baja para los organismos tanto acuáticos como terrestres, debido fundamentalmente a su baja solubilidad, su escasa absorción, su baja acumulación en los tejidos y su rápida excreción. La mayor parte de las pruebas de laboratorio con organismos acuáticos se han realizado con el cloruro de estaño (II) soluble. Las microalgas más sensibles son las diatomeas marinas *Skeletonema costatum* y *Thalassiosira guillardii*, con valores de la CE_{50} de los cationes de estaño (II) a las 72 h, basados en la inhibición del crecimiento, de unos 0,2 mg/l. Las CL/CE_{50} agudas del estaño (II) para los invertebrados acuáticos están en la gama de 3,6 a

140 mg/l, con una CE_{50} a los 21 días, basada en el éxito reproductivo en los dáfnidos, de 1,5 mg de estaño (II) por litro. Las pruebas de toxicidad en los peces demuestran claramente que el cloruro de estaño (IV) es menos tóxico que el cloruro de estaño (II), más soluble. Las CL_{50} a las 96 horas para los peces varía entre 35 mg de estaño (II) por litro y >1000 mg de estaño (IV) por litro. Los resultados de las pruebas embriolarvarias (es decir, las CL_{50} a los 7–28 días) en el caso de los peces y anfibios son de 0,1 a 2,1 mg/l para el estaño (II).

Las concentraciones que muestran toxicidad para los organismos son en general varios órdenes de magnitud más elevadas que las que se encuentran en el medio ambiente. Los resultados de las pruebas más sensibles fueron exposiciones de diatomeas de 72 h y estudios embriolarvarios de anfibios, habiéndose observado efectos tóxicos con 0,1–0,2 mg de estaño (II) por litro. Incluso con esas concentraciones, es poco probable que el estaño inorgánico provoque efectos tóxicos, incluso cerca de fuentes de contaminación local. Hay que señalar que cuando las concentraciones se expresan como estaño total, es probable que un porcentaje se encuentre en forma de estaños orgánicos (por ejemplo, tributilestaño), que son formas más biodisponibles y tóxicas. Para más información sobre el destino del tributilestaño en el medio ambiente y su toxicidad, véase el IPCS (1990, 1999).

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ISBN 92 4 153065 0