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EVALUATION OF CERTAIN FOOD ADDITIVES AND CONTAMINANTS

Sixty-seventh report of the
Joint FAO/WHO Expert Committee on
Food Additives

Food and Agriculture
Organization of the
United Nations

World Health
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In addition, the analytical method for determining triphenylphosphine oxide was transferred from the specifications monograph to Volume 4 of the *Combined Compendium of Food Additives Specifications*, as this method is described in more than one specifications monograph. The method of assay was improved in terms of clarity. The Chemical and Technical Assessment for zeaxanthin (synthetic) and zeaxanthin-rich extract prepared by the Committee at its sixth-third meeting was updated.

4. Contaminants

4.1 Aluminium (from all sources, including food additives)

Explanation

Various aluminium compounds had been evaluated by the Committee at its thirteenth, twenty-first, twenty-sixth, twenty-ninth, thirtieth and thirty-third meetings (Annex 1, references *20*, *44*, *59*, *70*, *73* and *83*). At the thirteenth meeting, an ADI "not specified" was established for sodium alumino-silicate and aluminium calcium silicate (Annex 1, reference *20*). At its thirtieth meeting, the Committee noted concerns about a lack of precise information on the aluminium content of the diet and a need for additional safety data. The Committee set a temporary ADI of 0–0.6 mg/kg bw expressed as aluminium for all aluminium salts added to food, and recommended that aluminium in all its forms should be reviewed at a future meeting.

In the evaluation made by the Committee at its thirty-third meeting, emphasis was placed on estimates of consumer exposure, absorption and distribution of dietary aluminium and possible neurotoxicity, particularly the relationship between exposure to aluminium and Alzheimer disease. The Committee set a provisional tolerable weekly intake (PTWI) of 0–7.0 mg/kg bw for aluminium, including food additive uses. This was based upon a study in which no treatment-related effects were seen in beagle dogs given diets containing sodium aluminium phosphate (acidic) at a concentration of 3% for 189 days, equivalent to approximately 110 mg/kg bw aluminium. A consolidated monograph was produced (Annex 1, reference *84*).

Aluminium was re-evaluated by the Committee at its present meeting, as requested by CCFAC at its Thirty-seventh Session (*4*). The Committee was asked to consider all data relevant to the evaluation of the toxicity and intake of aluminium (including bioavailability) used in food additives and from other sources, including sodium aluminium phosphate. CCFAC asked that the exposure assessment cover all compounds included in the Codex GSFA.

Two documents were particularly important in the evaluation made by the Committee at its present meeting: the International Programme on Chemical Safety (IPCS) Environmental Health Criteria document on aluminium (*5*) and a report of the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) on a water pollution incident that occurred in Cornwall, England in 1988 (*6*). The Committee used those assessments as the starting point for its evaluation and also evaluated other data in the scientific literature relating to aluminium compounds. No original toxicological data on aluminium-containing food additives were submitted.

Absorption, distribution, metabolism and excretion

Assessment of the bioavailability of aluminium compounds is confounded by limitations in the analytical methodology, particularly for older studies, by concurrent exposure to modifying factors and by dose-dependency. Speciation appears to be an important factor in absorption and it is widely assumed that soluble aluminium compounds, such as the chloride and lactate salts, are more bioavailable than insoluble compounds, such as aluminium hydroxide or silicates. Studies in laboratory animals and in human volunteers generally show that absorption of aluminium is less than 1%. However, because of the differences in methodology, it is not possible to draw precise conclusions on the rate and extent of absorption of different aluminium compounds. Concurrent intake of organic anions (particularly citrate) increases the absorption of aluminium, while other food components, such as silicates and phosphate, may reduce the absorption of aluminium.

Studies reviewed by the Committee at its thirty-third meeting showed no detectable aluminium in the urine of normal subjects given aluminium hydroxide gel (2.5 g/day expressed as elemental aluminium (Al), equivalent to 42 mg/kg bw per day assuming body weights of 60 kg) for 28 days. In contrast, faecal excretion of aluminium in patients with chronic renal disease given aluminium hydroxide (1.5–3.5 g/day expressed as Al, equivalent to 25–57 mg/kg bw per day, assuming body weights of 60 kg) for 20–32 days indicated a daily absorption of 100–568 mg of Al. Slight increases in concentrations of aluminium in plasma were reported over the study period.

Oral dosing of rats with aluminium compounds has been shown to result in increased concentrations of aluminium in blood, bone, brain, liver and kidney. Studies with ^{26}Al administered intravenously to a small number of human volunteers indicate a biological half-life of

about 7 years (in one individual) and interindividual variation in clearance patterns.

Aluminium compounds have been reported to interfere with the absorption of essential minerals such as calcium and phosphate, although the extent to which this occurs at dietary exposure levels is unclear.

Toxicological data

The available studies were from the published literature and were not designed to assess the safety of food additives. Most were conducted to investigate specific effects or mechanisms of action, and many do not provide information on the dose–response relationship. Some do not make clear whether the stated dose relates to elemental aluminium or to the aluminium compound tested. A further complication is that many studies do not appear to have taken into account the basal aluminium content of the animal feed before addition of the test material. Some studies refer to basal aluminium content in the region of 7 mg/kg, which would not add significantly to the doses of aluminium under investigation. However, it has been reported that there are diverse concentrations ranging from 60 to 8300 mg/kg feed and that substantial brand-to-brand and lot-to-lot variation occurs. For chow containing Al at a concentration of 200 mg/kg, applying the default JECFA conversion factors indicates doses of Al equivalent to 30 mg/kg bw for mice and 20 mg/kg bw for rats.

The toxicological data are influenced by the solubility, and hence the bioavailability, of the tested aluminium compounds, and the dose–response relationship will be influenced by the Al content of the basal animal feed.

Recent studies have identified effects of aluminium compounds at doses lower than those reviewed previously by the Committee. Studies in rats, rabbits and monkeys have indicated effects on enzyme activity and other parameters associated with oxidative damage and calcium homeostasis in short-term studies with aluminium at oral doses in the region of 10–17 mg/kg bw per day. Those studies involved administration at a single dose and did not take into account the aluminium content of the diet. The functional relevance of the observations is unclear and since the total exposure is unknown, they are not suitable for the dose–response analysis.

Mild histopathological changes were identified in the kidney and liver of rats given aluminium sulfate by gavage at a dose of 17 mg/kg bw per day, expressed as Al, for 21 days. Rats given drinking-water containing aluminium chloride at a dose of 5 or 20 mg/kg bw per day,

expressed as Al, for 6 months showed non-dose-dependent decreases in body weight and changes in haematological parameters and acetylcholine-associated enzymes in the brain. Histopathological changes were observed in the kidney and brain at doses of 20 mg/kg bw per day, expressed as Al, in the latter study. Such effects had not been observed in other studies and total exposure was unknown since the aluminium content of the diet was not taken into account.

Beagle dogs given diets containing sodium aluminium phosphate (basic) for 6 months showed decreased food intake and body weight and histopathological changes in the testes, liver and kidneys in the males at the highest Al concentration tested, 1922 mg/kg of diet, equal to 75 mg/kg bw per day. No effects were seen in female dogs at this dietary concentration, equal to 80 mg/kg bw per day, expressed as Al. The NOEL in this study was a dietary concentration of 702 mg/kg, equal to 27 mg/kg bw per day, expressed as Al. This study is similar to that providing the basis for the previously established PTWI, which used sodium aluminium phosphate (acidic). The Committee noted that there was no explanation for the observed sex difference, and limitations in the reporting made interpretation of this study difficult.

Special studies have highlighted a potential for effects on reproduction, on the nervous system and on bone. Few of those studies are adequate to serve as a basis for the determination of no-effect levels, as they were designed to address specific aspects, and only a very limited range of toxicological end-points were examined.

Soluble aluminium compounds have demonstrated reproductive toxicity, with lowest-observed-effect levels (LOELs) in the region of 13–200 mg/kg bw per day, expressed as Al, for reproductive and developmental effects with aluminium nitrate. None of those studies identified NOELs. The lowest LOELs were obtained in studies in which aluminium compounds were administered by gavage; taking into account the aluminium content of the diet, the total dose may have been in the region of 20 mg/kg bw per day or more, expressed as Al.

Neurotoxicity potential has received particular attention because of a speculated association of aluminium with Alzheimer disease. Many of the studies in laboratory animals have been conducted using parenteral administration and are of uncertain relevance for dietary exposure because of the limited bioavailability of aluminium compounds likely to be present in food. In contrast to studies with other routes of administration, the available data from studies using oral administration do not demonstrate definite neuropathological effects. Some studies indicate that certain aluminium compounds, especially

the more soluble forms, have the potential to cause neurobehavioural effects at doses in the region of 50 to 200 mg/kg bw per day, expressed as Al, administered in the diet. The studies indicating the lowest LOELs took account of the basal diet content of aluminium and one of those studies also indicated a NOEL of 10 mg/kg bw per day, expressed as Al.

The previously established PTWI of 0–7.0 mg/kg bw for aluminium was based upon a study in which no treatment-related effects were seen in beagle dogs given diets containing sodium aluminium phosphate (acidic) at a dietary concentration of 3% for 189 days, equivalent to approximately 110 mg/kg bw aluminium.

The new data reviewed at the present meeting indicated that soluble forms of aluminium may cause reproductive and developmental effects at a dose lower than that used to establish the previous PTWI. Although insoluble aluminium compounds may be less bioavailable, the evidence that other dietary components, such as citrate, can increase uptake of insoluble aluminium suggests that data from studies with soluble forms of aluminium can be used as a basis for deriving the PTWI.

Observations in humans

The previous evaluation of aluminium made by the Committee at its thirty-third meeting did not include epidemiology studies. Since then a number of epidemiology studies had been conducted, with most focusing on the potential association of oral exposure to aluminium in water, food or antacids with Alzheimer disease and cognitive impairment. Some epidemiology studies of aluminium in water suggested an association of consumption of aluminium in water with Alzheimer disease, but such an association was not confirmed in others. None of the studies accounted for ingestion of aluminium in foods, a potentially important confounding factor. The studies relied on concentrations of aluminium in the residential water supply as a measure of exposure, with the one exception of a study that also assessed ingestion of bottled water.

There was minimal information from the epidemiology literature about the association between intake of aluminium in food and neurological conditions, and the current information from a pilot case–control study evaluating Alzheimer disease was considered to be preliminary. The epidemiology studies of the use of antacids did not capture dose information and did not demonstrate an association with neurological conditions. In the literature there have been a few case reports of adults, infants and a child with normal kidney

function who experienced skeletal changes attributable to frequent use of aluminium-containing antacids considered to induce phosphate depletion.

In summary, no pivotal epidemiology studies were available for the risk assessment.

Exposure to aluminium from the diet and other sources

Only consumer exposure to aluminium in the diet and via other routes or commodities were considered by the Committee; occupational exposure was not taken into account. Dietary sources of exposure include natural dietary sources, drinking-water, migration from food-contact material and food additives. When dietary exposure was expressed on a kg body weight basis, a standard body weight of 60 kg for an adult was considered by the Committee, unless otherwise specified.

Soil composition has a significant influence on the Al content of the food chain. The solubility of Al compounds may increase when acid rain decreases the pH of the soil; as a consequence, Al content increases in surface water, plants and animals. Most foods contain Al at concentrations of less than 5 mg/kg. It is estimated that quantities of about 1–10 mg/day per person generally derive from natural dietary sources of aluminium, corresponding to up to 0.16 mg/kg bw per day, expressed as Al. The concentration of dissolved Al in untreated water at near pH 7 is typically 1–50 μg/l, but this can increase to 1000 μg/l in acidic water. Exposure through this source is therefore up to 2 mg/day, corresponding to 0.03 mg/kg bw per day based on the consumption of 2 l of water per day. Al may also be present in drinking-water owing to the use of Al salts as flocculants in the treatment of surface waters. The concentration of Al in finished water is usually less than 0.2 mg/l. Based on a daily consumption of 2 l per day, dietary exposure to Al from treated drinking-water may be up to 0.4 mg/day, corresponding to 0.007 mg/kg bw per day.

Al is utilized extensively in structural materials used in food-contact materials, including kitchen utensils. Al can be released into the foodstuff in the presence of an acidic medium. Conservative assessments suggest that mean potential dietary exposure through this source may be up to 7 mg/day. Such dietary exposure corresponds to 0.1 mg/kg bw per day.

The current and draft provisions made for aluminium compounds in the Codex GSFA are reported in Table 5. Some Al-containing additives are listed only in the current versions of Table 1 and 2 of the Codex GSFA, and for those additives reference is made to the PTWI

Table 5
Aluminium compounds used as food additives present in the current and draft GSFA

Name	Function	Applications	Levels of use (expressed as Al)	INS No.	JECFA evaluation[a]
SALP, acidic & basic	Acidity regulator, emulsifier in processed cheeses,raising agent in bakery products, stabilizer, thickener	Baking powder, flours, bakery products, cheese, cocoa powders, desserts, bakery wares, confectionery, mixes for soups and sauces, concentrates for water-based flavoured drinks	Up to 35 000 mg/kg in processed cheese and 45 000 mg/kg in flours	541(i), 541(ii)	PTWI for aluminium powder (GSFA Tables 1 and 2)
Aluminium ammonium sulfate	Firming agent, raising agent, stabilizer	Bakery products (including ordinary bakery products), egg products, herbs and spices, soya-bean products, snacks, processed fish, processed vegetables, candied fruit	Up to 10 000 mg/kg in bakery products GMP in starch and soya-bean products	523	PTWI for aluminium powder (GSFA Tables 1 and 2)
Sodium aluminium silicate	Anti-caking agent	Salt and salt substitutes, sugar, grain Permitted for use in food in general	Up to 20 000 mg/kg in salt GMP in grain and food in general	554	ADI "not specified"
Calcium aluminium silicate	Anti-caking agent	Salt and salt substitutes, sugar, Grape wines, grain Permitted for use in food in general	Up to 20 000 mg/kg in salt GMP in grain, grape wine and food in general	556	ADI "not specified" (GSFA Tables 1, 2 and 3)
Aluminium silicate	Anti-caking agent	Salt and salt substitutes Grain, herbs and spices Permitted for use in food in general	Up to 10 000 mg/kg in salt GMP in grain, herbs and spices and in food in general	559	ADI "not specified" (GSFA Tables 1, 2 and 3)

ADI: acceptable daily intake; GMP: Good manufacturing practice; GSFA: General Standard for Food Additives; SALP: Sodium aluminium phosphate
[a] As reported in current and draft (*3*) GSFA

for aluminium established in 1988 by JECFA. It is the case for aluminium ammonium sulfate and sodium aluminium phosphate (SALP) — acidic and basic. Those aluminium compounds may be used according to good manufacturing practice (GMP) in a large number of products and at maximum levels in other products. The Committee noted that maximum levels are generally expressed as Al (e.g. 35 000 mg/kg expressed as Al, for sodium aluminium phosphate used in processed cheese) but that in some cases the reporting basis is not specified (up to 10 000 mg/kg in bakery products containing aluminium ammonium sulfate).

The Committee also noted that some food additives containing Al are listed in Tables 1, 2 and 3 of the current and draft Codex GSFA. In Table 3, reference is made to an ADI "not specified", and sodium aluminium silicate, calcium aluminium silicate and aluminium silicate are allowed at concentrations consistent with GMP in food in general. Specifications for other aluminium compounds are available in the *Combined Compendium of Food Additive Specifications* (Annex 1, reference *180*), but no provision had yet been made for them in Codex GSFA. This is the case for aluminium lakes of colouring matters, aluminium sulfate, aluminium powder and potassium aluminium sulfate. Other aluminium compounds are used in a number of countries but are not reported in the Codex GSFA nor in the *Combined Compendium of Food Additive Specifications*. This was the case for aluminium oxide and potassium aluminium silicate.

The Committee was provided with an exposure assessment based on annual sales of SALP in Europe suggesting that the average exposure in the general population is about 0.1 mg/kg bw per day, corresponding to less than 0.01 mg/kg bw per day expressed as Al, based on the fact that tetrahydrate SALP acidic has an Al content of 8.5%. The Committee was also provided with disappearance data from the USA for a number of aluminium compounds used as food additives. Overall, aluminium present in SALP, basic and acidic; aluminium sodium sulfate; sodium aluminium silicate and aluminium lakes intended for human consumption sold in the USA in 2003 and 2004 would provide 9 mg of Al per capita per year, corresponding to 0.0004 mg/kg bw per day. Other data provided to the Committee suggest that there is a large range of exposure among consumers. A survey conducted in 1979 suggests that 5% of adults in the USA were exposed to more than 1.5 mg/kg bw per day, expressed as Al, from food additives.

Additional data were available to estimate exposure in the population of interest i.e. regular consumers of products containing food additives containing aluminium. In the USA, although aluminium-

containing additives were found to be present in only a limited number of foods, some processed foods have a very high Al content: processed cheese, 300 mg/kg; home-made corn bread, 400 mg/kg (owing to the use of Al-containing leavening agents); muffins, 130 mg/kg; baking powder, 2300 mg/kg; and table salt, 164 mg/kg. In Germany, the processed foods found to have the highest Al content were biscuits (22 mg/kg) and soft cheese (8–16 mg/kg). In the 2000 UK Total Diet Study, the miscellaneous cereals group was reported to have the highest mean concentration of Al (19 mg/kg). In the 1992–1993 Chinese Total Diet Study, cereal products were also found to have the highest Al content (50 mg/kg) owing to the use of leavening agents containing Al. The potentially high Al content of cereal products and, in particular, of ordinary baked goods may be of special importance in a number of countries where they constitute staple food and may therefore be consumed regularly in large quantities by a significant proportion of the population.

Total dietary exposure to Al from all sources has been estimated through duplicate diet studies performed in adults in a number of countries. Mean values varied between 3 and 13 mg/day. The highest single reported value was 100 mg/day. In a multicentre study, exposure at the 75th percentile ranged from 3 to 26 mg/day, according to country. Data reported in Germany suggest that the amount of Al in the diet decreased by about half between 1988 and 1996.

A number of market-basket studies have also been performed, allowing estimation of exposure in different population groups based on mean content of Al in food groups, and on mean consumption. Exposure for consumers with a high consumption of cereal products or in regular consumers of products that contain higher-than-mean concentrations of Al will therefore be higher than estimated in those studies. In the adult population, mean exposure to Al estimated by model diet or market basket varied from 2 mg/day in the most recent French survey to more than 40 mg/day in China.

The highest mean exposure to Al per kg bw was found in young children: 0.16 mg/kg bw per day in the 1.5–4.5 years age group in the UK, based on measured body weight; approximately 0.5 mg /kg bw per day in the USA in children aged 2 years, considering a standard body weight of 12 kg; approximately 1 mg/kg bw per day in China in age groups 2–7 years and 8–12 years, considering as standard body weight 16.5 kg and 29.4 kg, respectively.

Values for high levels of exposure, estimated on the basis of high levels of consumption, were available for UK children aged 1.5–4.5 years (0.33 mg/kg bw per day).

The issue of bioavailability was considered by the Committee, but available data were not sufficient to correct the exposure assessment on the basis of bioavailability. Aluminium contained in some food additives such as silicates may have a low bioavailability, but the main sources of exposure are sulfates and phosphates used in cereal products. A diet high in fruit and fruit-based products could lead to higher bioavailability owing to the increased absorption of aluminium in the presence of citric acid. Citric acid is one of the main organic acids present in fruit and may also be added to fruit-based products and to cheese.

The Al content of milk and formulae was considered when estimating exposure for infants. The Al content of human and cows' milk was found to be negligible (less than 0.05 mg/l), while cows' milk-based and soya-based formulae were found to contain high levels of Al, leading to concentrations of 0.01–0.4 and 0.4–6 mg/l, respectively, in the ready-to-drink product. The Committee estimated dietary exposure to aluminium based on the highest of those values in an infant aged 3 months weighing an average of 6 kg, considering as 1 l of reconstituted formula per day as consumption at the 95th percentile. Expressed on a kg body weight basis, dietary exposure to Al was estimated to be up to 1 mg/kg bw per day and 0.06 mg/kg bw per day in infants fed soya-based formulae and milk-based formulae respectively. In the case of infants fed human or cows' milk, high consumption would lead to Al exposures of less than 0.01 mg/kg bw per day.

Sources of exposure to Al other than in the diet that were considered by the Committee were air, cosmetic and toiletry products and medicines. Al from air, in industrial areas, contributes up to 0.04 mg/day and therefore constitutes a minor source of exposure. Estimates of dermal absorption of aluminium chlorohydrate used as an active ingredient of antiperspirant suggest that only about 4 μg of Al is absorbed from a single use on both underarms. Some medical applications of aluminium may lead to long-term exposure: aluminium hydroxides in antacids, phosphate-binders and buffered analgesics. If taken as directed, the daily intake of Al from antacids could be as much as 5 g, while Al-buffered aspirin used for rheumatoid arthritis could contribute 0.7 g of aluminium per day.

In conclusion, the present assessment confirms previous evaluations made by the Committee in which dietary exposure, particularly through foods containing aluminium compounds used as food additives, was found to represent the major route of aluminium exposure for the general population, excluding persons who regularly ingest aluminium-containing drugs.

Evaluation

The Committee concluded that aluminium compounds have the potential to affect the reproductive system and developing nervous system at doses lower than those used in establishing the previous PTWI and therefore the PTWI should be revised. However, the available studies have many limitations and are not adequate for defining the dose–response relationships. The Committee therefore based its evaluation on the combined evidence from several studies. The relevance of studies involving administration of aluminium compounds by gavage was unclear because the toxicokinetics after gavage were expected to differ from toxicokinetics after dietary administration, and the gavage studies generally did not report total aluminium exposure including basal levels in the feed. The studies conducted with dietary administration of aluminium compounds were considered most appropriate for the evaluation. The lowest LOELs for aluminium in a range of different dietary studies in mice, rats and dogs were in the region of 50–75 mg/kg bw per day expressed as Al.

The Committee applied an uncertainty factor of 100 to the lower end of this range of LOELs (50 mg/kg bw per day, expressed as Al) to allow for inter- and intraspecies differences. There are deficiencies in the database, notably the absence of NOELs in the majority of the studies evaluated and the absence of long-term studies on the relevant toxicological end-points. The deficiencies are counterbalanced by the probable lower bioavailability of the less soluble aluminium species present in food. Overall, an additional uncertainty factor of three was considered to be appropriate. The Committee confirmed that the resulting health-based guidance value should be expressed as a PTWI, because of the potential for bioaccumulation. The Committee established a PTWI for Al of 1 mg/kg bw, which applies to all aluminium compounds in food, including additives. The previously established ADIs and PTWI for aluminium compounds were withdrawn.

The potential range of exposure from dietary sources is summarized in Table 6.

The Committee noted that the PTWI is likely to be exceeded to a large extent by some population groups, particularly children, who regularly consume foods that include aluminium-containing additives. The Committee also noted that dietary exposure to aluminium is expected to be very high for infants fed on soya-based formula.

Further data on the bioavailability of different aluminium-containing food additives are required.

Table 6
Estimated ranges of mean exposure of the adult population to aluminium from different dietary sources

Mean exposure	Natural dietary sources	Water (assuming a consumption of 2 l/day)	Food-contact materials	Overall diet, including additives
Expressed as Al in mg/week	7–70	<0.7 (typical untreated water) 1.4–2.8 (water treated with aluminium salts) 14 (acidic untreated water)	0–49[a]	14–280
Expressed as percentage of PTWI (assuming a body weight of 60 kg)	2–120	1–20	<80[a]	20–500

[a] Theoretical exposure using conservative assumptions

There is a need for an appropriate study of developmental toxicity and a multigeneration study incorporating neurobehavioural endpoints, to be conducted on a relevant aluminium compound(s).

Studies to identify the forms of aluminium present in soya formulae, and their bioavailability, are needed before an evaluation of the potential risk for infants fed on soya formulae can be considered.

An addendum to the toxicological monograph was prepared.

The ten existing specifications monographs for food additives containing aluminium were not reviewed at this meeting. They were (INS numbers): Aluminium ammonium sulfate (523), Aluminium lakes of colouring matters, Aluminium potassium sulfate (522), Aluminium powder (173), Aluminium silicate (559), Aluminium sulfate (anhydrous) (520), Calcium aluminium silicate (556), Sodium aluminium phosphate, acidic (541(i)), Sodium aluminium phosphate, basic (541(ii)) and Sodium aluminosilicate (554).

Recommendations to Codex

The Committee recommended that provisions for aluminium-containing additives included in the Codex GSFA should be compatible with the newly established PTWI for aluminium compounds of 1 mg/kg bw expressed as Al. The Committee noted in particular that provisions for such additives used at levels consistent with GMP in staple foods may lead to high exposure in the general population and in particular in children.