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CODEX COMMITTEE ON FOOD ADDITIVES AND CONTAMINANTS
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DISCUSSION PAPER ON TIN

Governments and international organizations wishing to submit comments on the following subject matter are invited to do so **no later than 15 December 2002** as follows: Netherlands Codex Contact Point, Ministry of Agriculture, Nature Management and Fisheries, P.O. Box 20401, 2500 E.K., The Hague, The Netherlands (Telefax: +31.70.378.6141; E-mail: info@codexalimentarius.nl, with a copy to the Secretary, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme, FAO, Viale delle Terme di Caracalla, 00100 Rome, Italy (Telefax: +39.06.5705.4593; E-mail: Codex@fao.org).

INTRODUCTION

1. This paper was originally prepared by the delegations of Australia, Indonesia and Thailand for consideration at the 29th Session of CCFAC (ALINORM 97/12A, paras. 78-80). Following discussion at the 29th CCFAC and subsequent circulation for comments (CL 1997/6-FAC), the paper was revised for consultation at the 30th Session.

2. The 31st Session (March 1999) of the Codex Committee on Food Additives and Contaminants advanced the proposed draft maximum levels for tin (200 mg/kg in liquid canned foods, 250 mg/kg in solid canned foods) to the Commission for adoption at Step 5[1].

3. The 23rd session (July 1999) of the Codex Alimentarius Commission (CAC) decided to hold the proposed draft maximum levels at Step 5 pending the re-evaluation of the acute toxicity of tin by the Joint FAO/WHO Expert Committee on Food Additives (JECFA)[2].

4. The 55th Meeting of JECFA was held in Geneva, Switzerland, from 6 to 15 June 2000. In regard to tin, JECFA recommended that the provisional tolerable weekly intake (PTWI) of 14 mg/kg bw be maintained. JECFA assessed the acute toxicity of tin, but data were insufficient for establishing an acute reference dose. It reiterated the conclusion that it reached at its 33rd meeting (WHO Technical Report Series No. 776, 1989) that the limited human data available indicate that concentrations of 150 mg/kg in canned beverages and 250 mg/kg in other canned foods may produce acute manifestations of gastric irritation in certain individuals[3].

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[1] ALINORM 99/12A, para 131 and Appendix IX

[2] ALINORM 99/37, paras. 185-186

[3] Report of the 55th Meeting of JECFA, June 2000, WHO Technical Report Series 901, WHO Geneva.

5.   In consideration that the 55th JECFA had considered the toxicology and acute reference doses of tin, the 33rd Session (March 2001) of CCFAC agreed that the proposed draft levels for tin be re-examined at its next session[4].

6.   The 34th Session of CCFAC (March 2002) agreed that a drafting group, lead by Australia, would rewrite the Position Paper on Tin and report to the next session.

Occurrence

7.   Tin occurs in the earth's crust at an average abundance of 2 mg/kg and is concentrated in areas of tin bearing minerals. Tin is widely distributed in nature and has an average abundance in river water of 0.04 µg/l and 10 mg/kg in soil. Sewage sludge may contain 40-700 mg of tin/kg dry weight, therefore its use as fertiliser may increase tin concentrations in the soil in some areas (WHO, 1980).

8.   Although tin is present in sea water in concentrations of up to 3 µg/l there are few reports of its occurrence in marine plants and animals. Concentrations in marine and terrestrial plants and animals are low. There is limited and conflicting evidence for the uptake of tin by crops. Some reports suggest that soil concentrations do not markedly influence its uptake while others conclude that the considerable variation between areas reflects local soil concentrations (WHO, 1980).

9.   The combustion of fossil fuels releases tin into the air. Excluding sites of industrial emissions, ambient tin levels in air are generally less than 0.3 µg/m^3 (WHO, 1980).

Uses

10. Tin has been used since ancient times and has been highly valued for its ability to form alloys. Tin was used extensively in cooking and storage vessels and eating implements prior to the development of tinplate. Thus humans have been eating food that has been in contact with tin and probably absorbed some of the metal for many hundreds of years.

11. More than 50 percent of the world's production of tin is used for plating steel and other metals. Tin is used to cover the inside of food and beverage containers, cooking and food processing equipment, in the manufacture of engineering and electrical components and for other industrial applications where corrosion resistance is important.

12. The chemical industry uses about 5 percent of total tin production. Uses include the manufacture of glass, dyeing and printing of textiles and as a reducing agent in certain chemical processes. Tin is a constituent in products such as toothpaste and special alloys containing tin include dental amalgams, which are mainly silver-tin-mercury alloys.

Sources of Exposure

13. Drinking water is not a significant source of tin. Tin occurs occasionally in municipal water supplies, possibly released from bronze fittings.

14. Food, especially canned food, represents the major route of human exposure to tin. Tin occurs in most foods, however, levels are generally less than 1 ppm in unprocessed foods (Schroeder et al, 1964; Schafer and Fembert, 1984). Higher concentrations of tin are found in canned foods from dissolution of the tinplate to form inorganic tin compounds or complexes (Schafer and Fembert, 1984). The concentration of tin in canned foods depends on a number of factors, including, the type and acidity of the food, time and temperature of storage and the presence of air in the can headspace (Greger, 1987). Oxidising agents such as nitrates, iron and copper salts accelerate dissolution of tin, while sugars and colloids such as gelatine retard detinning.

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[4] ALINORM 01/12A, para. 112

15. Cans are often lacquered to reduce corrosion and prevent detinning. Tin concentrations in foodstuffs in unlacquered cans often exceed 100 ppm while food stored in lacquered cans have tin levels generally below 25 ppm (Jorhem and Slorach, 1987; WHO 1989). Storing food in opened unlacquered cans results in substantial increases in the tin levels in the food.

TOXICOLOGICAL REVIEW

Summary

16. The toxicological effects of oral ingestion of inorganic tin compounds have been studied in animals and humans. However, the toxicological evaluation of these studies were complicated by the fact that only limited data is available on the chemical forms present in food following dissolution of the tin coating from cans, and that the toxicological data base for compounds other than stannous chloride is poor.

17. The main hazard from ingestion of tin would appear to be from an acute exposure to high levels. Available human poisoning cases suggest a threshold acute dose of 200 ppm (5 mg tin/kg bw/day[5] in 60 kg adults based on consumption of 1.5 kg of food), but some individuals can tolerate up to 700 ppm (18 mg/kg bw/day). However, the chemical form of tin is unknown from these case reports, and as such toxicity would vary depending on the specific chemical form.

18. The toxicity of tin has been reviewed by the Joint Expert Committee on Food Additives (JECFA) (WHO; 1982, 1989 and 2000) and by the International Program on Chemical Safety (IPCS, WHO, 1980). The US Department of Health and Human Services (USDHHS) reviewed the toxicology of tin in 1992. An overview of the key toxicological findings from these reports and key research papers discussing tin toxicity are presented below.

JECFA

19. At the 26th meeting in 1982 JECFA determined that gastric irritation was the main problem associated with excessive levels of tin in foods, and that the threshold for this effect was about 200 ppm in food. The Committee allocated a provisional maximum tolerable daily intake (PMTDI) for tin of 2 mg/kg bw (WHO, 1982). However, it is unclear on what toxicological endpoint (acute or chronic) this PMTDI was based or what safety factors JECFA used to calculate the PMTDI, although it is assumed to be based on acute effects.

20. At the 33rd JECFA meeting in 1989 the Committee reaffirmed the previously established tolerable daily intake, but converted it to a Provisional Tolerable Weekly Intake (PTWI) of 14 mg/kg bw and indicated that this value was applicable to chronic tin exposure.

21. The Committee recommended that efforts be made to keep tin levels in canned foods as low as practicable and consistent with GMP. Previous case reports determined that tin concentrations as low as 150 ppm in canned beverages and 250 ppm in other canned foods may produce acute gastric irritation in certain individuals. However, it was noted that in some canned products containing levels of up to 700 ppm there were no reports of any toxic effects (WHO, 1989).

22. At the 55th JECFA meeting the acute toxicity of tin was assessed, however, it was considered that the data was insufficient to establish an acute reference dose. The Committee reiterated the conclusion that tin concentrations as low as 150 ppm in canned beverages and 250 ppm in other canned foods may produce acute manifestations of gastric irritation in certain individuals (WHO, 2000).

PHYSICAL AND CHEMICAL PROPERTIES

23. Tin is a soft, white, silvery metal that is insoluble in water. Tin metal is used to make cans for food, beverages and aerosols. It is present in brass, bronze, pewter, and some soldering materials.

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[5] A 60kg adult would have to consume 1.5kg of food containing 200ppm of tin to reach 5mg/kg bw/day.

24. Tin is a metal which can combine with other chemicals to form compounds, and when combined with chemicals such as chlorine, sulphur, or oxygen, it is referred to as an inorganic tin compound.

25. Tin can also combine with carbon-containing materials to form organotin compounds. These are used in making plastics, food packages, plastic pipes, pesticides, paints, wood preservatives, and rodent repellents.

Speciation

26. Tin forms two series of compounds, and may be present in the oxidation states of +2 or +4, i.e., the stannous compounds of bivalent tin, and the stannic compounds of quadrivalent tin. The most important inorganic compounds of tin are oxides, chlorides, fluorides and halogenated sodium stannates and stannites. Although little is known of the form in which tin occurs in food, attempts have been made to characterise the chemical form of tin in canned foodstuffs. Total tin in acidic foods can be transformed to many different chemical forms, but mainly remain in the form of inorganic complexes (Winship, 1988). Oxidation, hydrolysis and complex formations are three main processes of transformation of tin in food.

METABOLISM AND KINETICS

27. Tin is poorly absorbed in animals and humans (Hiles, 1974; Furchner and `Drake, 1976; WHO, 1982). In animals after oral administration of ^{113}Sn, approximately 95% or more of the administered radioactivity was recovered in the faeces, with 1% or less in the urine. Various forms of tin compounds were administered: stannous pyrophosphate, stannous fluoride, stannous citrate, and stannic citrate. Absorption appeared to be related to the chemical form of tin, with Sn (II) in rats being four times more readily absorbed than Sn (IV) compounds (Hiles, 1974). In humans the rate of absorption is closely related to levels in ingested food. When a diet containing 49.7 mg tin/day, was given to adult males only 3% was absorbed, whereas when intake was reduced to 0.1 mg/day absorption increased significantly to 50% (Johnson and Greger, 1982).

28. The presence of citric acid in canned foods can increase the rate of absorption of tin. Experiments in rats revealed that in the absence of citric acid 2.85 % of tin was absorbed from the gastrointestinal tract, while in the presence of citric acid 23.34 % of tin was absorbed (Kojima *et al*, 1982).

29. Tin is widely distributed in tissues, especially in bone, liver, kidney and spleen (WHO, 1982). Animals and humans accumulate more tin in the bone than soft tissues (Greger, 1987). The half-life of inorganic tin via the oral route in the bone of mice and rats has been estimated to be between 30 and 40 days (Hiles, 1974). The longest half-life estimated in animal tissues and organs after intravenous or intraperitoneal injection was 90-100 days (WHO, 1980).

30. Tin is mainly excreted in the faeces and to a much lesser extent urine. Several studies in animals and humans have found that greater than 90 percent of the inorganic tin compounds fed to rats were excreted in the faeces (WHO, 1982; Schafer and Fembert, 1984; Fritsch et al, 1977), with additional slow elimination in the urine. In rats following a single oral dose of Sn (II) or Sn (IV) approximately 50% of absorbed tin was excreted within 48 hours, 4-12% in bile in 24 hours and the remainder in the urine (Hiles, 1974).

ACUTE TOXICITY

ANIMAL STUDIES

31. Although inorganic tin compounds have relatively low toxicities, considerable variation exists in acute toxicity between tin compounds (Conine et al, 1975; WHO, 1980; WHO, 1982).

Table 1: Summary Table of Acute Toxicity Studies from WHO, 1982

Compound	Species	Route	LD 50 (mg/kg)	Reference
Sodium tin citrate	Mouse	Oral	2700	Ministry of Health and Welfare, Japan; 1969
Tin-citric acid complex (29.5% tin)	Mouse (M)	Oral	2700	Omari et al, 1973
Stannous chloride	Mouse Rat Rabbit	Oral Oral Oral	250-1200 700-3190 10,000	Pelikan et al, 1968; Calvery, 1942 Connine et al, 1975 Eckardt, 1909
Sodium pentafluoro-stannite (66.8% tin)	Mouse (M) Rat (M) Rat (F) Rat (M)	Oral Oral (fasted) Oral (fasted) Oral (fed)	593 223 219 573	Conine et al, 1975

32. Clinical signs of acute toxicity consist of vomiting, diarrhoea, and brief periods of excitation, apathy, anorexia, ataxia and muscle weakness. Slightly distended small and large intestines were observed at necroscopy of rats fed diets containing stannous chloride; however, there were no histopathological changes.

33. Other studies have found that the lowest oral dose that produced death in rats and mice following a single gavage administration was 473 and 378 mg/kg bw stannous chloride, respectively (NTP 1982). However, all rats and mice survived doses up to 945 and 2,457 mg/kg bw/day stannous chloride respectively when the compound was fed in the diet for 14 days.

Cats and dogs

34. The acute toxicity of orally administered stannous chloride has been also been studied in cats, and dogs. Groups of 11 cats were given single oral doses of stannous chloride in a fruit beverage (equivalent to 2.5-20 mg/kg bw) tin (Cheftel 1967; Benoy *et al*, 1971; WHO, 1982). Vomiting occurred in cats which received a dose equivalent to 5.4 mg or more of tin per kg bw. In another study, cats receiving stannous chloride, by gavage, showed excessive salivation, vomiting and diarrhoea at 9 mg/kg bw. In contrast a study using groups of 4 dogs given single doses of stannous chloride in beverage containing a dose equivalent to 2.5 - 14 mg/kg bw tin, or solid food containing a dose equivalent to 4.5 to 8 mg/kg bw showed no signs of acute toxicity (Benoy *et al*, 1971; WHO, 1982).

HUMAN STUDIES

35. There are no reported cases linking death in humans with oral ingestion of inorganic tin compounds.

36. The WHO (1989) re-examined the available human data on inorganic tin toxicity. The objective was to clarify some of the information presented in the 1982 review and to provide more information if available about the chemical forms of tin which cause gastric disturbances.

37. Various acute poisoning episodes have been reported in the literature. Clinical signs generally consisted of nausea, abdominal cramps and/or vomiting 1-2 h following ingestion, and lasting 2-48 h.

38. Poisoning from a fruit punch containing tin at 2000 ppm was reported in the early 1960s (Warburton *et al*, 1962). Other reports from ingestion of canned orange juice at 425 ppm (Omori *et al*, 1973), apple juice at 250-385 ppm (Benoy *et al*, 1971), and tomato juice ranging from 141-405 ppm (Barker and Runte, 1972) produced clinical signs of acute gastric irritation.

39. Canned foods such as cherries, asparagus, herrings, and apricots have been previously reported as causing gastro-intestinal disturbances but these reports are outdated and lack detail. Poisoning from consumption of other canned foods (salmon, fruit salad, and rhubarb) in which tin levels ranged from 250-650 ppm have been reported (Benoy et al, 1971).

40. In contrast, no toxic effects were observed in several studies in which the juice or food was processed specifically to increase tin concentrations up to 703 ppm. Samples of orange juice obtained from a reported poisoning episode were concentrated to yield a tin level of 498 ppm. Five volunteers showed no toxic effects after drinking a volume which provided 1.59-3.58 mg/kg bw (Benoy *et al*, 1971).

41. Human volunteers were administered fruit juice containing 1.4 g/L tin in amounts corresponding to 5-7 mg/kg bw (Benoy *et al*, 1971; WHO, 1980). Mild signs of toxicity in the form of gastric irritation were reported. Another study using human volunteers given canned juice (pH 3.9) containing 500 mg/L of tin (1.59-2.65 mg/kg bw) failed to show symptoms of acute toxicity (Dack 1955; WHO, 1989).

42. The WHO (1989) concluded that factors other than specific tin levels may potentiate adverse effects and yet others may moderate toxic effects. These considerations however lack detail, and in addition there is considerable lack of knowledge on the precise chemical form of tin which causes the gastric irritation. Due to the individual sensitivities between individuals (whereby concentrations as low as 150 ppm/can cause acute manifestations versus 700 ppm no adverse effects) the Committee recommended that efforts be made to keep tin to as low as reasonably achievable from good manufacturing practices.

43. In summary, the main acute effect from excessive oral consumption of tin compounds in food is acute gastric irritation, with wide variation in sensitivities between individuals. The clinical signs following acute ingestion were vomiting, diarrhoea, fatigue, and headaches.

SHORT-TERM REPEAT-DOSE TOXICITY AND SUBCHRONIC TOXICITY

Animal Studies

44. A key study examined the effects of feeding groups of ten male and female Wistar rats various salts or oxides of tin (stannic oxide, stannous oxide, stannous orthophosphate, oxalate and sulphide, stannous chloride, stannous sulphate, stannous oleate, and stannous tartrate) for a period of 4 or 13 weeks at 0, 300, 1000 or 10,000 ppm in the diet. For the 13 week study only, stannous oxide and stannous chloride were administered in the diet. For the 4 week study, no adverse effects were noted at any concentration of stannous sulphide or oleate, or of stannous or stannic oxides apart from a transient increase in hematocrit in male rats fed the highest dose of tin sulphide. However, severe growth retardation, decreased food efficiency, slight anaemia and slight histological changes in the liver (a typical homogenous liver cell cytoplasm and hyperplasia of the bile ducts) were observed with 3000 ppm or more of stannous chloride, orthophosphate, sulphate, oxalate and tartrate. Similar effects were noted with 3000 ppm stannous chloride in the 13 week study, but not with stannous oxide. An oral NOEL for stannous chloride was 1000 ppm (equivalent to 22-33 mg stannous chloride/kg bw/day for the 4 and 13 week study (deGroot *et al*, 1973). In conclusion, differences in bioavailability may explain the differential toxicities of the various tin compounds.

45. In another 13-week study, male and female rats were fed diets containing 35 or 250 ppm iron and 0, 50, 150, 500 or 2000 ppm stannous chloride. Reduced appetite, growth depression, and reduced food efficiency were observed in both sexes at tin levels of 500 and 2000 ppm. Transient decreases in haemoglobin occurred at 500 ppm, and distinct signs of anaemia at 2000 ppm, the degree of severity being more pronounced in animals receiving low iron diets. An oral NOEL for stannous chloride of 150 ppm equivalent to 7.5 mg/kg bw/day was determined from the effects observed at higher doses (deGroot, 1973). These studies suggested that a tin-iron interaction could occur leading to iron deficiency.

46. The effects of tin in the form of stannous chloride administered at doses of 0, 0.3, 1 or 3 mg tin/kg bw at 12 hourly intervals for 13 weeks in male weanling rats on biochemical parameters was studied. At 1 mg tin/kg bw, significant reductions in liver succinate dehydrogenase activity as well as decreased calcium content and alkaline phosphatase activity in the femoral epiphysis was observed. The relative weight of the femur, calcium concentration in the femur, and lactic dehydrogenase and alkaline phosphatase activity in the serum appeared to be significantly decreased in rats at the highest dose. Based on the 13-week study an NOEL for stannous chloride was estimated to be 0.3 mg/kg bw/day (Yamaguchi *et al*, 1980). In conclusion, the data suggest that there may be a tin: calcium interaction leading to leaching of calcium from the bones at 1 mg/kg bw/day.

Human Studies

47. Although there appears to be considerable controversy in the literature over the levels of tin in foods and beverages that can cause acute toxicity, some short-term studies, albeit few in number, have been conducted on human volunteers.

48. Dack (1955) reported no effects in a study in which 4 subjects ate canned pumpkin containing a tin concentration of about 380-480 ppm and canned asparagus containing about 360 ppm, for 6 days with no apparent adverse effects. The average daily ingestion of tin in this study ranged from 426 to 490 mg/person/day.

49. Nine male adult volunteers weighing between 65 and 83 kg ingested between 116 and 203 mg tin/day (equivalent to 1.6-2.9 mg tin/kg bw) for 23 consecutive days, without displaying any adverse effects (Calloway and McMullen, 1966; WHO, 1982). The chemical form of tin in the administered food in these studies was not stated.

CHRONIC TOXICITY

Animal Studies

50. Groups of mice received sodium chlorostannate in drinking water at a level of 1000 or 5000 ppm (equivalent to a dose of 150 or 750 mg/kg bw/day) or 5000 ppm (equivalent to 750 mg/kg bw/day) stannous oleate in the diet for a 1 year period. No adverse effects were noted (Walters and Roe, 1965).

51. Stannous chloride was added to the drinking water of male and female Long-Evans rats at a level of 5 ppm (equivalent to a dose of 0.25 mg/kg bw/day) over the life span of the animals. At this level no effect on growth rates or increased tumorigenicity was observed, however, longevity of the females was reduced slightly (Schroeder *et al*, 1968). There were no indications of increased tumorigenicity among the tin-exposed animals.

52. Groups of 60 male and female rats (Cpb-Wu, random bred) were maintained on diets containing 0, 200, 400 and 800 ppm (equivalent to 0, 10, 20 and 40 mg/kg bw/day) stannous chloride for 115 weeks. There were no differences in mortality between the various groups. There were no effects on growth or food intake, although food efficiency was decreased at the highest dose. No compound related effects were observed on haematology (apart from a transient decrease in haemoglobin and haematocrit at week 4 and 13), blood chemistry, urinalysis, histopathology (apart from an increase in the relative weight of the spleen), or tumour incidences (Sinkeldam *et al*, 1981).

53. A carcinogenicity bioassay was conducted in groups of 50 male and female F344 rats and B6C3F1 mice fed diets containing 0, 1000 or 2000 ppm stannous chloride (equivalent to 0, 50 and 100 mg/kg bw/day in the rat; and, 0, 150 and 300 mg/kg bw/day in the mice) for 105 weeks. C-cell adenomas of the thyroid in low-dose male rats, lung adenomas in the high-dose male rats, hepatocellular adenomas, carcinomas and histiocytic lymphomas in both low and high-dose female mice were observed. However, the incidences of the tumours relative to the histological controls were similar and not clearly related to administration of stannous chloride. It was concluded that stannous chloride was not carcinogenic for male or female rats or mice under the experimental conditions of the study (NTP, 1982).

54. In summary, from the available animals studies conduced in rats and mice there is no evidence to suggest that inorganic tin compounds have carcinogenic potential.

Human Epidemiology Studies

55. There are no studies available that have examined the long-term effects of tin in humans.

REPRODUCTIVE TOXICITY

56. A multi-generation reproduction study over 3 generations of rats (CPB:WU randomly bred) was performed, whereby, stannous chloride was administered in the diet at 0, 200, 400 or 800 ppm (equivalent to 0, 10, 20 or 40 mg/kg bw/day. Iron was added to the diet at 70 ppm, but for the F2 generation was increased to 140 ppm. There was no effect on fertility of females, number of young born/litter and body weight. Haematological studies showed a marked decrease in haemoglobin in the pups at weaning, however, this returned to normal after weaning. The mortality of the F_2 generation litters during the first 10 days of lactation was higher than controls, but decreased following an increase in iron in the diet (Sinkeldam *et al*, 1979).

57. In a 13-week study in rats, dietary levels ranging from 1.5 to 9.2 mg tin/kg/day as stannous chloride, caused testicular degeneration (De Groot et al, 1973). The significance of the findings was unclear, given that dosing over 3 generations in a reproductive study at doses up to 40 mg/kg bw/day did not reduce fertility parameters. However, it was not specifically stated that testicular degeneration was found in male rats in the multi-generation reproduction study.

58. No studies have been conducted regarding reproductive effects in humans after oral exposure to inorganic tin compounds.

DEVELOPMENTAL TOXICITY

59. Groups of mice, rats and hamsters were orally administered stannous chloride at 0, 0.5, 2.3, 11 or 50 mg/kg bw/day for 10 consecutive days (day 6-15 of gestation in pregnant mice and rats) and for 5 consecutive days (day 6-10) in pregnant hamsters. No effects were observed on nidation, or on maternal or foetal survival at doses up to 50 mg/kg bw/day (WHO, 1982). The number of abnormalities in either soft or skeletal tissues of foetuses from tin-exposed dams did not differ from that occurring spontaneously in the controls.

60. No studies have been reported suggesting teratogenic effects in humans after oral exposure to inorganic tin compounds.

GENOTOXICITY

61. No *in vivo* studies have been performed on genotoxicity effects after oral exposure to inorganic tin. Limited *in vitro* data is available on genotoxic capabilities of inorganic tin, and these have shown mixed results and have been mainly conducted with stannous chloride (USDHHS, 1992).

SPECIAL STUDIES

Effect of tin on bone strength

62. In a 4-week study in rats the effects of stannous chloride on the mechanical strength of bone was investigated. Groups of 22-30 male weanling rats were exposed to 0, 50, 150, 300 or 600 ppm (equivalent to 0, 5, 15, 30 or 60 mg/kg bw/day) tin in their drinking water and rat chow containing 52.4 ppm (5.2 mg/kg bw/day) tin. The compressive strength of the distal epiphysis of the femur was significantly decreased at doses of 30 and 60 mg/kg bw/day (Ogoshi *et al*, 1981). These studies suggested that excess tin in the diet may interfere with normal bone formation and/or maintenance.

Interaction with specific dietary components

63. From previous studies tin is known to interact with a number of essential trace elements in the body.

(a) Animals

64. Stannous chloride added to the diet of rats at 206 ppm (10 mg/kg bw/day) significantly decreased liver copper and zinc levels when assayed at the end of a 21-day feeding period compared to controls fed 1 ppm (0.05 mg/kg bw/day) (Greger and Johnson, 1981).

65. Whilst the mechanism by which tin affects zinc absorption is unknown it is quite dose-dependent. Rats fed 500 ppm stannous chloride for 21 days (equivalent to 25 mg/kg bw/day) or more had suppressed levels of zinc in the bone and soft tissues, while rats fed even higher levels of tin (>2000 ppm equivalent to 100 mg/kg bw/day) for 21 days had hypertrophied gastro-intestinal tracts and significantly increased endogenous losses of zinc in the faeces (Greger and Johnson, 1981; Johnson and Greger, 1984).

66. Ingestion of high dietary levels of tin for 21 days (500-2000 ppm equivalent to 25 or 100 mg/kg bw/day respectively) in rats depressed plasma copper levels to less than 20% of control animals (Greger, 1987). Anaemia in rats was reduced by addition of copper or iron to the diets when rats were fed tin in the form of stannous chloride at 150 ppm (equivalent to 7.5 mg/kg bw/day) for 13 weeks (deGroot *et al*, 1973).

67. An inhibitory effect of tin on intestinal absorption of calcium in rats orally dosed with stannous chloride (30 mg tin/kg bw every 12 hours for 3 days) has been observed (Yamaguchi *et al*, 1979). Other studies have reported reduced calcium content in both bone and serum, and increased kidney calcium levels following ingestion of tin. Male rats, received single IP injections of tin in the form of stannic or stannous chloride at dose levels ranging from 2.5 to 30 mg/kg bw. Calcium concentration in the kidneys of treated rats increased in a dose-dependent manner.

68. This accumulation of calcium in the kidneys was associated with a significant, dose-related decrease in serum calcium levels (Yamamoto *et al*, 1976). Male rats dosed by gavage with 30 mg tin/kg bw at 12-hour intervals for 3 or 10 days, increased renal calcium concentrations with concurrent reductions in serum and femoral calcium was observed (Yamaguchi *et al*, 1980).

69. More recently the effects of dietary tin on tissue trace elements and bone minerals have been examined in weanling rats (Rader *et al*, 1990; Rader 1991). In the first part of the study groups of 10 male Long-Evans rats (22 days old) received tin (in the form of stannous chloride) in the diets at 0, 100, 330, and 1100 ppm (equivalent to 0, 10, 33 or 110 mg/kg bw/day) for 4 weeks. A second part of the study was to study the effects of 100 ppm tin (10 mg/kg bw/day) on copper depletion and deficiency in rats fed copper-adequate and copper-deficient diets. The results indicated that copper depletion was observed in all tissues (duodenum, liver, kidney and femur) examined at tin levels in the diet as low as 100 ppm (10 mg/kg bw/day). Zinc levels in the kidney and femur, but not the liver were also significantly reduced. Levels of tin in the diet of 1100 ppm (110 mg/kg bw/day) significantly reduced concentrations of copper and zinc in all tissues examined. The effects at 100 ppm (10 mg/kg bw/day) were more pronounced in rats fed a copper-depleted diet.

70. In summary, administration of tin at doses as low as 10 mg/kg bw/day for 4 weeks reduces zinc and copper levels in tissues and bone; and, at doses of 60 mg/kg bw/day for 3 days reduced calcium level absorption from the gut.

(b) Humans

71. Humans excreted an additional 2 mg zinc in the faeces when dietary tin was ingested at 50 ppm (equivalent to 2.5 mg/kg bw/day in 60 kg adults) for 20 days (Johnson *et al,* 1982). This was confirmed by Valberg et al, (1984), who found that inorganic tin depressed the absorption of 65-Zn from zinc chloride and from a turkey test meal.

72. Additionally, high dietary levels of tin 500 ppm (13 mg/kg bw/day in 60 kg individuals) has also been found to lower absorption rate of selenium (Greger *et al*, 1982).

73. The addition of 100 ppm (2.5 mg/kg bw/day in 60 kg individuals) to the diets of human subjects for 20 days had no effect on the absorption of copper or calcium (Johnson *et al*, 1982).

SUMMARY OF TOXICOLOGY DATA

74. Acute ingestion of tin-containing beverages may cause gastric irritation in humans at a dose of 5 to 7 mg/kg bw, but an exposure to 2.6 mg/kg bw was without symptoms. Some animals, such as cats, will respond to a level of tin at 5.4 mg/kg bw in drinking water by vomiting, but dogs may tolerate tin levels up to 14 mg/kg bw in beverages (8 mg/kg bw/day in solid food) without any overt signs.

75. Humans may tolerate tin levels of 2.9 mg tin/kg bw for 23 days without symptoms of toxicity. Repeat-dose studies and sub-chronic studies in rodents indicate that exposure at doses at and above 25 mg/kg bw/day is associated with anaemia, reduced appetite and reduced growth. Animals whose diet was low in iron were more susceptible to tin-associated toxicity than rats whose diets were supplemented with this micronutrient. The lowest NOEL in repeat-dose studies in rodents was 7.5 mg/kg bw/day. In one study, a 13-week exposure indicated effects on calcium and bone density at doses as low as 1 mg/kg/day, with a NOEL for this effect at 0.3 mg/kg bw/day.

76. Limited evidence indicates that excessive intake of tin interferes with levels of essential micronutrients in the body, potentially resulting in deficiency and its systemic consequences. Repeat-dose studies indicate that iron levels in particular are affected, probably leading to anaemia and poor growth in affected animals, but zinc, copper, calcium and possibly selenium levels also appear to be affected at high doses.

77. At the 26th meeting in 1982 JECFA determined that gastric irritation was the main problem associated with excessive levels of tin in foods, and that the threshold for this effect was about 200 ppm in food. The Committee allocated a provisional maximum tolerable daily intake (PTDI) for tin of 2 mg/kg bw (WHO, 1982). However, it is unclear on what toxicological endpoint (acute or chronic) or safety factors JECFA used to calculate the PTDI as there was no evidence of chronic adverse effects in humans associated with chronic exposure to tin.

TIN CONTENT OF FOOD

78. In most unprocessed foods the levels of tin are less than 1 ppm (Schroeder et al, 1964; Schafer and Fembert 1984). Higher concentrations are found in canned foods due to the dissolutions of tin plate following removal of coating. The intake of tin by different sub-population groups depends on the amount and type of canned foods consumed and its tin level. Intakes can vary widely between sub-population groups.

79. The release of tin into canned foods depends on many factors including the presence of other chemicals such as nitrates, pH and storage conditions (Mannheim, 1987; Berkovic et al, 1995). The corrosion of tinplate cans is electrochemical where the tin serves as a sacrificial anode. The mechanism of corrosion depends on the type of food and the presence of a depolariser such as oxygen .

80. The uptake of tin by foods depends also on whether the cans are lacquered or not. The risk of contamination of food by tin is significantly reduced by lacquering. The lacquer protects the surface and tin dissolution occurs only around a scratch or through a pore. The contact area is small therefore corrosion is slow. Problems arise when the lacquer film lifts from the metal surface.

TIN CONTENT OF CANNED FOOD

81. Canned foods examined in a study in the UK found that most foods (95-100 percent of the samples) contained less than 200 ppm tin (Meah et al, 1991). Higher concentrations were found in oranges, tomatoes, pasta, asparagus and some exotic canned vegetables. Canned tomato juice made from tomato plants grown with nitrate fertilisers have been linked with an outbreak of acute tin poisoning. Juices which are highly acidic may corrode the tinplate releasing tin leading to concentrations between 100 and 500 ppm.

82. Fruits such as blackcurrants and raspberries contain anthocyanins which aggressively corrode tinplate cans. The acceleration in tinplate corrosion may be due to complex formation between tin and organic acids. The accelerated rate of corrosion observed in unlacquered cans of foods such as apricots and peaches has been attributed to derivatives of thio and dithiocarbamate fungicides. Unlike some fruits and vegetables, meat products are often contained in lacquered cans and are not aggressive to tin (do not cause rapid detinning), reflected in the low mean concentration of tin of 20 ppm in canned meats reported in the UK.

83. In contrast, a recent survey of pineapple products available in Indonesia revelaed that a small percentage of the samples contained high levels of tin, with three of them exceeding 250 ppm with the highest containing 445.82 ppm (Wuryani, 1996).

84. The 1994 AMBS conducted analysis on 72 composite samples of canned foods and showed tin levels below 120 mg/kg. Also, the most recent New Zealand total diet survey (1997/98) analysed 86 composite samples of canned foods and a few non canned foods and found concentration of 210 mg/kg and below. The highest value found was for canned pineapple.

EFFECT OF STORAGE

85. Canned foods accumulate more tin when stored for several months and corrosion accelerated at temperatures such as 40°C which can occur in warehouses in summer. A study in Thailand of pineapple products found a 90th percentile tin content range of 259.80 - 376.10 ppm after 3 years storage (Hotrabhavananda, 1996). The tin content of food increases considerably when an opened can is kept for a few days.

LEVELS OF INTAKE

United Kingdom

86. Estimates of tin intake based on the UK Total Diet Survey (1997) was 2.9 to 3.1 mg day. Results of the Total Diet Survey indicate that canned foods represent 5 percent of total food intake by weight but contribute 85 percent of the total tin intake. The mean levels of tin in all uncanned major food groups were less than 0.1 ppm except for canned vegetable and fruit products. Between 1976 and 1981 the mean daily intake of tin estimated from the Total Diet Survey fell successively each year from 4.4 mg/day in 1976 to 2.4 mg/day in 1981 due to a decrease in the tin concentration of canned foods. There appears to be no significant change in the dietary intake of tin for the UK population since 1981 (Sherlock and Smart, 1984).

87. A recent survey carried out by the UK Food Standards Agency (UK FSA, 2002) was undertaken to provide up-to-date information on the levels of tin in canned foods and identify whether measures introduced to reduce tin levels, such as fully lacquering the inside of the cans to contain acidic foods, are working.

88. The key findings of the survey are that:

a) The survey results do not raise any general food safety concerns.
b) Four hundred samples of tomato-based products and of other canned fruit and vegetables were analysed for tin.
c) Tin concentrations in 99.5 % of samples were below the UK regulatory limit of 200 mg/kg. One sample of spaghetti in tomato sauce and one sample of gooseberries were above this limit.
d) Tin concentrations were similar, or lower, than those reported in previous surveys.
e) Estimated dietary intakes of tin for average and high level consumers of canned fruit and vegetables (mean = 1.7 mg/person/day; 97.5 % level = 5.6 mg/person/day) are well within the PTWI of 120 mg/person/day (based on a daily limit for a 60 kg adult) set by the JECFA.

Australia

89. The 1994 Australian Market Basket Survey examined tin levels in canned foods. The estimated weekly intakes of tin in the survey were below 2 mg/kg bw in all age-sex categories assessed (ANZFA, 1996), which is less than 15% of the PTWI for tin of 14 mg/kg bw. Estimated dietary intakes of tin from the 1994 AMBS are shown below in Table 2.

Table 2: Dietary Intake Estimates for Tin from the 1994 AMBS

Dietary Intake of Tin	Mean Dietary Intake (Adults)	Dietary Intake at 95th Percentile Energy Intake
mg/day	4.6 (M) 3.5 (F)	7.5 (M) 5.8 (F)
mg/kg bw/day	0.061 (M) 0.059 (F)	0.099 (M) 0.098 (F)
% PTDI*	3 (M) 3 (F)	5 (M) 5 (F)

M = adult males; F = adult females
*PTDI 2 mg/kg/bw/day, average body weight of 75 kg males (M), 59.1 kg females (F) used in the 1994 AMBS

90. In the 1994 AMBS survey tomatoes contributed 46%, pineapple and juices other than orange juice contributed 46% and fruit salad 8%.

91. ANZFA (now FSANZ), conducted a dietary intake assessment for tin during the Review of Metal Contaminants in Foods (Proposal P157) in 1999. The estimated intakes were calculated using a computer program called DIAMOND (DIetAry Modelling Of Nutritional Data) that was custom built by ANZFA to conduct dietary intake assessments. Food consumption data used for this assessment were derived from the 1995 Australian National Nutrition Survey for the whole population (2+ years, survey sample = 13,858). The main sources of tin concentration data, in a variety of canned and non-canned foods, were from

- survey data submitted to ANZFA (now FSANZ) in response to a data call (including data from State Health departments, National Residue Survey (NRS) monitoring data from the department of Agriculture, Fisheries, Forestry Australia (AFFA); and
- 1994 Australian Market Basket Survey (AMBS).

92. The main results from the dietary modelling conducted during the Review are given below in Table 3.

Table 3: Dietary Intake Assessment for Tin from DIAMOND, based on the 1995 National Nutrition Survey

Dietary Intake of Tin	Mean Dietary Intake (all respondents)	95th Percentile Intake (consumers only)
Whole population (2+ years)		
mg/day	2.7	10.2
mg/kg bw/day	0.05	0.17
%PTDI*	2	8

*PTDI 2 mg/kg bw/day, average body weight of 67 kg for whole population (2+ years)
DIAMOND model where non-detects where assigned the limit of detection.

For adults, estimated dietary intake of tin, as calculated by DIAMOND, was less than the PTDI for both the mean consumer (2% PTDI) and high consumer (8%), assuming a the level of detection value for non-detect results as a worst case scenario.

93. No dietary intake of tin for high consumers of a single commodity group exceeded the PTDI.

94. The main foods contributing to total tin dietary intake (>5%) from the DIAMOND dietary model (zero for non-detects) were tomato (54%), pineapple (36%) and mushrooms (10%). Canned fruit salad was not assigned a tin concentration level because it is considered a mixed food in the DIAMOND program.

95. The results from the two Australian dietary intake assessments are similar and indicate that dietary intake of tin both for the average person and a high consumer[6] is low compared to the PTWI of 14 mg/kg bw.

New Zealand

96. The 1997/98 New Zealand Total Diet Survey (NZTDS) (Vannort et al, 2000) measured total tin in canned foods and a few non-canned foods. Dietary intakes were estimated using analytical results from this survey and the previous 1990/91 NZTDS (Vannort et al, 1995). In calculating estimated dietary intakes, not detected results were assigned half of the limit of detection (LOD).

97. Estimated weekly dietary intakes of tin ranged from 530 µg/kg bw/week for adult males, to 1560 µg/kg bw/week for young children. These results are 3.8% PTWI and 11% PTWI respectively. Results for all age groups are shown below in Table 4.

Table 4: Dietary intake estimates for tin from the 1997/98 NZTDS

Estimated intake	Young male	Adult male	Adult female	Vegetarian female	Child	Young child
mg/kg bw*/week	0.67	0.53	0.59	0.81	1.24	1.56
% PTWI**	5	4	4	6	9	11

*Body weights: young male 70kg, adult male 80kg, adult female 65kg, vegetarian female 65kg, child 20kg, young child 13kg.
**PTWI: 14 mg/kg bw/week

Canned foods (spaghetti, baked beans, apricots, tomatoes and peaches) contributed approximately 75% of the total estimated intake of tin.

REGULATIONS

International

98. The 33rd JECFA 1988 meeting confirmed a PTWI of 14 mg/kg bw and recommended that efforts be made to keep individual tin levels in canned food as low as practicable.

99. Codex specifies a maximum limit of 250 ppm for tin in certain canned foods including asparagus, tomato concentrates, peas, pears, pineapple, fruit cocktail and apricots. A maximum level of 250 ppm also exists for preservative free juices and nectars including orange, grapefruit, lemon, tomato and pineapple juices and peach and pear nectars. A maximum limit of 150 ppm applies to other fruit juices and nectars including apple, grape, blackcurrant and nectars of certain small fruits.

100.   UK regulations prohibit the sale and importation of any food that contains more than 200 mg tin/kg of food (FACC, 1983).

101.   Australia has established maximum permitted concentrations for tin in food i.e. 250 mg/kg for all canned foods (under new Australia New Zealand Food Standards Code as of December 2002).

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[6] The 95th percentile results are not strictly comparable because DIAMOND estimates the 95th percentile tin intake, derived from tin intakes of individuals , whilst that from the AMBS represents the tin intake at the 95th percentile level of energy intake. The AMBS assumption that tin intake at 95th percentile energy intake represents a high consumer's tin intake appears to underestimate the 95th percentile tin intake.

Sweden

102.   Sweden has established a maximum limit of 50 mg/kg for beverages and foods for infants and young children and 150 mg/kg for other foods. These maximum limits refer to foods packed in tinplate cans.

POTENTIAL HEALTH RISKS

103.   The level of 250 ppm tin which is set by many countries as a safe upper limit in canned foods is not based on toxicological evidence of safety but the levels of tin found in canned foods under normal conditions of processing and storage. Surveys in UK and in Australia indicate that the dietary exposure to tin is well below the PTWI of 14 mg/kg bw.

104.   The greater rate of absorption of tin in the intestinal tract in the presence of citrate suggests that the safe upper limits for fruit juices may be significantly lower than for other products.

105.   Increased rates of corrosion of tinplate in food stored in opened cans is also of concern. The tin concentration in aggressive foods stored in open unlacquered cans may reach levels able to cause acute toxicity within a few days.

106.   Reports of acute tin poisoning are rare. Chronic symptoms such as growth depression, changes in enzyme levels, anaemia and bone metabolism have been identified in animal studies. Some of these effects may be due to interaction of tin with other trace elements such as iron, zinc, copper and selenium.

TECHNOLOGICAL AND COMMERCIAL IMPLICATIONS

The following information was sourced from the literature and from the Canned Food Information Service, Inc – Australia (CFIS).

107.   Metal packaging faces strong competition from glass and plastics. Even with innovations such as easy opening tear top cans, metal containers are below the average growth of marketshare for packaging products.

108.   The best solution to prevent or reduce detinning of cans by aggressive foods is internal lacquering. The use of lacquers has permitted the extension of the use of cans to additional products, including highly aggressive ones.

109.   The coating thickness greatly affects the performance of the lacquered food can. Non-aggressive products such as apricots and beans require a thickness of 4-6µm while tomato concentrate needs layers of 8-12µm to prevent interaction between the can and its contents.

110.   Adhesion is required to prevent reactions between the can and its contents. Currently adhesion is tested by measuring the force required to lift a dry lacquer coating from the metal in a peel test. While this test readily identifies films which are unsuitable there is no guarantee that those which pass would give satisfactory long term results when in contact with specific foods.

111.   Toxicologically significant contamination of canned food from tin dissolution may arise as a result of poor manufacturing practices or prolonged/incorrect storage or both.

112.   Although lacquering of cans significantly reduces the risk of tinplate corrosion, the use of lacquer coatings is not always practicable or cost effective.

113.   It could be argued that "since lined cans are readily available, then why not use them for all canned foods and thus prevent any tin uptake?" There are, however, very valid technical and marketing reasons why some products require to be packed into plain cans.

Flavour and Colour

114.   The need for tin dissolution to maintain the desired colour and flavour attributes of products such as asparagus, light coloured fruits and juices and tomato based products has long been established. It is believed that the presence of tin creates a reducing atmosphere in the can preventing undesirable oxidative changes in these products, which would otherwise develop brown discolourations and unacceptable flavours. Such quality loss would severely affect their marketability and sales with significant implications for the canning industry and their suppliers.

115.   It is interesting to note that this concept also works in reverse – some highly pigmented foods, such as acidified beetroot and berry fruits, must always be packed into fully lined cans because, apart from their aggressive behaviour towards tin, colour bleaching via tin dissolution can be a significant problem.

Corrosion factors

116.   Most of the products normally packed into plain cans are relatively high acid products. In addition to the organoleptic considerations, should these products be packed into lined cans a change of corrosion mechanism would result. For the more aggressive products this would result in a greater tendency for underfilm corrosion/delamination (particularly for tomato products) and to pitting corrosion of the steel base and subsequent implications of potential for perforation failure.

117.   The tin level is dependent on a large number of factors, many of which relate to natural variations or occur after the can has left the control of the manufacturer:

Food chemistry

118.   The most obvious influence on internal corrosion in plain tinplate cans is the chemistry of the food product. It should be noted that fruits, vegetables and tomatoes will have significant natural variation in, for example, pH and acid type and concentration, dependent on variety, maturity, time/place/conditions of harvest, soil chemistry and agricultural practices. These are difficult for the canner to control and may ultimately impact on the level of tin uptake by the product.

Corrosion accelerators

119.   The presence of a chemical species with the ability to accept electrons will increase the rate of corrosion. Some products may contain such 'depolarisers' which will accelerate tin dissolution. Good process control by the canners helps to minimize the presence of headspace oxygen.

Storage temperature

120.   A further significant factor influencing tin levels is the length and temperature of storage subsequent to canning. Tin uptake will increase with time and most products exhibit first order reaction rates where the rate of dissolution doubles for every $10^{o}C$ rise in temperature.

CONCLUSIONS AND RECOMMENDATIONS

121.   Food, especially canned food, represents the major route of human exposure to tin. Levels are generally less than 1 ppm in unprocessed foods. Higher concentrations can be found in canned foods as a result of dissolution of the tinplate.

122.   The highest levels of tin are generally found in canned fruit and vegetable products such as pineapple, tomatoes, asparagus and fruit juices. High levels of tin have also been found in canned herrings.

123.   National surveys indicate that human exposure to tin through food is normally well within the limits set by the individual countries.

124.   The toxicity of ingested tin is low. The number of reported cases of acute tin poisoning are small. There is no evidence that inorganic tin compounds have carcinogenic or teratogenic effects or evidence to suggest cumulative adverse effects of low levels of tin in the human diet.

125.   The Committee might like to consider requesting JECFA to reassess whether an acute reference dose can be set for tin once appropriate studies have been completed (it is believed that comprehensive studies are underway in Europe), and to clarify the basis for setting the PMTDI and the PMTWI for tin.

126.   An upper limit of 250 ppm tin in solid foods in cans and 200 ppm in liquid foods in cans is suggested based upon what is reasonably achievable under normal conditions of processing and storage.

127.   The proposed limit of 200 ppm tin in liquid food in cans requires some clarification. It is believed this limit was originally meant to specifically cover fruit juices. The definition of what constitutes a "liquid food" needs to be clarified and agreed upon. For example, the CCFAC might like to consider whether products such as soups (i.e. tomato soup – normally packed in plain internal cans) and purees would be classified as solid foods or liquids. Such products are very concentrated and, if they are defined as liquids, it may be more appropriate for the 200 ppm limit to apply to the diluted form.

128.   Alternatively, the proposed limits might be better applied separately to solid food (250 ppm) and beverages (ppm, to be decided), or for simplicity, have one level for all canned foods, such as 250 ppm.

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