Please note that this document, published on 7 September 2005, replaces the earlier version which contained an error in pages 14 and 17.
Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to the Tolerable Upper Intake Level of Tin

(Request No. EFSA-Q-2003-018)

(adopted on 6 July 2005)

SUMMARY

The European Food Safety Authority is asked to derive an upper level for the intake of tin from food that is unlikely to pose a risk of adverse health effects.

Tin has not been shown to be nutritionally essential for humans. Tin occurs naturally in foods as stannous and stannic salts, and stannous chloride (SnCl\(_2\)) is a permitted food additive (E512). Data on tin intake in EU countries are limited. In the UK mean intake in adults from food is estimated at 1.8 mg/day, ranging up to about 6 mg/day, and appears to be decreasing, while in France the mean daily intake was estimated to be 2.7 mg tin/day. The main dietary sources of tin are tinned fruit and vegetables.

The absorption of inorganic compounds of tin from the gastrointestinal tract in humans and animals is very low with as much as 98% being excreted directly in the faeces. Because of their limited absorption, inorganic tin compounds have low systemic toxicity in man and animals.

In man and animals, gastrointestinal effects are the main acute manifestation of toxicity associated with ingestion of tin. These are caused by the irritant action of soluble inorganic tin compounds on the mucosa of the gastrointestinal tract. In humans, acute effects resulting from consumption of tin-contaminated foods and drinks have resulted in gastrointestinal symptoms, including abdominal distension and pain, vomiting, diarrhoea, and headache. The balance of evidence suggests that the concentration of tin in contaminated foods is critical to the development of acute gastrointestinal effects, and that tin concentrations of 250 mg/kg in canned foods and 150 mg/kg in canned beverages are more likely to be associated with this.

In rats, growth depression, loss of appetite and reduced feed conversion efficiency are observed at doses of stannous chloride greater than 150 mg tin/kg diet. This appears to be due to reduced absorption and status of trace elements, particularly zinc, but also iron and copper, as a result of formation of insoluble complexes (probably with phosphates) in the gastrointestinal tract. There is evidence of reduced status of iron, zinc and copper when rats are fed diets containing 50 mg tin/kg diet or greater. It is likely that other effects which occur at this or higher levels (e.g. reduced calcium content of bone at 50 mg tin/kg diet or pancreatic atrophy at a dose level of 2000 mg tin/kg diet), are not systemic effects of absorbed tin but rather manifestations of deficiency of one or more trace elements.

Short term studies in human adults indicate that high intakes of tin (about 30-50 mg tin/day or per meal) may reduce the absorption of zinc, but not other minerals such as iron, copper, manganese or magnesium. However, the possible long-term effects, if any, of such intake

levels on status of zinc or other minerals have not been investigated.

The Panel considered that the available data from human or animal studies are insufficient to derive a tolerable upper intake level for tin. The current daily intake of tin in the EU (e.g. ranging up to about 6 mg/day in the UK) appears to be well below the lowest intakes reported to cause adverse effects on zinc absorption. Regulatory limits of 200 and 100 mg/kg for the concentration of tin in canned foods and beverages, respectively, have been established to protect against the occurrence of acute gastrointestinal effects of tin.

KEY WORDS

Inorganic tin, stannous chloride, stannous oxide, stannic chloride, toxicity.

BACKGROUND

In 2002, the European Parliament and the Council adopted Directive 2002/46/EC\textsuperscript{1} related to food supplements containing vitamins and minerals.

In addition, and as announced in its White Paper on Food Safety, the Commission aims to put forward a proposal for harmonising legislation concerning the addition of vitamins and minerals to foods.

With a view to provide scientific support to the European Commission’s legislative work in this field, the Scientific Committee on Food (SCF) issued, from October 2000 to April 2003, a series of opinions on tolerable upper intake levels of individual vitamins and minerals and safety factors in relation to their use in fortified foods and food supplements (available on the Internet at: http://europa.eu.int/comm/food/fs/sc/scf/out80_en.html).

The SCF opinions covered 22 out of the 29 nutrients, which were considered to be within their mandate for this task. The SCF did not have sufficient time to adopt opinions for the following vitamins and minerals: vitamin C, chloride, fluoride, iron, phosphorus, potassium and sodium. In addition, during the decision making process for the adoption of Directive 2000/46/EC on food supplements the Parliament requested that boron, nickel, silicon, vanadium and tin should be allowed to be used in food supplements. Therefore, the European Food Safety Authority is asked to provide scientific opinions on the remaining 12 vitamins and minerals in accordance with the present terms of reference.

TERMS OF REFERENCE

With respect to the outstanding 12 vitamins and minerals, the European Food Safety Authority is asked 1) to review the upper levels of daily intakes that are unlikely to pose a risk of adverse health effects; 2) to provide the basis for the establishment of safety factors, where necessary, which would ensure the safety of fortified foods and food supplements containing the aforementioned nutrients.

1. INTRODUCTION

1.1 Chemistry

Tin is a metal of group 14 of the periodic table with an atomic weight of 118.71. It has 10 naturally occurring isotopes of atomic masses between 112 and 124 with abundances ranging from 0.34-32.97%. The oxides of tin are amphoteric, commonly forming stannous and stannic salts (oxidation state +2 and +4, respectively). Several reviews and evaluations have been prepared on inorganic tin (WHO, 1980; Thomas, 1984; Smith and Kumar Das, 1996; EGVM, 2002; ATSDR, 1992 and 2002; JECFA, 1982 and 2001).

1.2 Natural occurrence

Natural occurrence of tin in the metallic state is rare. The occurrence of tin in various organisms from different localities has been reviewed by Schroeder et al. (1964) and they noted that the concentrations found are highly dependent on the existence of local mineral sources of tin. Although not commonly present in fresh waters it occurs at a concentration of about 3 µg/L in sea water. Tin was present in all vegetable samples obtained in Vermont, an area with soil containing considerable amounts of tin, from 0.07-9.07 µg/g wet weight. It is found in tissues of local farm and wild animals (Schroeder et al., 1964; WHO, 1980; EGVM, 2002; ATSDR, 1992 and 2002).

1.3 Occurrence in food, food supplements and medicines

The widespread distribution in soils of some areas results in the presence of tin within certain foodstuffs. Within the European Union stannous chloride is a permitted food additive (E512) for bottled and canned white asparagus only (25 mg Sn/kg). The highest concentrations of tin in foods are found in tinned fruit and vegetables. Tin is present in some multi-vitamin and mineral food supplements (levels up to 10 µg tin/tablet) (EGVM, 2002).

At the 55th meeting of the Joint FAO/WHO Expert Committee on Food Additives in June 2000 the Provisional Tolerable Weekly Intake (PTWI) of 14 mg Sn/kg body weight was reconsidered and maintained (JECFA, 2001). In an opinion of the SCF on acute risks posed by inorganic tin in canned food, the Committee concurred with the JECFA conclusion that levels of 150 mg/kg in canned beverages or 250 mg/kg in other canned foods or higher may cause gastric irritation in some individuals (SCF, 2001).

Maximum levels for inorganic tin in canned foods (200 mg/kg) and canned beverages (100 mg/kg) have been established in EU legislation (EC, 2004).

2. NUTRITIONAL BACKGROUND

2.1 Deficiency

Tin has not been shown to be essential for humans or animals, and there are no data on deficiency effects resulting from an inadequate intake of inorganic tin (EGVM, 2002).
2.2 Absorption, distribution, metabolism and elimination

2.2.1 Absorption

The absorption of inorganic compounds of tin from the gastrointestinal tract in humans and animals is reported to be low with as much as 98% being excreted directly in the faeces. The nature of the inorganic tin compound and its oxidation state appears to determine the extent of absorption (Calloway and McMullen, 1966; Hamilton et al., 1972b; Tipton et al., 1966 and 1969; Fritsch et al., 1977a; WHO, 1980; ATSDR, 1992 and 2002).

2.2.1.1 Animals

It has been reported that gastrointestinal absorption of tin by the rat is extremely low. In one study, groups of 8 male Wistar rats (approximately 250 g) were fasted for 17 hours after which a dose of radiolabelled \( ^{113}\text{SnCl}_2 \) (50 mg/kg body weight; 0.5 \( \mu \text{Ci/mg tin} \)) was administered by gavage in either: (1) water; or with (2) aqueous sucrose at 5 g/kg body weight; (3) aqueous ascorbic acid at 0.5 g/kg body weight; (4) aqueous potassium nitrate 0.1 g/kg body weight; (5) an aqueous solution of all three compounds at the same dose; or in (6) 20% alcohol solution, equivalent to 2 g ethanol/kg body weight; or (7) a solution of albumin at 2.5 g/kg body weight; or (8) 1:1 (v/v) sunflower oil-1% Tween 20 emulsion at 10 mL/kg body weight. Rats were placed in metabolic cages, fasted for another 6 hours and then received a basal diet \textit{ad libitum}. Urine and faeces were collected from 0-24 and 24-48 hours. Animals were then sacrificed and excreta and selected organs and tissues analysed for radioactivity. Group mean values of the proportion of the administered dose excreted in the faeces within 48 hours or remaining in the gastrointestinal tract ranged from 98.7-99.8%. The mean percentage of the \( ^{113}\text{Sn} \) dose detected in the urine was less than 1.1% and in the organs and tissues examined was less than 0.005% (Fritsch et al., 1977a; WHO, 1980; ATSDR, 1992 and 2002).

The effect of the anion and oxidation state on the gastrointestinal absorption of inorganic tin salts, labelled with \( ^{113}\text{Sn} \), was studied in the rat. Following a 24-hour fast, groups of 10 female rats (Charles River, 200-225 g) were given a single 20 mg Sn/kg body weight oral dose of Sn\(^{2+}\) citrate, fluoride or pyrophosphate or Sn\(^{4+}\) citrate or fluoride. Changing the anion from citrate to fluoride did not alter the absorption of either oxidation state and approximately 2.8% and 0.6% of the Sn\(^{2+}\) and Sn\(^{4+}\), respectively, were absorbed. With pyrophosphate as the anion, absorption of Sn\(^{2+}\) was significantly lower than with the citrate or fluoride, an observation which the author ascribed to the greater tendency of pyrophosphate to form insoluble complexes with tin as compared to the citrate and fluoride anions (Hiles, 1974). In a 28-day study in which groups of 6 weanling female rats were fed with the Sn\(^{2+}\) and Sn\(^{4+}\) fluoride salts (20 mg Sn/kg body weight, on 6 days/week) the steady state urinary excretion was \textit{circa} 0.35% and 0.12% of the total dose of tin from the Sn\(^{2+}\) and Sn\(^{4+}\) salts, respectively, confirming the greater absorption of the Sn\(^{2+}\) ion (Hiles, 1974).

In a comparative study of the absorption of tin, tracer dose of \( ^{113}\text{SnCl}_2 \) (2.6-4.4 mg Sn) were administered intravenously, intraperitoneally and by gavage to female RF mice, male Sprague-Dawley rats, male African white-tailed rats, male rhesus monkeys and male beagle dogs. In all species more than 95% of the oral gavage dose was excreted via the faeces within 3 days, whereas a greater percentage (15.9-62.8%) of the parenteral doses was excreted via the urine during the same time (Furchner and Drake, 1976).
Orange juice containing 540 mg Sn/kg derived from corrosion of the can or a solution of tin citrate (1200 mg Sn) was administered to Wistar rats (gender not given), and faeces and urine were collected over 48 hours or 18 hours respectively. No tin was detected in the urine collections whereas the faecal excretion of tin was 99% or 94-98% respectively (Benoy et al., 1971).

2.2.1.2 Humans

The absorption of inorganic compounds of tin from the gastrointestinal tract in humans is very low with as much as 98% being excreted directly in the faeces at intakes around 10 mg/day or higher. Schryver (1909) reported the urinary excretion of tin in normal health adults weighing 65 kg, who ingested daily doses of sodium tin tartrate for 3 weeks. The doses were taken four times a day with meals and the total daily dose in the first week, of approximately 64.5 mg tin, was increased to 129 mg in the second week and to 193.5 mg in the third week (equivalent to approximately 1, 2 and 3 mg Sn/kg body weight per day in successive weeks). After the first week the tin excreted in 5-day periods in each week was related to the amount ingested, with 7.9 and 8.6% of the total excreted in the urine during the second and third weeks, respectively. There was no control period and no measures of dietary tin content were made (Schryver, 1909). In a study by Calloway and McMullen (1966) faecal excretion of tin was high and approximated dietary intakes when the diet provided 9-190 mg tin per day. In adults given 50 mg tin per day the apparent absorption was around 3%, while it was about 50% when the intake was 0.1 mg/day (Johnson and Greger, 1985).

2.2.2 Distribution

2.2.2.1 Animals

When expressed as a percentage of a dose administered orally to rats, tissue distributions for Sn^{2+} and Sn^{4+}, respectively were skeleton, 1.02% and 0.24%, liver, 0.08% and 0.02%; and kidneys 0.09% and 0.02% (Hiles, 1974). When radioactive stannous chloride was administered by stomach tube to anaesthetised rats the bulk of the dose was excreted in faeces, and there was highly variable distribution of the absorbed fraction in the internal organs as measured for periods of up to 21 days (Kutzner and Brood, 1971).

Tin concentrations were measured in the liver, kidneys and femur of groups of 6 male weanling Wistar rats administered 0, 0.3, 1.0 and 3.0 mg Sn^{2+}/kg body weight orally every 12 hours for a period of 90 days. There was a clear dose-related increase in femur concentration with statistical significance achieved at the 1.0 mg Sn^{2+}/kg body weight dose. In the highest dose group the femur concentrations were 10-fold higher than the control values of 2.05 ± 0.41 μg/g wet tissue and these were associated with significant reductions of the diaphysis and epiphysis concentrations of calcium. The concentrations of tin in the livers of control rats were 0.24 ± 0.01 μg/g wet tissue and the levels were significantly increased by 58% at the highest dose. There were no significant increases in the kidney concentrations of 0.22 ± 0.41 μg/g wet tissue (Yamaguchi et al., 1980).

Male Wistar rats were given SnCl_2·2H_2O in their drinking water for 1-18 weeks at concentrations of 100 mg/L (0.44mM), 250 mg/L (1.11 mM) or 500 mg/L (2.22 mM). Tin accumulated in the brain at the highest concentration (2.22 mM) throughout the experiment, but elevated tin concentrations in brain were found only after 15 and 18 weeks at 1.11 mM and tin did not increase in the brains of rats given 0.44 mM. Blood tin increased after one
week at the highest dose (2.22 mM) without further accumulation, whereas blood tin levels did not differ from controls at the 2 lower doses. Tin exposure caused a dose-dependent increase in the cerebral and muscle acetylcholinesterase activity at the two highest doses (Savolainen and Valkonen, 1986).

2.2.2.2 Humans

The mean concentration (± S.E.) of tin in 102 samples of human blood obtained through the UK National Blood Transfusion Service was 0.009 ± 0.002 μg/g wet weight. The concentrations ± S.E. (n) in various organs obtained at autopsy were: whole brain, 0.06 ± 0.01 (10); whole kidney (0.2 ± 0.04 (8); liver, 0.4 ± 0.08 (11); lung, 0.8 ± 0.2 (11), lymph node, 1.5 ± 0.6 (6); muscle, 0.07 ± 0.01 (6); testis, 0.3 ± 0.1 (5); ovary, 0.32 ± 0.19 (6), all μg/g wet weight; bone (hard water area), 4.1 ± 0.6 (22); bone (soft water area), 3.7 ± 0.6 (22), μg/g ash (Hamilton et al., 1972a).

2.2.3 Metabolism

The methylation of inorganic tin compounds by a mechanism involving the oxidation of a stannous compound to the Sn (III) radical and the reaction of this with the cobalt-carbon bond of vitamin B₁₂ to give a methylated tin derivative have been described. However, it is probable that this can only occur in anaerobic conditions (Ridley et al., 1977 a and b; Wood et al., 1978; ATSDR, 1992 and 2002).

2.2.4 Elimination

2.2.4.1 Animals

The disappearance of radioactivity following intraperitoneal injection of a tracer of $^{113}$SnCl₂ into 5 Swiss mice was followed by whole body counting. The biological half life of tin was estimated as 29 days (Brown et al., 1977). Intravenous injection of single bolus doses of 2 mg/kg body weight of either Sn²⁺ or Sn⁴⁺ (citrate and fluoride) resulted in the excretion of 30% of the dose in the urine, with 11% and 0% of Sn²⁺ and Sn⁴⁺ eliminated in the bile (Hiles, 1974).

2.2.4.2 Humans

A baby fed on evaporated milk from an unlacquered tin can for the first 5 weeks of life was estimated to have ingested 11.23 mg Sn/24 hours. Excretion in the faeces was estimated as 10.64 mg Sn/24 hours and in the urine as 0.23 mg Sn/24 hours. The faecal excretion of tin decreased by 98% within 36 hours after changing to milk from a lacquered can (Hamilton et al., 1972b). A 30-day balance study on a husband and wife aged 35 and 34 respectively, involved the collection of duplicate samples of their food and drink and total collection of faeces and urine. Mean daily faecal and urinary excretion of tin (measured by emission spectroscopy on dry-ashed samples) were, 2.13 and 0.11 mg, respectively for the wife, and 1.55 and 0.08 mg, respectively for the husband. The wife was in negative balance and the husband in positive balance (Tipton et al., 1966). The same group studied two males, 23 and 25 years old, using similar procedures for a period of 347 days. Both subjects were in positive balance and their mean daily faecal and urinary excretions of tin (mean ± S.E.) were 3.6 ± 0.7 and 0.085 ± 0.011 mg, respectively for the first subject, and 3.6 ± 0.5 and 0.058 ± 0.006 mg for the second subject. It was calculated that less than 10% of the amount of tin ingested was
excreted within 24 days (Tipton et al., 1969). A study of the tin content of army rations which had been stored at either 1 or 37° C for a period of 20 months indicated that these would provide mean tin intakes of 26.3 and 162.8 mg per day respectively as compared with a freshly prepared control diet (9.5 mg Sn per day). During ingestion of the control diet the faecal excretion of tin by 9 young adult male volunteers was slightly greater than the estimated intake and, during consumption of the high tin diet, faecal excretion was slightly lower than the intake; only trace amounts of tin were detected in the urine and these were unaffected by the diet (Calloway and McMullen, 1966). One study has reported results which were somewhat different from the other toxicokinetic studies. In adult males fed daily diets containing either 0.1 or 50 mg of tin in a 40-day study with a 20-day cross over period apparent absorption was 50 and 3% of the ingested tin, respectively (Johnson and Greger, 1982).

2.3 Interactions

2.3.1 Animals

Groups of 7 young male Sprague-Dawley rats were assigned to study groups in which they were: a) fed for 7 days with either a diet supplemented with 1954 mg Sn/kg or were pair-fed with a control diet; b) fed for 27 days with various concentrations of tin and zinc in a block design; and c) fed as in b with different concentrations of tin and zinc for 6 or 7 days. The absorption of zinc by rats on diets containing 200 or 500 mg/kg tin was decreased. At the higher dietary concentration, the retention of zinc in tibia, kidney, liver and plasma was significantly decreased and the plasma, liver and kidney levels of copper were reduced (Johnson and Greger, 1984 and 1985).

Groups of 10 weanling male long-Evans rats were administered diets containing 0, 100, 330 or 1100 mg Sn/kg diet, and a control group were pair-fed with 0 mg Sn/kg to match the 1100 mg/kg diet group, for a period of 28 days. The copper, zinc, iron contents of various tissues were then assessed. There were significant dose-related reductions of body weight gain in all treatment groups. The highest dietary concentration of tin significantly reduced the copper and zinc concentrations of most tissues studied. There were dose-related reductions in the liver concentrations of copper and in the kidney concentrations of zinc. Also, when the rats were fed a diet deficient in copper, the 100 mg Sn/kg diet caused a significant reduction of blood haemoglobin and serum ceruloplasmin concentrations (Rader et al., 1990; Rader, 1991). Similar results were reported in a study on the effects of 100 mg Sn/kg diet in rats fed additional dietary glucose or fructose while consuming Cu-deficient or Cu-adequate diets (Reicks and Rader, 1990).

Groups of 12 weanling Wistar rats were fed semi-synthetic diets containing 1 (control) or 100 mg Sn/kg diet (the tin was added as SnCl₂) for 28 days. The test diet had no effects on body weight gain or feed intake but resulted in significantly reduced concentrations of copper in plasma, liver and kidneys. The biliary excretion rate of copper was reduced to approximately 40% of that of the control group. The authors concluded that tin affected copper status by inhibiting the copper absorption (Yu and Beynen, 1995).

A 28-day study with male Wistar rats fed diets containing 0, 1, 10, 50, 100 and 200 Sn mg/kg diet, incorporated as stannous chloride, provided evidence for dose-related changes to the iron, copper and zinc status of the animals, with changes claimed to occur at dietary
concentrations lower than 50 mg/kg (Beynen et al., 1992; Pekelharing et al., 1994; EGVM, 2002; ATSDR, 1992 and 2002).

Tissues of rats and mice fed tin in drinking water for life were analyzed for the essential metals, chromium, copper, manganese and zinc. Contrary to what has been shown for competitive effects of tin on copper in some other studies, the concentrations of copper were significantly higher in the livers of rats fed tin than in controls (Schroeder and Nason, 1976).

2.3.2 Humans

The consumption of canned foods providing 163 (116-203) mg of tin per day by nine adult males was associated with an apparent greater retention of iron in the body; however, the iron content of the diet was higher than that of a low-tin-content diet (Calloway and McMullen, 1966).

During a 40-day study, with 20-day cross over periods, eight adult males (69-82 kg body weight) were fed either a mixed diet providing 0.1 mg tin per day (controls) or a similar test diet providing 50 mg tin per day. When the subjects were fed the test diet the subject’s excretion of zinc was increased in the faeces and decreased in the urine, and the apparent absorption of zinc was reduced by 16%: there was no significant effect on the excretion of copper, iron, manganese and magnesium (Johnson et al., 1982). In a similar, and possibly the same study, there was no effect of incorporation of tin in the diet on calcium excretion or serum levels of calcium (Johnson and Greger, 1982). Also, on the high-tin diet there was a statistically significant increase in the faecal excretion of selenium, while the urinary excretion and overall apparent retention of selenium were decreased but non-significantly (Greger et al., 1982).

A single test meal containing 36 mg Sn as stannous chloride dihydrate administered to 10 healthy volunteers aged 18-46 years reduced the absorption of radiolabelled $^{65}\text{ZnCl}_2$ (molar ratio of Sn:Zn = 5) from the test meal by circa 29%, as measured by whole body counting 2-4 hours and 7-10 days after the meal (Valberg and Chamberlain, 1984). However, Solomons et al. (1983) found no effect on zinc absorption, assessed by plasma zinc concentrations during 4 hours post-dose, in humans given increasing amounts of stannous chloride (from 25, 50 and 100 mg Sn, respectively) together with 12.5 mg zinc (as zinc sulphate) in 100 mL soft drink in single-meal studies.

2.4 Requirement and recommended daily intake

Tin has not been shown to be essential for humans. Although some authors (Gelfert and Stauffebiel, 1998) suggested that tin could be essential, there is no experimental evidence that tin is an essential element for animals or man.

2.5 Dietary intake

Information on dietary intakes of tin is limited, as it is not in the nutrient databanks for dietary surveys.

A total diet study in The Netherlands was used to investigate the content of minerals in market basket samples representing the diet of Dutch 18 year old males and purchased at 3-monthly interval over a period of 2½ years (1984-1986). The mean daily intake of tin was
estimated to be 0.65 mg as compared with 1.7 mg in a study carried out eight years earlier. Canned fruits contributed 82% of the dietary intake of tin (Van Dokkum et al., 1989), which probably is due to migration from the can into the food.

A study in the UK of the concentration of tin in canned foods provided evidence that canned fruits (tomato and tomato products, pineapple, orange, grapefruit and pear) are the most likely to contain elevated concentrations of tin, with the tomato, tomato products and pineapples categories each having some samples containing more than 250 mg Sn/kg. The mean upper and lower bound estimated total dietary intakes of tin for the years 1976 to 1982 ranged from 4.35-2.41 (upper bound) and 4.42-2.30 (lower bound) mg Sn per day. There was a decreasing tendency until 1982, and the authors quote references suggesting that intake via inhalation and drinking water are likely to be 2 to 3 orders of magnitude less than dietary intake (Sherlock and Smart, 1984). In a duplicate diet study of 29 adult females in north-eastern England in 1982, it was noted that the concentration of tin in the duplicate diets was higher than in the earlier total diet samples (Evans and Sherlock, 1987).

Analyses of samples from 1997 Total Diet Studies (TDS) showed that the population average intake of tin was 1.8 mg/day, and the upper level (97.5 percentile) tin intake was estimated at 6.3 mg/day using the TDS concentrations combined with consumption data from the 1986/87 Dietary and Nutritional Survey of British Adults. The population average intake of tin had decreased since the previous TDS estimate of 2.4 mg/day in 1994. Table 1 shows the concentrations of tin in each of the 1997 TDS food groups and the intake from each group. This shows that the highest concentrations of tin were in the canned vegetables group followed by the fruit products group. Canned food products are the main contributors to the intake of tin in the UK (EGVM, 2002).

In a study in France, the tin contents in fresh food or in food stored in lacquered or unlaquered cans were determined in order to estimate the average daily tin intake in a French citizen. Tin levels were 76.6 ± 36.5 mg/kg in foods preserved in unlaquered cans, 3.2 ± 2.3 mg/kg in foods stored in lacquered cans, and 0.03 ± 0.03 mg/kg in fresh foods. Tin intake is essentially dependent on food stored in tin cans (98%), which represents 5.6% of the total daily consumption of foods by a French citizen. The estimated tin intake was 2.7 mg/day which is equivalent to 0.04 mg/kg body weight (Biégo et al., 1999).

3. HAZARD IDENTIFICATION

3.1 Animal toxicity data

3.1.1 Acute toxicity

Single oral administration of inorganic tin caused a number of acute symptoms, such as severe salivation and emesis, with vomiting in cats and dogs (Benoy et al., 1971). LD₃₀ values for inorganic tin compounds are shown in Table 2.

3.1.2 Short-term toxicity

Feeding rats with SnCl₂ in tap water at intakes equivalent to 1.4 or 14 mg SnCl₂/kg body weight/day or in an aqueous suspension of yeast at intakes equivalent to 14 mg SnCl₂/kg body weight/day for 21 days resulted in a reduction of about 30% in the activity of serum lactate
dehydrogenase for all treatments but no effect was observed on serum glutathione peroxidase, carbonic anhydrase, alkaline phosphatases or leucine aminopeptidase (Pfaff et al., 1980; EGVM, 2002; ATSDR, 1992 and 2002).

Table 1. Concentrations of tin in 1997 Total Diet Study samples and estimated average intake (EGVM, 2002)

<table>
<thead>
<tr>
<th>Food Group (TDS)</th>
<th>Mean Sn concentrations (mg/kg fresh weight)</th>
<th>Intake of Sn (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread</td>
<td>0.025</td>
<td>0.003</td>
</tr>
<tr>
<td>Misc. cereals</td>
<td>0.771</td>
<td>0.078</td>
</tr>
<tr>
<td>Carcass meat</td>
<td>0.007</td>
<td>0.00015</td>
</tr>
<tr>
<td>Offal</td>
<td>0.014</td>
<td>0.0001</td>
</tr>
<tr>
<td>Meat products</td>
<td>0.18</td>
<td>0.008</td>
</tr>
<tr>
<td>Poultry</td>
<td>0.006</td>
<td>0.00011</td>
</tr>
<tr>
<td>Fish</td>
<td>0.032</td>
<td>0.00045</td>
</tr>
<tr>
<td>Oils &amp; fats</td>
<td>0.011</td>
<td>0.00030</td>
</tr>
<tr>
<td>Eggs</td>
<td>0.003</td>
<td>0.00004</td>
</tr>
<tr>
<td>Sugars and preserves</td>
<td>0.046</td>
<td>0.003</td>
</tr>
<tr>
<td>Green vegetables</td>
<td>0.003</td>
<td>0.0001</td>
</tr>
<tr>
<td>Potatoes</td>
<td>0.004</td>
<td>0.00049</td>
</tr>
<tr>
<td>Other vegetables</td>
<td>0.05</td>
<td>0.004</td>
</tr>
<tr>
<td>Canned vegetables</td>
<td>41¹</td>
<td>1.353</td>
</tr>
<tr>
<td>Fresh fruit</td>
<td>0.019</td>
<td>0.001</td>
</tr>
<tr>
<td>Fruit products</td>
<td>7.21¹</td>
<td>0.317</td>
</tr>
<tr>
<td>Beverages</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Milk</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>Dairy produce</td>
<td>0.297</td>
<td>0.018</td>
</tr>
<tr>
<td>Nuts</td>
<td>0.029</td>
<td>0.00006</td>
</tr>
</tbody>
</table>

Total Intake (mg/day) 1.8 mg/day

¹ High levels resulting from migration from cans

Table 2. LD₅₀ values for inorganic tin compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Species, gender</th>
<th>Dose route</th>
<th>LD₅₀ (mg/kg body weight)</th>
<th>Duration</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SnCl₂</td>
<td>Rat, M</td>
<td>p.o.</td>
<td>700</td>
<td>over 21 days</td>
<td>Pfaff et al., 1980</td>
</tr>
<tr>
<td>SnCl₂</td>
<td>Rat, M</td>
<td>p.o.</td>
<td>&gt; 1500</td>
<td>16 days</td>
<td>NTP, 1982</td>
</tr>
<tr>
<td>SnCl₂</td>
<td>Rat, F</td>
<td>p.o.</td>
<td>&gt; 1500</td>
<td>16 days</td>
<td></td>
</tr>
<tr>
<td>SnCl₂</td>
<td>Mouse, M, F</td>
<td>p.o.</td>
<td>&lt; 600</td>
<td>16 days</td>
<td></td>
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<tr>
<td>SnCl₂/Na citrate complex</td>
<td>Mouse, M, F</td>
<td>p.o.</td>
<td>2700</td>
<td>Unknown</td>
<td>Omori et al., 1973</td>
</tr>
<tr>
<td>SnF₂</td>
<td>Rat, M</td>
<td>p.o.</td>
<td>188.2</td>
<td>Fasted, 24h</td>
<td>Lim et al., 1978</td>
</tr>
<tr>
<td>SnF₂</td>
<td>Mouse, M</td>
<td>p.o.</td>
<td>128.4</td>
<td>Fasted, 24h</td>
<td></td>
</tr>
<tr>
<td>NaSnF₅</td>
<td>Mouse, M</td>
<td>p.o.</td>
<td>592.9</td>
<td>24h</td>
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<tr>
<td>NaSnF₅</td>
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<td>p.o.</td>
<td>218.7</td>
<td>Fasted, 24h</td>
<td>Conine et al., 1975</td>
</tr>
<tr>
<td>NaSnF₅</td>
<td>Rat, M</td>
<td>p.o.</td>
<td>573.1</td>
<td>24h</td>
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<tr>
<td>NaSnF₅</td>
<td>Rat, M</td>
<td>p.o.</td>
<td>223.1</td>
<td>Fasted, 24h</td>
<td></td>
</tr>
</tbody>
</table>

p.o. oral gavage
Consumption of diets containing 1900-30,000 mg SnCl₂/kg diet for a period of 14 days by rats resulted in a dose-related decrease in weight gain in rats and, at the highest dietary concentrations, roughened coats and distended abdomens. In mice similarly treated, there was reduced weight gain on diets containing 15,000 and 30,000 mg SnCl₂/kg (NTP, 1982).

Consumption of diets by rats and mice containing (in mg/kg) SnCl₂ at levels of 0, 500, 1000, 1900, 3800, 7500 (in both species) and 15,000 and 30,000 (in mice only) mg SnCl₂/kg diet for 13 weeks resulted in reduced weight gain in rats at the 7500 mg/kg dose level and distension of the caecum and reddening of the mucosal surface of the stomach at the 3800 and 7500 mg/kg dose levels. No histological changes were observed in any tissue. In the mice, there was a 30% decrease in body weight gain in the animals receiving 30,000 mg SnCl₂/kg diet and gross distension of the caecum was observed in all groups receiving dietary concentrations of 3800 mg/kg diet or greater. No histological changes were observed in any tissue (NTP, 1982).

Increasing dietary concentrations of SnCl₂.H₂O from 0.1% in the first week to 0.8% in weeks 8 to 13 in rats reduced body weight gain, haemoglobin concentration and haematocrit and induced pancreatic atrophy, histological changes to the gastrointestinal tract, liver, kidney and thyroid. The authors considered the pancreatic changes to be the most specific manifestation of the toxicity of tin (Dreef-van deer Mullen et al., 1974).

Administration of diets containing 0, 4000 or 8000 mg Sn/kg diet as SnCl₂ to rats for 6 months caused pancreatic atrophy and histological changes in the kidney, adrenal medulla and adrenal cortex, signs of irritation in the gastrointestinal tract in both treatment groups (Fritsch et al., 1978).

Feeding a diet containing 5000 mg Sn/kg food as SnCl₂, labelled with radioactive ¹¹³SnCl₂, equivalent to about 700 mg Sn/kg body weight, to young male rats for one month resulted in reduction of body weight and food consumption, anaemia characterised by a significant drop in haemoglobin and haematocrit values, congestion of the kidneys and the cortex of the adrenals, and congestion and desquamation of the mucosa in the upper gastrointestinal tract from the stomach to ileum. About 99% of the administered labelled tin was excreted in the faeces with less than 1% in the urine, while radioactivity in the gastrointestinal tract, organs and carcass was negligible (Fritsch et al., 1977b).

Feeding weanling rats diets containing 0, 300, 1000, 3000 and 10,000 mg/kg diet as SnO₂, SnCl₂, Sn₃(orthophosphate)₂, SnSO₄, SnS₂, Sn-olate, Sn-oxalate or Sn-tartrate for 4 weeks resulted in no deleterious effects of SnO₂, SnS₂, and Sn-olate (all insoluble tin compounds) but there was severe growth retardation, decreased food efficiency, slight anaemia and slight histological changes in liver with 3000 mg Sn/kg diet with SnCl₂, Sn₃(orthophosphate)₂, SnSO₄, Sn-oxalate or Sn-tartrate (all water soluble tin compounds). Dietary supplements of iron partly protected against tin-induced anaemia but did not protect against the other adverse effects. The authors suggested that the observed adverse effects of these tin compounds might be explained by the inhibition of iron absorption (de Groot et al., 1973).

In a 90-day study weanling rats were fed diets containing either SnO or SnCl₂ at dietary concentrations of 0, 300, 1000, 3000, 10,000 mg/kg. There were no toxic effects of SnO at any dose. Animals receiving SnCl₂ at 10,000 mg /kg diet showed loss of appetite, retarded growth and abdominal distension within 7 days; autopsy after 9 weeks showed distension of the intestines, severe pancreatic atrophy, testicular degeneration, and histological damage to

liver, and brain. Animals fed SnCl₂ at 3,000 mg/kg diet showed some abdominal distension and loss of appetite and retarded growth during the first 2 weeks. After the second week, appetite returned to normal as did growth. Significantly lower haemoglobin levels were determined between the fourth and ninth week but this returned to control values for female, but not male, animals by the end of the study. Minor histological changes were observed in liver. There were no treatment-effects in rats fed SnCl₂ at 300 or 1000 mg/kg diet (equivalent to 450-650 mg Sn/kg diet or 22-33 mg Sn/kg body weight) (De Groot et al., 1973).

An additional 90-day study investigated the influence of iron concentration in the diet on the toxicity on inorganic tin. Rats were fed diets containing either 35 or 250 mg iron/kg diet which also contained 0, 50, 150, 500, or 2000 mg Sn/kg diet as SnCl₂. Growth depression, reduced appetite and reduced feed conversion efficiency were observed at the 500 and 2000 mg Sn/kg diets. Distinct signs of anaemia occurred in the 2000 mg Sn/kg diet group, but only a transitory decrease in haemoglobin was seen in rats receiving the 500 mg Sn/kg diet. Pancreatic atrophy and histological changes in the liver, kidneys, spleen, testicles and heart were seen in some animals in the highest tin group. In all instances where effects of dietary tin were determined, the degree of severity was usually more pronounced in animals receiving the lower iron diets (De Groot et al., 1973b as cited by JECFA, 1982).

De Groot et al. (1973) considered that the adverse effects seen in these studies were due to inhibition of iron absorption. However, this only partly explains effects on haemoglobin and it does not at all explain the other effects. For example, the paper describes distinctly improved haemoglobin levels (although they remained low) at 10,000 mg/kg stannous chloride by further enrichment of the test diet with iron but the reduced growth rate was not improved. There may be alternative explanations which were not considered by the authors, e.g. interference with intestinal absorption of other trace elements (as described in Section 2.3) which were only reported some years after this study. Loss of appetite is the earliest sign of zinc depletion in rats. The authors did not consider interaction of Sn with any trace element except iron and made no tissue measurements for zinc or copper.

### 3.1.3 Long-term toxicity and carcinogenicity studies

Available evidence indicates that orally ingested tin salts are not carcinogenic.

In lifetime studies in rats and mice in which SnCl₂ was given in drinking water at dose levels of 0.35 mg Sn/kg body weight per day (mice) and 0.34-0.38 mg Sn/kg body weight per day (rats) there was no evidence of any effect of tin on the survival of the animals, or on the incidence or classification of tumours (Kanisawa and Schroeder, 1967 and 1969; Schroeder et al., 1968).

Treatment of mice for one year from birth (with the mothers being given the appropriate diet or drinking water solution) through weaning and into adulthood with stannous oleate (5000 mg/kg diet) or sodium chlorostannate (5000 or 1000 mg Sn/L in the drinking water) had no effect on the incidences of hepatomas, malignant lymphoma and lung adenoma (Walters and Roe, 1965). Feeding rats diets containing either sodium chlorostannate (5000 mg Sn/diet) or stannous 2-ethylhexoate (4500 mg Sn/kg diet) until 8 weeks of age, and then 2250 mg Sn/kg diet until 80 weeks did not result in any increase in tumours in either group which could be attributed to the treatment (Roe et al., 1965).
Based on long-term feeding studies (105 weeks) with SnCl₂ in the diet at concentrations of 0, 1000 and 2000 mg SnCl₂/kg diet to rats and mice commencing at an age of 6 week, it was concluded that SnCl₂ was not carcinogenic in either species (NTP, 1982; ATSDR, 1992 and 2002; EGVM, 2002).

In a study reviewed by JECFA but not otherwise available (Sinkeldam et al. 1979b) in rats at a high dose (800 mg Sn/kg diet) there were no compound-related effects on tumour site or incidence were observed (JECFA, 1982).

3.1.4 Reproductive and developmental effects

Available evidence indicates that orally ingested tin salts are not teratogenic.

Pregnant rats were administered SnCl₂ by gavage on gestation days 7-12 inclusive at doses of 0, 20, 100, 500 mg/kg body weight; teratogenic effects in the form of protruding tongue of foetus were reported but at unspecified doses (Wu et al., 1990). Stannous and stannic chloride had estimated LD₅₀ of 10 and 20 mg/egg respectively when injected into yolk of 4-day old White Leghorn chicken embryos. No abnormalities of embryonic development were detected (Ridgway and Karnofsky, 1952).

A multi-generation reproduction study in rats with an incorporated developmental toxicity study with dose levels of 0, 200, 400 and 800 mg stannous chloride in the diet revealed transient adverse effects only at specific stages. These were a decrease in body weight gain during lactation, decreased haemoglobin in pups prior to weaning, and microscopic changes in the liver and spleen of pups of the F3b generation at weaning. The iron content in the diet for these pregnant rats was, respectively, 70 and 140 mg/kg feed, greater than the minimal adequate level of iron for adult non-pregnant rats (35 mg/kg feed). At the higher iron content in the feed the effects were less in the suckling pups. This led the investigators to the conclusion that the 70 mg iron/kg feed is a sub-optimal content for pregnant dams. No adverse effects were observed in the dams. Visceral and skeletal examination did not reveal any tin-related teratogenic effects (Sinkeldam et al., 1979a). As the effects in the pups seen in this study were transient and disappeared after the animals were weaned, the NOAEL is 800 mg stannous chloride/kg feed which is equivalent to 40 mg/kg body weight.

3.1.5 Genotoxicity

A non-standard in vitro mutagenicity test was carried out with the aim of studying the role of DNA repair genes in the repair of SnCl₂-induced damage in Escherichia coli (Cabral et al., 1998). The results showed that the product of the x th a gene, exonuclease III, was required for the repair of DNA lesions induced by SnCl₂, most of which were gene mutations of base substitution type. Cytogenetic studies gave positive responses with SnCl₂ for chromosomal aberrations and sister chromatid exchanges (SCEs) in Chinese hamster ovary (CHO) cells with or without metabolic activation (Gulati et al., 1989; ATSDR, 1992 and 2002). SnCl₂ was also able to induce chromosomal aberrations in cultured human peripheral lymphocytes (Ganguly et al., 1992). SnCl₂ produced extensive DNA damage, detected as single strand breaks by alkaline sucrose gradient analysis in Chinese hamster cells (McLean et al., 1983). Tin (II) produced about 200 times more DNA damage, on equimolar basis, than did Cr (IV). SnCl₄ did not produce such damage. DNA damage was also induced by SnCl₂ in plasmid DNA (De Mattos et al., 2000) as well as in the K562 cell line, resistant to reactive oxygen species (ROS) (Dantas et al., 2002).
SnCl₂ did not induce micronuclei in the bone marrow cells when given by intraperitoneal injections to mice at 0, 26.3, 52.5, 105 or 210 mg/kg body weight/day for 3 days (Shelby et al., 1993). Similarly, SnF₂ was unable to induce micronuclei in bone marrow cells of mice at the intraperitoneal doses of 0, 9.8, 19.6 or 39.5 mg/kg body weight given 24 hours apart (Gocke et al., 1981).

Based on the presently available data, SnCl₂ appears to be an in vitro genotoxic agent, able to induce gene mutations in bacterial cells, chromosome aberrations, sister chromatid exchanges and single strand breaks (SSBs) in mammalian cells. SnCl₂, as well as SnF₂, were unable to induce micronuclei in bone marrow cells of mice treated in vivo. Overall, there is a limited evidence of genotoxicity for soluble tin salts, likely due to generation of reactive oxygen species.

3.1.6 Studies on calcium metabolism

In a study in which groups of male weanling Wistar rats were given drinking water containing 0, 50, 150, 300, or 600 mg SnCl₂ per litre for a period of 28 days together with a diet which contained 52.4 mg Sn/kg diet, the compressive strength of the distal epiphysis was significantly reduced in the groups receiving 300 and 600 mg SnCl₂/litre. The NOAEL for this study calculated from the intake via drinking water and the amount which was present in the diet corresponds to 17.5 mg/kg body weight SnCl₂ (Ogoshi et al., 1981). Daily oral dosage of male Wistar rats with SnCl₂ at a dose level of 1.0 mg Sn²⁺/kg body weight twice daily for 28 or 90 days reduced the calcium content of the femoral epiphysis, but without significantly altering serum calcium, intestinal calcium uptake or calcium excretion (Yamaguchi and Okada, 1980; Yamaguchi et al., 1982). In a 90-day study, the effects on weanling Wistar rats of SnCl₂ in the diet at 0, 10, 50, 100 and 250 mg Sn/kg diet were investigated. At the 50 mg Sn/kg level (equivalent to 2.5 mg Sn/kg body weight) and above there were significant reductions of the calcium content of serum and the femoral epiphysis (Yamaguchi et al., 1981). The authors suggested that these effects could be due to a systemic effect of absorbed tin; however, they did not consider the possible involvement of trace element depletion in these effects.

3.1.7 In vitro toxicity

Stannous and stannic oxides were not cytotoxic to fibroblasts cultivated from human gingival tissue (Hanawa et al., 1992).

3.2 Human toxicity data

3.2.1 Acute and short-term toxicity

Acute gastrointestinal effects such nausea, vomiting and diarrhoea, abdominal pain and sickness have been reported in humans from the ingestion of tin dissolved from internal surfaces of tin cans or saucepans since the late 19th century (Sedgwick, 1988; Luff and Metcalfe, 1890; Davidson, 1927; Savage, 1939).

Illness was reported in a group of 38 women who attended a banquet, of whom 37 completed a questionnaire and 31 reported symptoms. The symptoms included nausea (96.7%), abdominal cramps (86.7%), vomiting (70.0%), headache (56.7%), chills (36.7%) and diarrhoea (33.3%). The onset of symptoms was within 2 hours of the meal and they were
reported to have persisted for 2-48 hours. Tests on food items did not reveal any pathogenic bacteria. The response data implicated a vodka punch as the causative agent, and analysis revealed that it contained 2000 mg tin/L; tests for copper, zinc and cadmium were negative. The punch had a pH of approximately 3 and had been stored in a re-tinned 5-gallon milk churn in which there were signs of corrosion (Warburton et al., 1962).

Benoy et al. (1971) cited an unpublished report of the Metal Box Co. Ltd (1967) as recording that nausea, vomiting and diarrhoea were observed in a large, unspecified number of persons in Kuwait who had consumed formulated orange juice and apple juice containing 250-385 mg tin/kg. Omori and colleagues (1973) report several outbreaks of poisoning with limited data in Japan associated with canned orange juice; the main symptoms were nausea, vomiting, diarrhea, fever and headache. The toxicity was attributed to tin on the basis of exclusion of microbiological contamination and the detection of 425 mg tin/kg in a toxicity-associated sample compared with concentrations ranging from 84-337 mg tin/kg in other purchased samples. Other published case reports of toxicity associated with canned orange or tomato drinks containing tin in concentrations ranging from 100 to 494 mg/kg were reviewed by JECFA (JECFA, 1982; Omori, 1966a and b; Horio et al., 1967a and b; EGVM, 2002). In well-documented cases severe abdominal bloating, vomiting, diarrhea, and headache were noted after the consumption of canned tomato juice with tin levels ranging from 141 to 405 mg tin/kg; the mean concentrations ranged from 245 to 363 mg tin/kg in the various lots implicated as the cause of the intoxication. The cans were visibly de-tinned, an effect which was attributed to unusually high nitrate levels on the tomatoes used to prepare the juice (Barker and Runte, 1972).

In an early study that Schryver (1909) performed on himself, he ingested sodium tin tartrate for a period of 3 weeks at total daily doses of approximately 1, 2 and 3 mg Sn/kg body weight in successive weeks, no symptoms were reported. Analyses of faecal and urinary total nitrogen, and urinary ammonia, urea and uric acid were reported as indicating that no disturbance of metabolism had occurred (EGVM, 2002).

Five volunteers were given orange juice containing tin at concentrations of 0-1400 mg/kg on various occasions. The volunteers were unaware of the nature of the test substance. All experienced either nausea (3 individuals), diarrhoea (1 individual) or both (1 individual) when they first drank the juice containing 1400 mg tin/kg, which corresponded to a dose of tin of 4.4-6.7 mg/kg body weight; administration 1 month later resulted in only one case of nausea (Benoy et al., 1971).

Solomons et al. (1983) reported noxious gastrointestinal symptoms (nausea, cramps and loose stools) in 4 subjects given a single dose of 100 mg Sn as stannous chloride together with 12.5 mg zinc (as zinc sulphate) in 100 mL soft drink. Symptoms were not observed when single doses of 25 or 50 mg Sn were given.

A limited number of case-reports of acute gastrointestinal disorders after consumption of food containing 100-500 mg tin/kg have been reported. Controlled clinical studies on acute effects of tin migrated from packaging suggest a threshold concentration for adverse effects of >730 mg/kg. Two separate randomised, single-centre, double-blind, cross-over investigations of the tolerability of tin added as stannous chloride at concentrations of <0.5, 161, 264 and 529 mg tin/kg in 250 mL juice in 20 volunteers (study 1) and tin migrated from packaging at concentrations of <0.5, 201 and 267 mg tin/kg in 250 mL tomato soup in 24 volunteers (study 2) were carried out. A clear dose-response relationship was only observed when tin was added
as stannous chloride in tomato juice (study 1). No clinically significant adverse effects were reported in study 2 and comparison of the incidence of tin-related adverse effects showed no difference between the dose levels (including control). Studies on the distribution of low molecular weight (<1000 Da) tin species in the beverage showed that the chemical form of tin, and not the elemental concentration per se, determined the severity of the adverse effects in the gastrointestinal tract. Tin species of low molecular weight in supernatant represented 31-32% of total tin in canned tomato soup versus 56-61% in juice freshly spiked with stannous chloride. The differences in the incidence of adverse effects following administration of tomato juice with 161 and 264 mg of tin per kg and tomato soup with 201 and 267 mg of tin per kg probably resulted from differences in the concentration of low molecular weight tin species and in the nature of tin complexes formed. According to the investigators the results of this work demonstrated that tin concentrations up to 267 mg/kg in canned food cause no adverse effects in healthy adults (Boogaard et al., 2003). Regulatory limits of 200 mg/kg for the concentration of tin in canned foods and 100 mg/kg in canned beverages have been established to protect against the occurrence of episodes of acute human poisoning by tin (EC, 2004).

A few short-term human studies indicate that high intakes of tin (30-50 mg tin/day) may reduce the absorption of e.g. zinc (Johnson et al., 1982; Valberg and Chamberlain, 1984), while no effect was seen in one (Solomons et al., 1983). The long-term effects on zinc status and effects on other minerals are, however, not known.

### 3.2.2 Long-term toxicity and carcinogenicity

No carcinogenic effects of orally ingested inorganic tin in humans have been reported. Stannosis, a benign pneumoconiosis consequent of prolonged industrial exposure to tin oxide dusts, has been described from several countries (Barnes and Stoner, 1959; Bartak et al., 1948; Pendergrass and Pryde, 1948; Robertson et al., 1961).

### 4. DOSE-RESPONSE ASSESSMENT

#### 4.1 Gastrointestinal acute effects

Acute toxicity of stannous compounds results from irritation of the mucosa of the gastrointestinal tract. Vomiting and diarrhoea were reported in cats given soluble salts of tin, but there was no clear dose-relationship, and the vehicles in which the tin was administered may have affected its toxicity.

Episodes of human poisoning resulting from the consumption of foods and drinks contaminated with tin have resulted in abdominal distension and pain, vomiting, diarrhoea, and headache. These symptoms commonly start within 0.5-3 hours, and recovery occurs within 48 hours. The doses of tin ingested in such episodes of poisoning were generally not estimated. In one study five volunteers experienced symptoms when they ingested juice containing 1400 mg Sn/kg. Administration of the same dose to these individuals one month later resulted in symptoms in only one person. In another human study with in total 44 volunteers the lowest dose of SnCl₂ in canned beverage (tomato juice) without acute gastrointestinal effects was 200 mg tin/kg. In an experimental study Solomons et al. (1983) reported adverse gastrointestinal symptoms (nausea, cramps and loose stools) in 4 adults given a single dose of 100 mg Sn as stannous chloride together with 12.5 mg zinc (as zinc
sulphate) in 100 mL soft drink. Symptoms were not observed when single doses of 25 or 50 mg Sn were given. The balance of evidence suggests that the concentration of tin in contaminated foods is critical to the development of acute gastrointestinal effects, and that tin concentrations of 250 mg/kg in canned foods and 150 mg/kg in canned beverages are more likely to be associated with this (SCF, 2001).

4.2 Inhibition of trace element absorption

There is evidence of reduced status of iron, zinc and copper when rats are fed diets containing 50 mg Sn/kg diet or greater. This appears to be due to reduced absorption of trace elements, particularly zinc, but also iron and copper, as a result of formation of insoluble complexes (probably with phosphates) in the gastrointestinal tract. Such effects probably explain growth depression, loss of appetite and reduced feed conversion efficiency observed in rats at doses of stannous chloride greater than 150 mg Sn/kg diet. It is likely that other effects of tin e.g. pancreatic atrophy at a dose level of 2000 mg tin/kg diet or reduced compressive bone strength at a dose level above 50 mg Sn/kg diet are not systemic effects of absorbed tin but manifestations of deficiency of one or more trace elements.

In human adults a diet containing 50 mg tin/day (compared to 0.1 mg/day) reduced apparent absorption of dietary zinc by 16% but had no effect on absorption of copper, iron, manganese or magnesium, while inclusion of 36 mg tin as stannous chloride reduced the absorption of zinc from a test meal by 29%.

4.3 Systemic toxicity

There are no data on systemic toxicity of orally ingested tin salts in humans. Orally ingested inorganic tin compounds generally have low systemic toxicity in animals because of limited absorption from the gastrointestinal tract, limited accumulation, and rapid excretion, primarily in the faeces. Because soluble tin salts can cause depletion of essential trace elements, particularly zinc, copper and iron, as a result of gastrointestinal interactions, it is difficult to distinguish between the effects of such nutritional deficiencies and possible systemic effects of absorbed tin. Given the very low absorption of tin it is likely that adverse effects which occur at levels of 50 mg Sn/kg diet e.g. reduced bone compressive strength at 50 mg tin/kg diet or pancreatic atrophy at a dose level of 2000 mg tin/kg diet, are not systemic effects of absorbed tin but rather manifestations of deficiency of one or more trace elements.

Available evidence indicates that orally ingested tin salts are neither carcinogenic nor teratogenic.

Based on the results of in vitro and in vivo tests, the evidence of genotoxic activity of soluble tin salts is considered limited.

4.4 Conclusions

The absorption of inorganic compounds of tin from the gastrointestinal tract in humans and animals is very low with as much as 98% being excreted directly in the faeces. Because of their limited absorption, orally ingested inorganic tin compounds have low systemic toxicity in man and animals.
In man and animals, gastrointestinal effects are the main acute manifestation of toxicity associated with ingestion of tin. These are caused by the irritant action of soluble inorganic tin compounds on the mucosa of the gastrointestinal tract. The balance of evidence suggests that the concentration of tin in contaminated foods is critical to the development of acute gastrointestinal effects, and that tin concentrations above 250 mg/kg in canned foods and 150 mg/kg in canned beverages are more likely to be associated with this. The regulatory limits of 200 mg/kg for the concentration of tin in canned foods and 100 mg/kg in canned beverages have been established to protect against the occurrence of episodes of acute human poisoning by tin (EC, 2004).

In rats, growth depression, loss of appetite and reduced feed conversion efficiency are observed at doses of stannous chloride greater than 150 mg Sn/kg diet. This appears to be due to reduced absorption and status of trace elements, particularly zinc, but also iron and copper, as a result of formation of insoluble complexes (probably with phosphates) in the gastrointestinal tract. There is evidence of reduced status of iron, zinc and copper when rats are fed diets containing 50 mg Sn/kg diet or greater. It is likely that other effects which occur at this or higher dietary levels of tin e.g. reduced calcium content of bone (femoral epiphysis) at 50 mg Sn/kg diet or pancreatic atrophy at 2000 mg tin/kg diet, are not systemic effects of absorbed tin but rather manifestations of deficiency of one or more trace elements.

In short term studies in human adults a diet containing 50 mg tin/day (compared to 0.1 mg/day) reduced apparent absorption of dietary zinc by 16% but had no effect on absorption of copper, iron, manganese or magnesium, while inclusion of 36 mg tin as stannous chloride reduced the absorption of zinc from a test meal by 29%.

CONCLUSIONS AND RECOMMENDATIONS

1. DERIVATION OF A TOLERABLE UPPER INTAKE LEVEL (UL)

The Panel considered that the available data from human or animal studies are insufficient to derive a tolerable upper intake level for tin.

2. RISK CHARACTERISATION

Occasional high intakes of tin are associated with high consumption of canned foods, and regulatory limits of tin content in canned foods (200 mg/kg) and beverages (100 mg/kg) have been established to protect against possible local acute effects on the gastrointestinal tract.

Short-term human studies indicate that high intakes of tin (about 30-50 mg tin/day or per meal) may reduce the absorption of zinc, but not other minerals such as iron, copper, manganese or magnesium. However, the possible long-term effects, if any, of such intake levels on status of zinc or other minerals have not been investigated.

The current mean daily intake of tin in EU countries (e.g. ranging up to about 6 mg/day in the UK) appears to be well below the lowest intakes reported to cause adverse effects on zinc absorption.
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PANEL MEMBERS


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