Risk Assessment Tin

General information

Chemistry

Tin is a metallic element. It is rarely found as the metallic element in nature and is usually found combined with other substances, most commonly as the dioxide (SnO_2). It has oxidation states of II and IV and the corresponding oxides of these states are amphoteric. Organotin compounds can be synthesised and are highly toxic, but these are not found in food, beverages or food supplements. Within this risk assessment, the word tin refers to ionic tin, except where specific tin compounds are mentioned.

Natural occurrence

The occurrence of tin in various organisms from different localities is highly dependent on the existence of local mineral sources of tin. Although not commonly present in fresh water, it occurs at a concentration of about 0.003 mg/kg in seawater.

Occurrence in food, food supplements and medicines.

The presence of tin in fresh food of both vegetable and animal origin is highly dependent on the concentration of tin in the soil of the area in which the food is produced. Canning may result in dissolution of the tin lining of the can, particularly if the products are acidic. The regulatory limit for total tin in canned products is 200 mg/kg. The major dietary sources of tin are fruit products and canned vegetables. Stannous chloride, $SnCl_2$, is a permitted food additive (E512). Tin is present in some multivitamin and mineral food supplements at levels of up to 0.01 mg in the daily dose recommended by the manufacturer.

No medicinal products containing tin have been licensed.

Other sources of exposure

Trace quantities of tin are detectable in the air, the concentrations in any area depending on the extent of industrial activity. Water and airborne tin provide only minimal exposure for humans.

Recommended amounts

There are no recommended daily intakes for tin compounds since it has not been proven to be an essential element.

Analysis of tissue levels and tin status

Tin levels can be measured by spark source mass spectrometry, radioactivation analysis or x-ray fluorescence analysis. Tin concentrations in fluids, tissues, or organs of the human body have been measured. There is no measurement used to indicate tin status.

Brief overview of non-nutritional beneficial effects

Tin is present in some dietary supplements and has been claimed to delay hair loss, male pattern baldness and hearing loss.

Function

There is no proven biological function for tin. It has been suggested that, because of its coordination chemistry, it may contribute to macromolecular structure and function at the active site of metalloenzymes.

Deficiency

Naturally occurring deficiency of tin in free-living humans or animal species has not been demonstrated. Experiments on induced deficiency of experimental animals in isolators have been criticised and other evidence claimed to support the hypothesis that tin is an essential element is not convincing.

Interactions

In humans, ingestion of tin has been shown to lower net retention of zinc. It can also alter the excretion of selenium in faeces and urine, but without affecting the overall balance. In rats the absorption of copper has been reported to be decreased by ingestion of tin.

Absorption and bioavailability

The gastrointestinal absorption of tin is low. The solubility and bioavailability of inorganic tin compounds varies and is dependent on the oxidation state.

Distribution and metabolism

The tissues and organs that accumulate the highest concentrations of tin are bone, lymph nodes, liver, lung, ovary, testis and kidney. No metabolism of tin has been demonstrated.

Excretion

The majority of ingested inorganic tin is excreted in the faeces (about 95-99% of ingested dose in animal studies), with the remainder in the urine.

Toxicity

Human data

Reports of acute poisoning have been associated with high concentrations of tin in drinks or solid foods. Subjects presented with gastrointestinal effects (abdominal cramps, nausea, vomiting, diarrhoea), and headache and chills within 1-2 hours of consuming the implicated foodstuff, and recovered within 1-2 days. However, there is little consistency in the reports in terms of the nature of the foodstuff, or the concentration and chemical form of the tin, all of which may influence human toxicity.

Animal data.

In studies of the acute oral administration of tin to animals, cats have shown a vomiting response, similar to that of humans.

Most studies of the subchronic toxicity of tin have been carried out in rats, a species which lacks an emetic reflex. Reduction in body weight gain, reduced appetite and reduced feed conversion efficiency have been reported. These, together with abdominal distension and at autopsy, distended caeca, reddening of the mucosal surface of the stomach and histopathologic changes in the gastrointestinal tract (from the stomach to the ileum), are indicative of gastrointestinal effects in the rat. Haematological changes included reduced haematocrit and haemoglobin, which are indicative of anaemia, although no biologically significant changes to leucocytes occurred. These effects may result from disturbance to the pathways of haem biosynthesis and degradation, as tin reduces the activity of the enzyme 5 aminolaevulinate dehydratase and increases haem oxidase.

Pathological changes to the pancreas, including atrophy with single-cell necrosis and destruction of complete acini, have been suggested as being characteristic of tin toxicity. Pathological changes to the liver, spleen, kidneys, adrenals and testicles have also been reported. Various authors have investigated the effects of tin, given orally or parenterally, on calcium balance and bone metabolism in experimental animals. Some changes were detected at low doses of tin. The results of reproductive and developmental toxicity studies were negative.

The available data on chronic administration of tin are limited and it is difficult to draw conclusions due to adverse effects being observed in all groups (including controls). However, the available data indicate that doses of up to 100 mg/kg bw/day as stannous chloride are well-tolerated and do not affect survival.

Carcinogenicity and genotoxicity

Various tin compounds were not carcinogenic in long-term studies in animals. The conformation of DNA is disrupted by *in vitro* exposure to stannous chloride, but it has been suggested that this is a result of the generation of reactive oxygen species under the conditions used. Mutagenicity studies on tin have not been identified.

Mechanism of toxicity

No relevant data have been identified.

Dose-response characterisation

There are no data on which to determine a threshold of intake at which adverse gastrointestinal effects will not occur in humans.

Vulnerable groups

No vulnerable groups have been identified.

Genetic variation

No genetic variations in the susceptibility to tin have been identified.

Studies of particular importance in the risk assessment

(For full review see http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers or the enclosed CD).

De Groot et al., 1973

Groups of 10 male and 10 female weanling Wistar-derived rats were administered diets containing either stannous oxide or stannous chloride for 90 days, at concentrations of 0, 300, 1000, 3000 and 10,000 mg/kg of diet. There were no toxic effects of stannous oxide at any dose. Animals receiving the 10,000 mg/kg stannous chloride diet showed effects within the first 7 days, including abdominal distension and loss of appetite. This particular group was terminated in the ninth week because of a high rate of mortality. Upon autopsy, various gross pathological conditions were found, including distension of the intestines, small oedematous pancreases and greyish-brown livers. Histopathological evaluations revealed moderate testicular degeneration, severe pancreatic atrophy, a spongy state of the white matter of the brain, acute bronchopneumonia, enteritis and distinct liver changes (atypical homogenous liver cell cytoplasm and mild proliferation of bile duct epithelium). In view of the marked reduction in appetite in the 10,000 mg/kg group, it is difficult to assess the extent to which tin was responsible for the observed pathological changes. Animals fed the 3000 mg/kg diet showed some abdominal distension and loss of appetite during the first 2 weeks of the 90-day study. After the second week, appetite and growth returned to normal. Significantly lower haemoglobin levels were detected in both sexes between the fourth and ninth week. However, by the end of the study only males on the 3000 mg/kg stannous chloride diet had lower ($p < 0.05$) haemoglobin and haematocrit values.

Autopsy and histological evaluations of the 3000 mg/kg group showed only minor treatment-related changes in some of the animals of both sexes (e.g., atypical homogenous cytoplasm of the hepatocytes and bile duct epithelial proliferation). There were no treatment-related effects in rats fed the 300 or 1000 mg/kg stannous chloride diets. Leucocyte total and differential counts of blood taken at autopsy were unaffected, as were the serum activities of glutamate-oxaloacetate and glutamate-pyruvate transaminases. At termination, there was a dose-related decrease in the activity of serum alkaline phosphatase in both male and female rats. However, this achieved statistical significance only at the 3000 mg/kg dietary concentration of stannous chloride. The authors indicated that unpublished pair feeding experiments suggest that the growth depression observed in some of the tin feeding

experiments cannot be explained by a lack of palatability of the diet. In addition, on the basis of other studies involving iron supplementation and deficiency, the authors suggested that the toxicity of cationic tin compounds is inversely dependent on the iron content of the diet. The authors suggested that the tin compounds that cause adverse effects *in vivo* had no-effect levels corresponding to 1000 mg/kg of stannous chloride in the diet, which is equivalent to 450-650 mg/kg of tin, providing an intake in the range of 22-33 mg tin/kg bw per day.

Dreef-van der Meulen et al., 1974

Male and female Wistar-derived rats were fed dietary concentrations of stannous chloride dihydrate increasing by weekly increments from 1000 mg/kg in the first week to 8000 mg/kg in weeks 8 to 13. Body weight in the male animals was significantly reduced at the end of this period. Haemoglobin concentration and haematocrits were reduced compared to controls in males and females. Reduced serum alkaline phosphatase activity was recorded in female rats. Autopsy revealed pancreatic atrophy as well as changes to the gastrointestinal tract. Histological studies confirmed these observations, with severity of pancreatic changes ranging from necrosis of individual acinar cells to complete destruction of the pancreas. In addition, changes in the kidney and thyroid were observed. The authors considered the pancreatic atrophy to be the most specific manifestation of the toxicity of tin. Effects on the pancreas were observed in this study, which utilised an increasing concentration of tin in the diet, from 1000 mg/kg up to a final dose of 8000 mg/kg (equivalent to 310 mg/kg bw/day).

Fritsch et al., 1978

In a study of 6 months duration, groups of 10 male Sprague-Dawley CD rats were administered diets containing 0 (control), 4000, or 8000 mg tin/kg of diet as stannous chloride. Groups of five rats were treated in the same manner to provide control and treated animals for histological studies. Body weights were recorded twice weekly and in the 8th, 16th and 24th weeks the consumption of diet was measured. It is noted that all the treated animals exhibited a fatty degeneration, with lymphocytic infiltration and atrophy of the exocrine tissue of the pancreas. The kidneys and adrenal medulla were oedematous and there was karyolysis in the adrenal cortex. In the gastrointestinal tract there were generalised signs of irritation, with oedema and excessive mucus in the fundal and pyloric regions of the stomach. There was congestion in the jejunum and oedema with lymphocytic infiltration in the caecum. Effects on the pancreas were observed at 4000 mg/kg of tin in the diet (equivalent to 240 mg/kg bw/day).

Exposure assessment

Total exposure/intake:

Food	Mean: 1.8 mg/day in adults. 97.5th percentile: 6.3 mg/day (TDS, 1994)
Supplements	0.01 mg/day (Annex 4; OTC, 2001)
Estimated maximum intake:	6.3 + 0.01 = 6.31 mg/day

No potential high intake groups were identified.

Risk assessment

Gastrointestinal effects are the main manifestation of toxicity associated with ingestion of foods or drinks contaminated with tin. These are caused by the irritant action of soluble inorganic tin compounds. Recovery from the effects is rapid.

Some subchronic feeding studies have resulted in haematological changes in rats. Other reports of other chronic carcinogenicity studies and one multigeneration reproduction study have either not recorded any such effects, or have noted that the observed changes were transient. Pancreatic atrophy has also been observed in subchronic studies in rats.

ESTABLISHMENT OF GUIDANCE LEVEL

There is no convincing evidence to suggest that tin is an essential element and it should be noted that tin in food is generally considered to be a contaminant.

There are insufficient data from human or animal studies to establish a safe upper level for tin. Nausea and vomiting have been reported following ingestion of food contaminated with tin. However, the balance of evidence suggests that the concentration of tin in contaminated foodstuff is critical to the development of acute gastrointestinal effects, and that tin concentrations above 200 mg/kg foodstuff are more likely to be associated with this. The regulatory limit of 200 mg/kg for the concentration of tin in foodstuffs therefore provides protection against the occurrence of episodes of acute human poisoning by tin. No groups vulnerable to this form of toxicity are known to exist.

For guidance purposes it should be noted that subchronic toxicity studies in rats indicate that pancreatic atrophy occurs at doses of about 240 mg tin/kg bw/day (Fritsch *et al.*, 1978). In addition, changes to liver cells and anaemia have been observed in a study in which a NOAEL of 22-33 mg tin/kg bw/day can be derived (de Groot *et al.*, 1973). Applying uncertainty factors of 10 for inter-species variation and 10 for inter-individual variability to this NOAEL, gives a daily intake of about 0.2-0.3 mg tin/kg bw/day. The lower end of this range 0.22 mg/kg bw/day, has been used for guidance purposes only and would be expected not to produce adverse effects in humans. This is equivalent to 13 mg tin/day in a 60 kg adult

Current maximum dietary intakes are estimated at 6.3 mg/day.

References

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