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Review

Tin in canned food: a review and understanding of occurrence and effect

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Abstract

Tinplate is light gauge, steel sheet or strip, coated on both sides with commercially pure tin and has been used for well over a hundred years as a robust form of food packaging. Altogether, about 25,000 million food cans are produced and filled in Europe per annum, about 20% of these having plain internal (unlacquered) tin-coated steel bodies. Worldwide, the total for food packaging is approximately 80,000 million cans. Tinplate is also extensively used for the production of beverage cans. Europe produces and fills over 15,000 million tinplate beverage cans per annum all of which are internally lacquered. The use of tinplate for food and beverage packaging, will result in some tin dissolving into the food content, particularly when plain uncoated internal surfaces are used. The Provisional Tolerable Weekly Intake for tin is 14 mg/kg body weight and recommended maximum permissible levels of tin in food are typically 250 mg/kg (200 mg/kg UK) for solid foods and 150 mg/kg for beverages. However, the question arises as to whether evidence exists that such elevated levels of tin in food in any way constitute a risk to human health. This review considers the factors affecting the dissolution of tin, the reported measurements/surveys of actual levels of tin in canned foods and the studies and reports of acute (short term) toxicity relating to the ingestion of elevated levels of tin in food products. Chronic studies are mentioned, but are not covered in detail, since the review is mainly concerned with possible effects from the ingestion of single high doses. From published data, there appears to be a small amount of evidence suggesting that consumption of food or beverages containing tin at concentrations at or below 200 ppm has caused adverse gastrointestinal effects in an unknown but possibly small proportion of those exposed. However, the evidence supporting this assertion is derived from reports of adverse effects which offer data that are limited, incomplete or of uncertain veracity. Clinical studies provide greater confidence regarding the effects of exposure concentration and dose, but few relevant studies have been made. Adverse gastrointestinal effects were observed in limited clinical studies at concentrations of 700 ppm or above, although no adverse gastrointestinal effects were also reported in two studies at higher concentrations. Overall, therefore, the published data do not present a particularly comprehensive profile on the toxic hazard to man of acute exposure to divalent inorganic tin. A food survey suggested that the contents of almost 4% of plain internal tinplate food cans contain over 150 mg/kg of tin and over 2.5 million such cans are consumed every year in the UK alone. Despite this, in the last 25 years, there have been no reports of acute effects attributable to tin contamination in the range 100–200 ppm. These facts strongly suggest that there is little evidence for an association between the consumption of food containing tin at concentrations up to 200 ppm and significant acute adverse gastrointestinal effects. Clearly though, only further clinical studies will generate unequivocal evidence that current legislative limits provide safe levels for adults in the general population.

Keywords: Tin; Canned food; Permitted levels; Concentration; Dissolution; Acute toxicity; Clinical studies

Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry (USA); COT, Committee on Toxicity of Chemicals in Food (UK); FDA, Food and Drug Administration (USA); FSA, Food Standards Agency (UK); JECFA, Joint Expert Committee on Food Additives; MAFF, Ministry of Agriculture Fisheries and Food (UK); MPMA, Metal Packaging Manufacturers Association (UK); NOAEL, No Observable Adverse Effect Level; NCI, National Cancer Institute (USA); ppm, parts per million; PTWI, Provisional Tolerable Weekly Intake; TDS, Total Dietry Study; WHO, World Health Organisation.

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Contents

1. Introduction

Tinplate is light gauge, cold reduced, low-carbon steel sheet or strip, coated on both sides with commercially pure tin. It combines in one material the strength and formability of steel and the corrosion resistance and good appearance of tin.

Just under one third of the world's total tin production goes into the manufacture of tinplate, for which food packaging is by far the largest of many diverse applications. Tinplate has been used for preserving food for well over a hundred years and today provides a robust form of packaging, allowing minimisation of headspace oxygen and sterilisation of the foodstuff within the hermetically sealed can, giving a long, safe, ambient shelf life with no, or minimal, use of preservatives.

Altogether, about 25,000 million food cans are produced and filled in Europe per annum, about 20% of these having plain internal (unlacquered) tin-coated steel bodies. Worldwide, the total for food packaging is approximately 80,000 million cans.

Plain internal tinplate cans are used for specific food types, including tomatoes and other tomato-based products, white fruits and some vegetables (e.g. mushrooms, asparagus). They are used, in preference to lacquered cans, in situations where a small lacquer discontinuity (e.g. scratch) would result in concentrated attack of the base steel (the small area of tin would quickly disappear) and could potentially lead to pinholing and microbial ingress. Additionally, the presence of a bare tin surface inside the can leads to protection of the natural flavour and appearance of the food, through oxidation of the tin surface in preference to oxidative degradation of the food. This process retains the quality attributes that consumers expect from these products throughout the long shelf life.

As well as for food cans, tinplate is also extensively used for the production of beverage cans. Europe produces and fills approximately 40,000 million cans per annum for beverages (beers, carbonated soft drinks, water, wine), of which almost half are made of tinplate and all are internally lacquered. Some liquid products, such as fruit juices, including tomato, grapefruit, orange

and pineapple, are filled into food cans and then in-can sterilised in the manner of foods.

As a result of the use of tinplate for food and beverage packaging, it is obvious that some tin will dissolve into the food content, particularly when plain uncoated internal surfaces are used. The Provisional Tolerable Weekly Intake for tin is 14 mg/kg body weight (JECFA, 1988a, 1988b) and recommended maximum permissible levels of tin in food are typically 250 mg/kg (200 mg/kg UK; MAFF, 1992) for solid foods and 150 mg/kg for beverages (Codex, 1998). However, the question still arises as to whether there is evidence that such elevated levels of tin in food in any way constitute a risk to human health. This review will attempt to answer this question by considering the factors affecting the dissolution of tin, the reported measurements/surveys of actual levels of tin in canned foods and the studies and reports of acute (short term) toxicity relating to the ingestion of elevated levels of tin in food products. Chronic studies will be mentioned, but not covered in detail, since the review is mainly concerned with possible effects from the ingestion of single high doses. Also, as a result of the changes in can making technologies, such as the elimination of soldered side-seams, and improvements in can filling procedures, only reports published after 1970 will, in general, be considered, unless they are of particular relevance.

2. Background chemistry

The chemistry of inorganic tin has been reviewed elsewhere (Smith, 1997), but in order to understand the behaviour of tin in different food matrices, a basic knowledge of some of its chemical properties is desirable.

In addition to the metal, tin can exist in two different chemical oxidation states, namely divalent tin (Sn^{2+}, tin (II) or stannous tin) and tetravalent tin (Sn^{4+}, tin (IV) or stannic tin).

Disollution of metallic tin from the inside of a can body into the food content will result in it being present in the divalent form. The precise chemical nature of the divalent tin in a canned food product is important, as it is likely to have a major influence on its ability to cause an acute toxicological response. However, the exact species present and their distribution will be different in each individual food type, since a number of factors have a role to play.

One of the main considerations affecting the species present is pH. In aqueous solution, at pH greater than 2, divalent tin will form $Sn(OH)_2$, which has very low solubility. However, other chemicals may be present causing ionised tin to preferentially form complexes, the most stable being those with citric, tartaric and oxalic acids. The quantity of such complexed tin increases with the concentration of available ionised carboxylate groups (Weber, 1987).

The importance of pH for the speciation of tin in foods has also been demonstrated by computer modelling (Duffield et al., 1990). Using a program taking into account the various physicochemical parameters, the distribution of tin in food and in saliva was calculated. It was found that there would be preferential formation of citric acid complexes in foods and amino acid (cysteine, arginine, histidine) complexes in saliva.

Other chemicals which may also be present in foodstuffs and which are known to complex with tin are alcohols, esters and higher fatty acids (Lemanceau, 1963).

Reactions involving the reducing properties of tin can also occur. In this context, reactions of metallic tin with oxygen, sulphur, sulphur dioxide, sulphur-containing amino acids, e.g. cystine and cysteine, and nitrates have been reviewed elsewhere (Marsal, 1987; Horio, 1972).

Another factor affecting the potential bioavailability of tin in food, is that tin species (both inorganic and organotin) are known, from environmental studies, to readily adsorb onto solid particles (Blunden and Evans, 1990). Therefore in foodstufs tin may become fixed onto solid particles (fibres) or onto pectins. Tin fixed in this way is not readily released by treatment with hydrochloric acid (Weber, 1987). Similarly, the attachment between tin and solid food is difficult to break using artificial gastric juices and intestinal enzymes are not involved in the solublisation of tin adhered to proteins. However, alkaline intestinal juices cause the release of 90% of tin adsorbed onto the solid fraction of foodstuffs (Horio, 1972).

It is therefore apparent that the bioavailability and potential toxicity of tin in food will depend not only on the quantity ingested but also on numerous other factors, e.g. pH, valence, extent of complexation or adsorbtion, solubility etc. All of these factors change as the food moves from the can, to contact saliva, gastric juices or intestinal fluids. The tin concentration levels involved are below that of any laboratory technique for speciation analysis and so experimental confirmation of the exact species present is extremely difficult. Therefore computer modelling has also been used to predict chemical speciation (Morris and Williams, 1986–1987) and has shown the complexity of tin speciation and distribution, in canned tomato juice, before and after ingestion (Morrish, 1991). It was concluded that tin would not be absorbed after ingestion and that observed toxic responses would be due to gastrointestinal irritation and not systemic poisoning.

3. Factors affecting tin dissolution

A number of studies of the general nature of tin dissolution from the inside of tinplate cans have been made (Board and Steele, 1978; Marsal, 1985; Anon. *Canmaker*,

1989; Warwick, 1972; Massini, 1975; Aubrun, 1990; Mahadeviah, 1997).

The actual rate of dissolution of tin is dependent on a number of factors. Of these, the presence of oxidising agents or depolarizers that corrode tin by direct chemical attack without evolution of hydrogen is probably most significant. Nitrates, possibly originating from fertilisers in the ingredients of the food, are the most frequently found oxidising agents. When sufficient concentrations of nitrates are present, detinning may proceed at a rapid rate. This occurs without loss of a vacuum and only when all the tin has dissolved does the unprotected steel begin to corrode very rapidly, with vigorous evolution of hydrogen. Nitrates are chemically reduced (Lemanceau, 1963) during the course of detinning, and little or no nitrate may remain in a detinned container even though it may have been the agent responsible for the corrosion. Many studies have been made of the effect of elevated nitrate concentation in food, all of which conclude that it dramatically increases the rate of tin dissolution (Johnson, 1966; Herbert, 1970; Farrow et al., 1971; Sherlock and Britton, 1973; Boneva et al., 1974; Marsal, 1977; Chakravorty and Ghosh, 1981; Helwig, 1986; Henshall et al., 1983; Palmieri et al., 2002).

Another chemical group, anthocyanins, has also been suggested to accelerate the rate of dissolution of tin (Sherlock and Smart, 1984), and has been used to explain the difference in solubility of tin between grape juice, which has relatively low levels of anthocyanins, and plum juice, which is rich in anthocyanins (Davis, 1979).

Storage conditions, particularly temperature, will also affect the rate of dissolution of tin into canned food. In a study of canned US military rations, the tin content of five types of fruit in unlacquered cans after 20 months was 12-fold higher at 37 °C than at 1 °C (420 and 34 mg/kg, respectively). For seven types of mixed dishes in unlacquered cans the tin content was 6-fold higher at 37 °C than at 1 °C (190 and 32 mg/kg, respectively) (Calloway and McMullen, 1966)

Other factors that have been investigated include can size (Marsal and Darre, 1976), types of base steel (Anon., *Canner*, 1994) and the level of hydrogen in the base steel (Reznik, 1991).

4. Levels of tin in foods

The exposure of the general population to tin is essentially dietary in origin, coming particularly from the consumption of foods stored in unlacquered tin cans (ATSDR, 1992), and may account for 98% of the total ingested tin (Biégo et al., 1999). Dietary products (food, not beverage) stored in tin cans represent 5.6% of the French diet, from which it was estimated that the daily intake of tin is 2.7 mg per day, or 0.04 mg/kg bodyweight per day, (Biégo et al., 1999). This is much lower than the PTWI of 14 mg/kg, which is equivalent to a daily intake of 2 mg/kg. However, it has also been estimated that an adult in the Western world could additionally consume another 109.1 μg of tin per day, the majority coming from fruits (fruits 500 μg/kg; meat 2 μg /kg; potatoes 22 μg /kg; spinach 2 μg /kg; cereals 47 μg/kg) (Rojas et al., 1999).

Studies of the increasing concentration of tin in food with respect to the time after filling the can have been made in canned vegetables (Arvanitoyannis, 1990a), canned meat (Arvanitoyannis, 1990b) and canned juices (Arvanitoyannis, 1990c).

Table 1 shows reported concentrations of total tin in conserves of acidic fruit, such as fruit juice (Ratana-Ohpas et al., 1996). Levels of tin have also been compared in fresh food (0.03 mg/kg) and food contained in lacquered cans (3.2±2.3 mg/kg) and unlacquered cans (76.6±36.5 mg/kg) (Biégo et al., 1999).

In the USA, grapefruit juice, orange juice, tomato sauce and pineapple in unlacquered or partially lacquered cans contained 51–150 mg tin per kg of food when the cans were first opened. The mean concentration of tin in unlacquered cans was 88 mg/kg of food (Greger and Baier, 1981).

In a total diet study (TDS) performed in the UK, samples for 20 TDS groups were obtained from 20 towns during 1994 and analysed for various metals, including tin. The results of the tin survey showed that canned vegetables contributed 66% and fruit products 31% of the estimated total intake of 2.4 mg/day (MAFF, 1997).

Concentrations of tin in a wide range of canned pineapple products on sale in the UK (January 1999 and March 1999) were measured and revealed a wide range from 50 mg/kg up to 210 ppm, which is just over the UK legal limit (MAFF, 1999a).

A survey was also performed to determine the concentrations of lead and tin in a range of canned fruit and vegetable foods on sale in retail outlets in the UK. Results showed that tin concentrations in all but two samples of gooseberries were below the statutory limit (200 mg/kg). In general, higher levels, but below

Table 1
Concentrations of total tin in conserves of acidic fruit (Ratana-Ohpas et al., 1996)

	Tin concentration mg/l
Guava	49.8–59.4
Lychee	43.9–45.7
Tomato	59.7–69.7
Mango	64.3–77.4
Pineapple	57.8–69.1

the statutory limit, were found in asparagus, tomatoes, apricots and grapefruit. It was observed that there was no significant difference between the tin contents of fruits packed in juice compared with the same fruit packed in syrup (MAFF, 1999b).

The survey of levels of tin in canned fruit and vegetables was repeated in the UK in 2002 (FSA, 2002). In all but two of the four hundred samples tested, the tin level was below the regulatory limit of 200 mg/kg. The average tin concentration in 234 food samples packaged in unlacquered cans was 59 mg/kg and overall the tin concentrations were lower than those found in the earlier surveys (MAFF, 1997, 1999b).

5. Toxicity

The toxicology pattern of tin and its compounds has been previously reviewed by many authors (Barnes and Stonor, 1959; Browning, 1969; Piscator, 1979; WHO, 1980; Blunden et al., 1985; Magos, 1986; US Department of Health and Human Services 1992; Thayer, 1995; Smith and Kumar Das, 1996).

Most of the above references discuss the toxicological profile of both inorganic tin and organotins (compounds possessing at least one Sn–C bond). However, whereas the pattern for organotins is complex, being dependent on both the number and nature of the organic group attached to tin, inorganic tin species do not exhibit the same properties and have been described as 'essentially non-toxic' (Smith and Kumar Das, 1996). There is no possibility of inorganic tin in food, originating from the inside of a tinplate can, being converted into the organic form. Chemical formation of a Sn–C bond requires severe reaction conditions, typically high temperature and specific reactants, such as alkyl aluminium or Gignard reagents, and biological methylation, demonstrated with certain bacteria, is a very slow process and would not take place in the timescale that the tin remained in the body. Therefore, any toxic property associated with organotin species can be ignored in the context of this review.

6. Acute effects

Clinical studies, offer controlled conditions and thus potentially the best data on exposure and effect monitoring. On the other hand, reports of toxic effects, following the unintended ingestion of tin, typically involve some uncertainty that the material analysed is the same as that to which the event was attributed, and that the composition of the test material has not changed during the time elapsing between the event and analysis. Also, in some cases, data reviewers may not have always transposed primary study or report data accurately. For these reasons, reports of studies and incidents have been reviewed separately.

6.1. Clinical studies

6.1.1. Primary reports

In a limited clinical study, five adult participants were given 240 ml orange juice containing 0, 498, 540 or 1370 ppm tin, or 730 ppm tin and 50 ppm nitrate, before a light meal. The pH of the test juices was apparently 3.9. Any overt adverse effects occurring during the following 24 h were recorded. Nausea and/or diarrhoea were reported by all participants, following ingestion of the highest tin concentration. Lower concentrations were apparently without effect. Re-administration of the highest concentration one month later was associated with nausea in one of the five participants (Benoy et al., 1971).

A study was conducted to evaluate the faecal excretion of tin in nine US Army personnel who were, for 24 days, given tinned combat rations (four cycles of six menus) which as a result of extended storage at extreme temperatures had elevated concentrations of tin (Calloway and McMullen, 1966). The concentration of tin in various constituents of the diet ranged from not detectable to 538 mg/kg wet weight, in tinned peaches. The average tin content of the daily menus ranged from 99 (72–125) mg/kg to 310 (273–356) mg/kg dry solids and the average daily ingestion of tin, for the full cycle of ration menus, was 162.8 (115.8–206.7) mg. Although not designed to identify gastrointestinal effects, no such effects were mentioned in the report of this study.

In order to examine the effect of dietary tin on the metabolism of certain essential elements, eight men were given a daily diet containing 49.67 mg tin for a period of 20 or 40 days. Again, although not specifically mentioned, it is presumed unlikely that these studies would have been continued had overt gastrointestinal or any other effects resulted from such treatment (Johnson and Greger, 1982; Johnson et al., 1982).

6.1.2. Secondary reports

Four participants were given diets that included canned pumpkin (383–476 mg/kg tin) and canned asparagus (361 mg/kg tin) for 6 days without any overt adverse gastrointestinal effects (Dack, 1955).

A report of an unpublished study indicates that a vegetable juice mixture (tomato juice with other vegetable extracts including celery) containing 700 ppm tin (derived from the corrosion of cans), caused slight nausea, or nausea and diarrhoea, in two of eight subjects, although no information on either the volume of juice or dose of tin ingested is provided. Subsequent ingestion, apparently by the same eight subjects, of a pH 4.5 citrate buffer solution containing stannous chloride (700 mg/kg tin), before a meal, caused nausea and vomiting

in two and diarrhoea in one of these (Feaster). It was suggested that the lesser effect seen following ingestion of vegetable juice might be due to the combination of tin with constituents of the juice (Cheftel, 1967).

Ingestion of a fruit juice containing 342 mg caused symptoms of gastrointestinal irritation in an unspecified number of volunteers. Similar juice containing between 125 and 182 mg had no effect (MAFF, 1983).

6.2. Reports of episodes of consumption of tin-containing foods or beverages

6.2.1. Primary reports

Acute effects have been reported following the ingestion of inorganic tin via dietary products stored in tin cans. These generally take the form of digestive disturbances with symptoms of acute gastro-enteritis, i.e. nausea (97%), abdominal cramps (87%), vomiting (70%), headaches (57%), diarrhoea (33%) fever (13%) (Piscator, 1979; Schafer and Femfert, 1984; Dewitte et al., 2001). The incubation period averages 15 to 30 min and the symptoms can last from half an hour to 3 weeks. (Barker and Runte, 1972).

In general, the levels of tin in foods, which are responsible for these effects, are between 250 and 2000 mg/l. The dietary products which are most responsible are acidic foods such as fruits and fruit juices. (Piscator, 1979; Schafer and Femfert, 1984; Dewitte et al., 2001).

A Swedish report of adverse effects following the consumption of canned peaches by 110 young adult participants at a meeting, is apparently unique, since according to the translation no other food or drink was consumed (Svensson, 1975). When the contents of the "remaining cans" were subsequently analysed, the fruit contained between 413 and 597 mg/kg tin and the juice, which had a pH of 3.9–4.1, contained 398 mg/kg tin. Data from the 85 responses to a questionnaire sent to all meeting participants showed that among this group 89% (76) had suffered gastrointestinal symptoms (nausea, vomiting and diarrhoea). The data supplied also indicated that 50 of 53 individuals consuming 440 g (a full can), 18 of 19 consuming 330 g and 6 of 6 consuming 220 g peaches and syrup were affected — the incidence of adverse effects in those who had consumed 220 g canned peaches, or more, was 95%. By contrast, only two of seven (29%) consuming 110 g peaches suffered.

An investigation of 113 cases of acute gastrointestinal illness, reported in Washington and Oregon over a 3-month period in 1969, indicated that canned tomato juice from a single production unit might have been responsible. These cases occurred at two banquets (43 and 22 cases) and in 30 "family outbreaks" in homes or restaurants. As well as the symptoms most commonly reported, bloating, abdominal cramps, headache, fever and mouth lesions were also seen. About 65% of those consuming the juice at the banquets were affected, while in the case of the family outbreaks 98% (48 of 49) were said to be affected. Subsequent analysis of the contents of full (presumably unopened) cans from the banquets, or from the same lot as those supplied to the banquets, found mean tin levels ranging from 327 to 392 ppm and 154 to 289 ppm. Samples taken from four opened cans implicated in the family outbreaks had tin levels ranging from 131 to 405 ppm, but it is not possible to say exactly which consumed concentration resulted in the acute response. However, it was evidently clear from a visual inspection that "virtually all" the cans sampled were corroded. Analyses of further samples from the implicated lots subsequently obtained from the warehouse, showed that those which were "partially-detinned" contained from 227–294 ppm tin; while those described as "completely detinned" contained from 381 to 477 ppm. The detinning was attributed to elevated nitrate (or possibly sodium chlorate) levels present in or on the crop at harvest (Barker and Runte, 1972).

Peaches containing 350–600 ppm tin (the liquor contained 220–440 ppm) caused nausea and vomiting in 91 individuals out of an unknown number exposed. Elevated nitrate levels, described as being over twice the 45 mg/l International Standard, were considered possibly responsible for the dissolution of tin (Nehring, 1972).

Of 78 people who ingested 100 mg or more of tin in canned peaches, 74 presented digestive disturbances, and in a group of 7 that ingested 50 mg of tin, 2 presented the same problem. (Piscator, 1979). Studies carried out on volunteers revealed no signs of poisoning resulting from the consumption of fruit juice containing 500 mg of tin per litre, though digestive disturbances were observed when the levels ingested reached 1370 mg/l. No signs of toxicity were seen following repeated ingestion (3×24 days) by 9 volunteers of 13, 33 and 204 mg of tin in canned foods (Piscator, 1979).

Very brief notes indicate that gastrointestinal effects, in an unspecified number of consumers, were associated with the consumption of orange and grapefruit juice containing 330–400 ppm tin (Anon., *FDA Consumer*, 1986), and grapefruit juice containing 450 ppm tin, from cans that were visibly corroded (Anon., *The Guardian*, 1972).

6.2.2. Secondary reports

Other occurrences of gastrointestinal effects attributed to the ingestion of tin-containing foods or beverages have been described, often only with scant data. In a few cases there is some discrepancy in the details given of a single toxic event. In others, it appears possible that the same event has been reported in a slightly different way or with different attribution.

At least fifteen students suffered typical gastrointestinal effects following the ingestion of orange juice reported to contain 100–494 ppm (Horio et al., 1967; JECFA, 1971, 1982). Fifteen of 26 individuals who

consumed an orange drink containing about 300 ppm also showed typical gastrointestinal symptoms (Kojima, 1971). (The numbers affected and tin concentrations suggest that this report may also be describing the event reported by Horio et al., 1967.). Adverse effects were evidently seen in 1838 Japanese consuming an orange-based drink, from clearly corroded cans, which contained 425 ppm tin (or 452 ppm, the reports differ) (Omori, 1966). Orange and apple juice containing 250–385 ppm caused nausea, vomiting and diarrhoea in a large but unspecified number in Kuwait (Metal Box Co., 1967).

Vomiting, diarrhoea and other unspecified effects were reported in eight cases following the consumption, by an undisclosed number of people, of tomato juice said to contain 156–247 ppm tin (Kojima, 1969). Samples of juice from the same manufacturer contained tin in the range 75–500 ppm, but it was considered possible that the juice that had caused the adverse effects came from cans with tin levels approaching or exceeding the 247 ppm upper value apparently reported by Kojima (JECFA, 1971, 1972, 1982). Similar symptoms were reported in eight out of ten people consuming tomato juice containing 156–221 ppm tin (Horio et al., 1967), although similarities in the data suggest that these two reports might relate to one and the same event.

Gastrointestinal symptoms that were described as severe affected 32 people who drank a vodka punch (containing pineapple and grapefruit juice; pH 3) containing 2000 ppm tin. The drink had been stored in a re-tinned container that showed signs of corrosion (Warburton et al., 1962).

Vomiting, weakness, diarrhoea or abdominal pain were seen in a family of three consuming tinned salmon subsequently found to contain 650 ppm tin, and in 64 of 127 individuals served canned rhubarb containing 350 ppm in a school canteen (Kwantes, 1966).

6.2.3. *Non-human, oral studies*

Table 2 shows the acute oral toxicity of a few divalent inorganic tin compounds, as assessed by LD_{50} tests on animals:

Gastrointestinal irritation (vomiting) was seen in cats (groups of about ten), but not dogs (groups of four), given 5 or 10 ml/kg body weight of an orange juice containing 540 or 1370 ppm tin, but not 498 ppm, by stomach tube. Apple juice and pear nectar containing 605 and 750 ppm, respectively, were not emetic. It was noted that concentration rather than dose appeared important in eliciting this effect. No tin could be detected in the urine, almost all being recovered in the faeces, and it was concluded that the emetic effect was caused by local irritation of gastric mucosa rather than a systemic (nervous system mediated) mechanism (Benoy et al., 1971). A Japanese study reports vomiting in five of six cats given 10 ml/kg body weight orange juice containing 452 ppm tin, but not 337 ppm (Omori et al., 1973).

7. Chronic effects

In a clinical study, the zinc metabolism of the volunteers was affected by a 40-day diet, containing around 50 mg tin. This effect was not examined at lower doses and data on the tin concentration of the diet are not presented (Johnson et al., 1982).

In several rat studies, repeated exposure, via the oral route, to low tin concentrations (e.g. 5 ppm in the drinking water or less than 50 ppm in the diet) and low daily doses (less than 1 or 2.5 mg tin/kg body weight in the drinking water or diet, or 2 mg/kg body weight by stomach tube) have been associated with effects on the metabolism and body levels of the essential elements iron, copper, zinc and calcium, anaemia or slight changes to the structure of the liver and kidney or to the activity of various enzymes (Yamaguchi et al., 1980; Schroeder and Nason, 1976; Pekelharing et al., 1994; Beynon et al., 1992; Reiks and Rader, 1990; Rader, 1991; Yu and Beynon, 1995; De Groot, 1973; Greger and Johnson, 1981; Johnson and Greger, 1985). It is not possible to deduce a no-observed-adverse-effect level (NOAEL) for any of these studies. Also, an interdependence in the way that mammalian species handle (the cations of)

Table 2
The acute oral toxicity (LD_{50}) of divalent inorganic tin compounds

Compound	Species	LD50 (mg/kg bw)	Reference
Stannous chloride	Mouse	1200	Pelikan et al., 1968
Tin -citric acid complex (30% tin)	Mouse	2700	Omori et al., 1973
Sodium penta fluorostannite (67%tin)	Mouse	590	Conine et al., 1975
Stannous chloride	Rat	700	Calvery, 1942
Stannous chloride	Rat (fasted)	2300	Conine et al., 1975
Stannous chloride	Rat (fed)	3200	Conine et al., 1975
Sodium penta fluorostannite (67%tin)	Rat (fasted, F)	220	Conine et al., 1975
Sodium penta fluorostannite (67%tin)	Rat (fasted, M)	220	Conine et al., 1975
Sodium penta fluorostannite (67%tin)	Rat (fed, M)	570	Conine et al., 1975
Stannous chloride	Rabbit	10,000	HSDB, 1999; JECFA, 1982; RTECS, 1999; WHO, 1980

certain metals, particularly those that are, or are similar to, essential elements, is well established. In the healthy state, the body would be expected to have a reservoir of essential elements and small disturbances to this reservoir would not automatically result in adverse consequences, although large perturbations could theoretically do so.

There was no indication of reproductive toxicity in limited studies in rats, mice and hamsters, in which stannous chloride was provided in the diet or administered by stomach tube (Sinkeldam et al., 1979; FDRL, 1972; De Groot et al., 1973; JEFCA, 1982; Sloof et al., 1993).

Good quality studies in mice and rats provided no clear evidence that stannous chloride possesses carcinogenic potential (NCI, 1981; NTP, 1982; NTP 2000; Sinkeldam et al., 1981; JECFA, 1982; Schroeder et al., 1968; Schroeder and Balassa, 1967; Kanisawa and Schroeder, 1967; Walters and Roe, 1965; Roe et al., 1965).

Stannous chloride gave no evidence of genotoxic potential in a well conducted in vivo study involving administration by injection to mice (Shelby et al., 1993).

7.1. Other toxicity considerations

7.1.1. Absorption, distribution and excretion

Inorganic tin is said to be poorly absorbed from the gastrointestinal tract in humans and animals (2.8% of Sn^{2+} compounds and 0.64% of Sn^{4+} compounds), possibly as a result of low solubility. In humans and laboratory species, more than 90% of an ingested dose of inorganic tin is recovered in the faeces (e.g. ATSDR, 1992; Codex, 1998; COT, 1998; JECFA, 1982; Fritsch et al., 1977; Haguenoer and Furon, 1982; Hiles, 1974; Kutzner, 1971; Piscator, 1979; WHO, 1996; Winship, 1988; Tipton, 1969).

There is some evidence from a human study that the level of tin in ingested food may influence its uptake from the gastrointestinal tract. The average retention of tin by adult males given a daily diet containing 49.7 mg tin for 20 days was around 3% (the range was −7–9%) of the administered dose; the figure when these subjects received the control diet, providing 0.1 mg tin/day, was around 27% (−4–71%) of dose). Tin appeared in the faeces up to 18 days after the end of a study. It was assumed that what was taking place was absorption followed by slow elimination in the bile or that the tin was retained in the gastrointestinal tract before being eliminated (Johnson and Gregor, 1982).

Absorption by the digestive tract does not seem to be dose-dependent (Schafer and Femfert, 1984; Johnson et al., 1982). Fifty percent is absorbed by humans following oral ingestion of 0.11mg Sn/day against 3% following ingestion of 49.7 mg/day. This would indicate that the absorption mechanism for tin could become saturated above a certain concentration.

A study in rats suggests that valence may influence uptake from the gastrointestinal tract, the Sn^{2+} salt (citrate or fluoride) being about four times more readily absorbed than the corresponding Sn^{4+} salt (Hiles, 1974). In this study, around 3% of a single oral dose of 20 mg Sn^{2+}/kg body weight was said to be absorbed, half of which was excreted within 48 h. The identity of the anion complement may also influence the uptake of tin from the gastrointestinal tract- reduced absorption was reported for an anion (pyrophosphate) with a greater propensity to form insoluble complexes with the tin cation (Hiles, 1974). It has been suggested that in rats the presence of citric acid may enhance the absorption of tin (Kojima et al., 1978; Schafer and Femfert, 1984) although another study apparently found other dietary components to be without influence (Fritsch et al., 1977).

With regard to distribution throughout the body, tin accumulates particularly in the bone and to a lesser extent in the liver, lung, tongue, lymph nodes and kidney (Codex, 1998; WHO, 1996, Greger and Lane, 1987; Winship, 1988; Hamilton et al., 1972/1973; Hassett et al., 1984; Durbin, 1957).

Following oral administration in the rat 1.02% of Sn^{2+} and 4% of Sn^{4+} were found in the bones, 0.08 and 0.02%, of Sn^{2+} and Sn^{4+}, respectively were found in the liver and 0.09 and 0.02%, respectively in the kidneys. In addition, 35% and 46%, of Sn^{2+} and Sn^{4+} respectively (inorganic tin) administered by IV was found in bone 2 days after the injection. (Haguenoer and Furon, 1982; Piscator, 1979). In rats, after an oral administration of greater than 100 μg of $SnCl_2$ per g of food, the concentration of tin found in bone were 5 times greater than the concentration in the kidney, and 20 times greater than the concentrations found in the liver. The concentration found in bones, kidney and liver increase with the quantity of tin ingested (Johnson and Greger, 1982).

The half-life of tin in bones is estimated to be 34 days (Sn^{2+}) and 40 days (Sn^{4+}) in the rat, though half lives of even 100 days have been quoted for ^{113}Sn as well as 10–20 days in the kidney and the liver (Piscator, 1979). In man, the clearance of absorbed tin can apparently be separated into three phases. The first 20% is cleared with a half-life of 4 days and the second 20% with a half-life of 25 days. The final 60% has a much longer half-life of 400 days (Winship, 1988). The biological half-lives in the rat for tin in the bone, spleen and liver were 30–40, 50 and 85 days, respectively (Codex, 1998; JECFA, 1982; WHO, 1996).

7.2. Solubility and gastric irritation

Reviews that have examined the relationship between absorption and solubility of inorganic tin report that much (37–82% in one study) of the tin in canned vegetables and fruits is present as insoluble (non-dialyzable)

complexes, found to be resistant to simulated gastric digestion. Polyphenolic compounds and proteins have been identified as the possible chelating (complexing) agents (Codex, 1997; JECFA, 1982).

It has been suggested the gastrointestinal disturbances which have been attributed to irritation of the gastric mucosa, may be associated with contact with tin (Sn^{2+}), present in an acidic medium and not strongly attached to a substrate, such as might be the case for canned drinks (Cheftel, 1967; Thomas, 1984). In canned foods, on the other hand, it is thought that tin may form complexes with larger molecules, rendering it less soluble and apparently less irritant. It is also noted that although the majority of adverse events following the ingestion of canned products have been associated with drinks, it is likely that tinned drinks are consumed in larger quantities than tinned foods (Cheftel, 1967).

8. Overview

From the references cited herein, there appears to be a small amount of evidence suggesting that consumption of food or beverages containing tin at concentrations at or below 200 mg/kg has caused adverse gastrointestinal effects in an unknown but possibly small proportion of those exposed. However, the evidence supporting this assertion is derived from reports of adverse effects that offer data that are limited, incomplete or of uncertain veracity. In many reports it is not possible to ascertain that the tin concentration declared to be associated with the event was indeed the concentration to which those affected were exposed, and in every case it can be presumed that those unaffected are under reported. Furthermore, in most cases, little detail is presented on the volume of tin-containing food or beverage consumed or the composition of the affected population. Most striking, however, was the age of the reports, since only one was published in the last quarter of a century.

Greater confidence regarding exposure concentration, dose and effects can be provided by clinical studies. Adverse gastrointestinal effects were observed in limited clinical studies at concentrations of 700 ppm or above, although no adverse gastrointestinal effects were also reported in two studies at higher concentrations. Of the studies reviewed, only five of those that supplied data on the concentration of tin in the ingested food or beverage were in fact conducted in order to examine gastrointestinal effects. Also, the study group sizes in the clinical studies were small, ranging from four to ten subjects.

The immediacy of the gastrointestinal effects, which typically occur within one hour of exposure, indicates that the mechanism may be local rather than systemic - probably the result of local irritation of the mucosa of the gastrointestinal tract. This view would be supported by the indications of mucosal irritation seen in gross and microscopic examinations of tissues from the gastrointestinal tract in animal studies.

The limited human data suggest that concentration as well as ingested dose may be important in eliciting gastrointestinal effects. Data from animal studies would support this view. A particular ingested dose would presumably confer a defined concentration within the gastrointestinal tract, that would be influenced by factors such as the volume of food or beverage consumed at the same time.

It also appears that other factors, besides concentration or dose, may potentiate or moderate the effect of ingested tin on the gastrointestinal tract. One of these may be the presence of particular large molecular species capable of forming complexes with the stannous ion, making it less soluble and apparently less irritant, as well as the physical adsorbtion of tin species onto solid food particles.

Overall, the published data do not present a particularly comprehensive profile on the toxic hazard to man of acute exposure to divalent inorganic tin. The human data are limited quantitatively and qualitatively and the acute animal studies tend to examine effects at very high doses/concentrations, and so are of little relevance to the human exposure being assessed.

There is no evidence to suggest that the ingestion of food containing inorganic tin would be associated with significant risks due to carcinogenicity, genotoxicity, reproductive toxicity or sensitisation. Studies in laboratory animals and a few clinical studies in humans indicated that the ingestion of about 0.5–1 mg tin/kg body weight daily for an extended period could alter the metabolism and body levels of zinc and other essential elements. An interdependence in the way that mammalian species handle (the cations of) certain metals, particularly those that are, or are similar to, essential elements, is established. In the healthy state, the body would be expected to have a reservoir of essential elements and small variations in the levels of these would not be expected to cause significant toxic effects.

Based on the data reviewed, a concentration of 200 mg/kg tin in foodstuffs would be very unlikely to impinge on the current JECFA limit for chronic exposure of 2 mg/kg body weight/day. As a worst case scenario, if all canned foods and beverages contained 200 mg/kg tin, the average daily ingestion of tin, from a 1 kg daily diet composed of 4–8% canned foods (MAFF, 1998) would be 8–16 mg/day, or around 0.13–0.3 mg/kg body weight for a 60-kg adult. Although these values do not take into account the range of consumption of canned foods, these values are at least 7-fold lower than the current JECFA figure of 2 mg/kg body weight/day.

The UK is the highest per capita European consumer of canned food and the largest consumer of plain

unlacquered cans (around 2,500 million annually) (MPMA, 2000), of which the contents of almost 4% probably contain at least 150 mg/kg tin (MAFF, 2002). Even if only 1% of UK cans contained food or drink with at least 150 mg/kg tin, this would suggest that the contents of 25 million cans of food or drink, containing this level of tin are still consumed annually. Also, as mentioned above, during the last 25 years, there have been no published reports of adverse effects attributed to tin contamination in the range 100–200 mg/kg. When put together, these two facts strongly suggest that there is little if any evidence for an association between the consumption of food containing tin at concentrations up to 200 mg/kg and significant acute adverse gastrointestinal effects.

In conclusion, despite the absence of recent reports, the potential for rare adverse acute gastrointestinal effects following the ingestion of foodstuffs containing 200 mg/kg tin cannot be totally discounted. In this respect, only well-defined clinical studies will ultimately provide the evidence that the current levels of tin in food are safe for adults in the general population.

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