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Safety of aluminium from dietary intake[1]

Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC)

(Question Nos EFSA-Q-2006-168 and EFSA-Q-2008-254)

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SUMMARY

Following a request from the Commission, the Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC) was asked to provide a scientific opinion on the safety of aluminium from all sources of dietary intake. In the event the estimated exposure for a particular sub-group(s) is found to exceed the Provisional Tolerable Weekly Intake, a detailed breakdown by exposure source should be provided.

Aluminium occurs naturally in the environment and is also released due to anthropogenic activities such as mining and industrial uses, in the production of aluminium metal and other aluminium compounds.

A variety of aluminium compounds are produced and used for different purposes, such as in water treatment, papermaking, fire retardant, fillers, food additives, colours and pharmaceuticals. Aluminium metal, mainly in the form of alloys with other metals, has many uses including in consumer appliances, food packaging and cookware.

The major route of exposure to aluminium for the general population is through food. Aluminium in drinking water represents another, minor, source of exposure. Additional exposures may arise from the use of aluminium compounds in pharmaceuticals and consumer products.

Most unprocessed foods typically contain less than 5 mg aluminium/kg. Higher concentrations (mean levels 5 to 10 mg/kg) were often found in breads, cakes and pastries (with biscuits having the highest levels), some vegetables (with mushrooms, spinach, radish, swiss card,

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lettuce and corn salad having the highest levels), glacé fruits, dairy products, sausages, offals, shellfish, sugar-rich foods baking mixes, and a majority of farinaceous products and flours. Foods with very high mean concentrations included tea leaves, herbs, cocoa and cocoa products, and spices.

Under normal and typical conditions the contribution of migration from food contact materials would represent only a small fraction of the total dietary intake. However, the Panel noted that in the presence of acids and salts, the use of aluminium-based pans, bowls, and foils for foods such as apple puree, rhubarb, tomato puree or salted herring could result in increased aluminium concentrations in such foods. Also, the use of aluminium vessels and trays for convenience and fast food in might moderately increase the aluminium concentrations, especially in foods that contain tomato, different types of pickles, and vinegar.

Total dietary exposure to aluminium from all sources has been estimated from duplicate diet studies (the Netherlands, Hungary, Germany, Sweden, and Italy), and market basket and total diet studies (UK, Finland, and France). Mean dietary exposure from water and food in non-occupational exposed adults showed large variations between the different countries and, within a country, between different surveys. It ranged from 1.6 to 13 mg aluminium per day, corresponding to 0.2 to 1.5 mg/kg body weight (bw) per week in a 60 kg adult. Children generally have higher food intake than adults when expressed on a body weight basis, and therefore represent the group with the highest potential exposure to aluminium per kg body weight.. Large individual variations in dietary exposure to aluminium can occur. In children and young people the potential estimated exposure at the 97.5th percentile ranged from 0.7 mg/kg bw/week for children aged 3-15 years in France to 2.3 mg/kg bw/week for toddlers (1.5-4.5 years) and 1.7 mg/kg bw/week for those aged 4-18 years in the UK. Cereals and cereal products, vegetables, and beverages appeared to be the main contributors (>10%) to the dietary aluminium exposure in the general population.

In infants aged 0-3, 4-6, 7-9 and 10-12 months, potential dietary exposures from infant formulae and other foods manufactured specially for infants were estimated to be respectively 0.10, 0.20, 0.43 and 0.78 mg/kg bw/week.

Potential exposure to aluminium in 3-month infants from a variety of infant formulae was estimated by the Panel. At the mean it was up to 0.6 mg/kg bw/week for milk-based formulae and was 0.75 mg /kg bw/week for soya-based formulae; at high percentiles of exposure it was up to 0.9 mg/kg bw/week for milk-based formulae and was 1.1 mg /kg bw/week for soya-based formulae.

The Panel noted that in some individual brands of formulae (both milk-based and soya-based) the aluminium concentration was around 4 times higher that the mean concentrations estimated above, leading to a 4 times higher potential exposure in brand-loyal infants.

Potential exposure in breast-fed infants was estimated to be less than 0.07 mg/kg bw/week.

The oral bioavailability of the aluminium ion in humans and experimental animals from drinking water has been estimated to be in the range of 0.3%, whereas the bioavailability of aluminium from food and beverages generally is considered to be lower, about 0.1%. However, it is likely that the oral absorption of aluminium from food can vary at least 10-fold depending on the chemical forms present. Although the degree of water solubility of an aluminium compound appears to increase the bioavailability of the aluminium ion, the presence or absence in the intestines of dietary ligands may either increase (e.g. citrate, lactate, and other organic carboxylic acid complexing agents, fluoride), or decrease the absorption (e.g. phosphate, silicon, polyphenols).

After absorption, aluminium distributes to all tissues in animals and humans and accumulates in some, in particular bone. The main carrier of the aluminium ion in plasma is the iron binding protein, transferrin. Aluminium can enter the brain and reach the placenta and fetus.

Aluminium may persist for a very long time in various organs and tissues before it is excreted in the urine. Although retention times for aluminium appear to be longer in humans than in rodents, there is little information allowing extrapolation from rodents to the humans.

Although at high levels of exposure, some aluminium compounds may produce DNA damage in vitro and in vivo via indirect mechanisms, the Panel considered this unlikely to be of relevance for humans exposed to aluminium via the diet.

The database on carcinogenicity of aluminium compounds is limited. In the most recent study no indication of any carcinogenic potential was obtained in mice given aluminium potassium sulphate at high levels in the diet. Overall the Panel concluded that aluminium is unlikely to be a human carcinogen at dietary relevant doses.

Aluminium has shown neurotoxicity in patients undergoing dialysis and thereby chronically exposed parenterally to high concentrations of aluminium. It has been suggested that aluminium is implicated in the aetiology of Alzheimer's disease and associated with other neurodegenerative diseases in humans. However, these hypotheses remain controversial. Based on the the available scientific data, the Panel does not consider exposure to aluminium via food to constitute a risk for developing Alzheimer's disease.

The Panel noted that several compounds containing aluminium have the potential to produce neurotoxicity (mice, rats) and to affect the male reproductive system (dogs). In addition, after maternal exposure they have shown embryotoxicity (mice) and have affected the developing nervous system in the offspring (mice, rats). The Panel also noted that there are very few specific toxicological data for food additives containing aluminium. Thus the Panel considered it prudent to take these effects into account when setting a tolerable intake for all dietary sources. The available studies have a number of limitations and do not allow any dose-response relationships to be established. The Panel therefore based its evaluation on the combined evidence from several studies in mice, rats and dogs that used dietary administration of aluminium compounds. In these studies the lowest-observed-adverse-effect levels (LOAELs) for effects on neurotoxicity, testes, embryotoxicity, and the developing nervous system were 52, 75, 100, and 50 mg aluminium/kg bw/day, respectively. Similarly, the lowest no-observed-adverse-effect levels (NOAELs) for effects on these endpoints were reported at 30, 27, 100, and for effects on the developing nervous system, between 10 and 42 mg aluminium/kg bw per day, respectively.

In view of the cumulative nature of aluminium in the organism after dietary exposure, the Panel considered it more appropriate to establish a tolerable weekly intake (TWI) for aluminium rather than a tolerable daily intake (TDI). Based on the combined evidence from the above-mentioned studies, the Panel established a TWI of 1 mg aluminium/kg bw/week.

The estimated daily dietary exposure to aluminium in the general population, assessed in several European countries, varied from 0.2 to 1.5 mg/kg bw/week at the mean and was up to 2.3 mg/kg bw/week in highly exposed consumers.

The TWI of 1 mg/kg bw/week is therefore likely to be exceeded in a significant part of the European population. Cereals and cereal products, vegetables, beverages and certain infant formulae appear to be the main contributors to the dietary aluminium exposure.

Due to the design of the human dietary studies and the analytical methods used, which only determine the total aluminium content in food, and not the individual aluminium compounds or species present, it is not possible to conclude on the specific sources contributing to the

aluminium content of a particular food, such as the amount inherently present, the contributions from use of food additives, and the amounts released to the food during processing and storage from aluminium-containing foils, containers, or utensils. Thus a detailed breakdown by exposure source is not possible.

Key words:

Aluminium, CAS number 7429-90-5, Aluminium sulphate, Aluminium sodium sulphate, Aluminium potassium sulphate, Aluminium ammonium sulphate, Sodium aluminium phosphate (acidic), Sodium aluminium silicate, Potassium aluminium silicate, Calcium aluminium silicate, Aluminium silicate (Kaolin), Potassium aluminium silicate, Bentonite, Aluminium silicate (Kaolin), Starch aluminium octenyl succinate, aluminium lakes, E 173, E 520, E 521, E 522, E 523, E 541, E 554 E 555, E 556, E 558, E 559, E 1452

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BACKGROUND AS PROVIDED BY THE COMMISSION

European Parliament and Council Directive 95/2/EC on food additives other than colours and sweeteners (as amended) allows a number of aluminium-containing additives to be used in some foodstuffs. Notably aluminium sulphates (E 520-523) are permitted to be used in egg white and candied, crystallised glace fruit and vegetables; acidic sodium aluminium phosphate (E 541) is permitted in scones and sponge wares; aluminium silicates (E 553-559) are permitted in a limited range of food categories and starch aluminium octenyl succinate (E 1452) is permitted in food supplements.

Moreover, the European Parliament and Council Directive 94/36/EC on colours for use in foodstuffs (as amended) also permits the use of aluminium (E 173) for the external coating of sugar confectionery for decoration of cakes and pastries, in addition to allowing the use of aluminium lakes of the permitted colours.

Food additives are reported to be the greatest contributors to intake of aluminium from food, but other sources also contribute to the overall intake, e.g. aluminium naturally present in plant products and migration from food contact materials.

Plants can take up aluminium from the soil and from water in which aluminium (the third most abundant element, constituting approximately 8% of the earth's crust) is present.

As regards food contact materials, aluminium may migrate to food from aluminium cookware, kitchen utensils, cans, foils, etc. Aluminium and some aluminium salts are permitted to be used in plastics under Commission Directive (EC) No 2002/72/EC relating to plastic materials and articles intended to come into contact with foodstuffs, however, no specific migration limit is set for aluminium. Within Council of Europe Guidelines on Metals and Alloys used as food contact materials (13.02.2002), recommendations to minimise migration of aluminium were included.

Previously the Scientific Committee for Food (SCF) evaluated the safety of aluminium-containing food additives in 1990 at which time they endorsed the Provisional Tolerable Weekly Intake (PTWI) of 7 mg/kg bw for aluminium for all intake sources, established previously by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).

Recently at its sixty-seventh meeting, JECFA re-evaluated aluminium from all sources, including food additives, and established a PTWI of 1 mg/kg bw which is 7 times lower than the previous PTWI. JECFA also noted that *´the PTWI is likely to be exceeded to a large extent by some population groups, particularly children, who regularly consume foods that included aluminium-containing additives´*.

In view of the above, EFSA is requested to assess the possible risk for human health from the presence of aluminium in food, considering all sources of dietary intake. Such an assessment should take into account the exposure of the most vulnerable groups of the population.

TERMS OF REFERENCE AS PROVIDED BY THE COMMISSION

In accordance with Article 29 (1) (a) of Regulation (EC) No 178/2002, the European Commission asks the European Food Safety Authority to provide a scientific opinion on the safety of aluminium from dietary intake. In the event the estimated exposure for a particular sub-group(s) is found to exceed the Provisional Tolerable Weekly Intake, a detailed breakdown by exposure source should be provided.

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ASSESSMENT

This opinion on the safety of aluminium from dietary exposure covers all sources of aluminium in the diet. These sources include the background levels inherently present in food plants and animals due to the widespread environmental occurrence of aluminium, the contributions from the use of aluminium-containing food additives, and the amounts released to the food during processing and storage from aluminium-containing food contact materials such as foils, containers, or utensils. An additional exposure may arise from aluminium in drinking water.

In the main opinion only brief summaries of the data are given in the sections on Dietary exposure (section 4) and Biological and toxicological data (section 5). Detailed information on these data and the relevant references are given in the Annex (Annex to the scientific opinion on safety of aluminium from dietary intake).

1. Chemistry

1.1. Description

Aluminium is a silvery, white metal. It is ductile and malleable, non-magnetic and non-combustible (IAI, 2007). Its CAS number is 7429-90-5. It is the thirteenth element in the periodic system, with atomic number 13 and a relative atomic mass of 26.98. Its melting point is 660°C and its boiling point is 2467 °C. The density is 2.7 g/cm^3. The naturally occurring stable isotope is ^{27}Al. The isotope ^{26}Al has a long half life but a low natural abundance and is used as a tracer in biological studies (Jouhanneau *et al.*, 1994). The small ionic radius (54 pm) and the electric charge gives Al^{3+} a strong polarizing effect on adjacent atoms; indeed, aluminium is too reactive to be found free in nature, where aluminium exists only in the oxidation state Al^{3+} (Giordano *et al.*, 1993; Martin, 1991).

1.2. Aluminium chemistry in complex formation

The basic electronic configuration of aluminium is $1s^2$, $2s^2$, $2p^6$, $3s^2$, 3p. In the oxidation state of Al^{3+} the aluminium ion has the electronic stable configuration of $1s^2$, $2s^2$, $2p^6$. In solution the ion may easily form complexes due to the hybridisation of the external atomic orbitals 3s, 3p and 3d that are empty and therefore form six hybrid orbitals of d^2sp^3 type arranged in octahedral geometry (Kirk Othmer, 1963). The coordination number is mainly six and less frequently four (Ohman, *et al.*, 1996). However, Swaddle et al. (Swaddle *et al.*, 2005) found kinetic evidence for five-coordination in the $Al(OH)^{2+}$ ion. A variety of complexes may be formed with the ligands present in biological systems and/or in foods. The complexes between ligands and aluminium have different physicochemical properties, such as solubility in aqueous medium, stability towards hydrolysis at different pH, electric charge etc. This can greatly influence the toxicokinetic and toxicodynamic profile of aluminium.

In aqueous media, water molecules form relatively strong bonds with the Al^{3+} ion and it has been recognised that in aqueous solution the ligands that form stable complexes with the Al^{3+} ion are fluoride ion and ligands coordinating by means of oxygen donor atoms. It is well known that the number of water molecules in this first sphere of coordination is six, and that these water molecules are regularly coordinated in a octahedral geometry, forming the species $[Al(H_2O)_6]^{3+}$, usually abbreviated as Al^{3+}. This species has a greater tendency to exchange protons than water molecules. In fact the $[Al(H_2O)_6]^{3+}$ ion behaves as a weak acid due to ion-

dipole forces between Al^{3+} and the oxygen atoms of the coordinated water molecules. It should be stressed that whatever ligands may be present in biological systems the equilibrium between aluminium and the hydroxide anion must be always considered (Ohman, *et al.*, 1996).

In acidic aqueous solutions with pH <5, the aluminium ion exists mainly as $[Al(H_2O)_6]^{3+}$. With increasing pH, in less acidic solutions, a series of successive deprotonations of $[Al(H_2O)_6]^{3+}$ occur to yield $Al(OH)^{2+}$, $Al(OH)_2^{+}$ and soluble $Al(OH)_3$, with a corresponding decrease in the number of water molecules. Neutral solutions give an $Al(OH)_3$ precipitate which redissolves owing to the formation of the aluminate anion $Al(OH)_4^-$; a mixture of these species occurs in the pH range of 5-7, but at pH > 6.2 $Al(OH)_4^-$ is the predominant soluble aqueous species (Martin, 1991).

2. Sources

2.1. Natural sources

Aluminium occurs naturally in the environment, and is the most abundant metallic element in the earth's crust where it is frequently found as alumino-silicates, hydroxides, phosphates, sulphates and cryolite (WHO, 1997). Levels in soil vary widely, ranging from about 7 to over 100 g/kg. Natural processes such as soil erosion, weathering of rocks and volcanic activity result in the release and redistribution of aluminium compounds to other environmental compartments including water, air and biota. Release of aluminium from geological sources to the environment has increased due to acid rain, resulting in a lowering of soil pH and increased solubility of the aluminium compounds. Aluminium is also released due to anthropogenic activities such as mining and industrial uses, in the production of aluminium metal and other aluminium compounds.

2.2. Other sources

Aluminium metal

Aluminium metal is produced all over the world. The aluminium metal production process involves two main stages: refining of aluminium oxide from the bauxite or cryolite ores in a caustic soda-high temperature process and then electrolytic smelting process which reduces the aluminium oxide trihydrate (alumina) into metallic aluminium and oxygen. Subsequently other elements are generally added to obtain different alloys (IAI, 2007).

Aluminium compounds

Aluminium may form inorganic compounds and compounds with organic moieties especially with organic acids (e.g. lactic acid, stearic acid etc), that are produced for different purposes. In aqueous solution, aluminium in the compounds is typically present in its 3+ oxidation state (Silvestroni, 1977).

Table 1 reports basic physicochemical properties of some commonly used aluminium compounds.

Table 1. **Basic physicochemical properties of some commonly used aluminium compounds**

Name	Synonyms	Molecular formula	E num.	MW	solubility in water	Notes	References (from ATSDR† when not specified)
Aluminium ammonium sulphate	ammonium alum	$AlNH_4(SO_4)_2$	E 523	237.15	freely soluble		JECFA, 1985a
Aluminium ammonium sulphate dodecahydrate		$AlNH_4(SO_4)_2 . 12H_2O$	NA*	453.32	freely soluble		JECFA,1985a
Aluminium chloride		$Al Cl_3$	NA*	133.34	Reacts evolving hydrochloric acid and heat		
Aluminium chlorohydrate (anhydrous)		not available $Al_nCl_{(n-m)}(OH)_m$	NA*	not available	55% w/w	colloidal solution	
Aluminium fluoride		AlF_3	NA*	83.98	5.59 g/l at 25 °C, sparingly soluble in acids and alkali		
aluminium hydroxide		$Al(OH)_3$	NA*	78.01	insoluble, soluble in alkaline and acid solutions		
Aluminium lactate		$C_9H_{15} AlO_9$	NA*	294.19	freely soluble		
Aluminium nitrate		$Al (NO_3)_3$	NA*	213.00	freely soluble		
Aluminium oxide	Aluminium trioxide, alumina,	Al_2O_3	NA*	101.94	0.98 mg/L in cold water, insoluble in hot water, slightly soluble in acid and alkali		
Aluminium phosphate		$AlPO_4$	NA*	121.95	insoluble		
Aluminium potassium sulphate		$AlK(SO_4)_2$	E 522	258.2	50 g/L in cold water, 1g/1ml in boiling water		
Aluminium silicate (Kaolin)		$Al_2O_3.2SiO_2.2 H_2O$	E 559		insoluble		NNT,2000
Aluminium sodium sulphate		$AlNa(SO_4)_2$	E 521	241.11	soluble in cold and hot water		Sargent-Welch, 2007
Aluminium sulphate		$Al_2(SO_4)_3$	E 520	342.14	soluble in 1 part water 370 g/l		Lenntech, 2007
Aluminium citrate		$C_6 H_8 O_7$.X-AL	NA*		soluble in water		
Bentonite		$(AlMg)_8(Si_4O_{10})_4(OH)_8 .12 H_2O$	E 558	819			

† Agency for Toxic Substances and Disease Registry
* NA: non authorised as a food additive

Name	Synonyms	Molecular formula	E num.	MW	solubility in water	Notes	References (from ATSDR† when not specified)
Calcium aluminium silicate			E556		insoluble		NNT, 2000
Potassium aluminium silicate		$KAl_2[AlSi_3O_{10}](OH)_2$	E 555	398	insoluble	natural mica consists of mainly potassium aluminium silicate	
Sodium aluminium phosphate, acidic	SALP, SALP, acidic	$NaAl_3H_{14}(PO_4)_8.4\ H_20$ $Na_3Al_2H_{15}(PO_4)_8$	E 541	949.88 897.82	insoluble; soluble in hydrochloric acid	jecfa: 541 i	JECFA, 1985 b
Sodium aluminium phosphate, basic	KASAL SALP, basic	approx. $Na_8Al_2(OH)_2(PO_4)_4$ + 30% NaH_2PO_4	NA*		soluble in hydrochloric acid; sodium phosphate moiety : soluble in water; sodium aluminium phosphate moiety:sparingly soluble in water	jecfa: 541 ii	JECFA 1985 c
Sodium aluminium silicate	sodium silicoaluminate	a series of hydrated sodium aluminium silicates	E 554		insoluble; partially soluble in strong acids and alkali hydroxides		JECFA, 1973

3. Uses

A variety of aluminium compounds are produced and used for different purposes, such as in water treatment, papermaking, fire retardants, fillers, food additives, colours and pharmaceuticals. Aluminium metal, mainly in the form of alloys with other metals, has many uses including as structural materials in construction, automobiles, aircraft and machinery, in consumer appliances, food packaging and cookware. Aluminium compounds also have a wide variety of uses, including production of glass, ceramics, rubber, waterproofing textiles, wood preservatives, pharmaceuticals and food additives. Natural aluminium minerals such as bentonite and zeolite are used in water purification or in the detergent sector (as builder in phosphate-free detergents), and in the sugar refining, brewing, wine making, and paper industries.

3.1. Use of aluminium and aluminium compounds in food contact materials

The use of aluminium in food contact materials fall into two main fields: use of aluminium and its alloys as food contact materials and use of aluminium and aluminium organic and inorganic compounds as additives for food contact materials.

3.1.1. Aluminium and its alloys

Aluminium metal and its alloys are used to manufacture articles that are destined to be used for processing, packaging, and storage of foods at the industrial, the retail and the domestic level.

A variety of industrial applications of aluminium food containers are now available, in which aluminium is the main component (e.g. cans for beverages, fish or meat, small flexible tubes, caps or tear open closures) or is included in a multilayer structure composed of several materials (e.g. beverages cartons, plastic laminates etc). In these applications aluminium is generally not in direct contact with foods, being coated or coupled with plastic barrier layers. However, uses of aluminium metal exist also in food industry applications in which aluminium is in direct contact with foods, such as industrial pans and utensils to process foods, or foil and trays for long term packaging of chocolate and cakes. Moreover, aluminium is widely used in the food industry as a component of materials and machinery used in food processing (e.g. surfaces, accessories, tanks etc).

Typical examples of domestic use are pans, coffee pots, baking trays, kitchen utensils and accessories, containers for dried spices, sugar and coffee, and wrapping foils for cooking and storage of foods.

Finally, disposable food trays and foils are extensively used at the retail level for take away food and especially at the catering level, but food trays for frozen or refrigerated oven-ready meals are also widely used at the industrial level.

The use of aluminium and alloys as a food contact material is regulated at the EU level by the general provisions under Regulation (EC)1935/2004 (Framework Regulation on materials and articles in contact with foods (EC, 2004)); according to Art.3 materials and articles intended to come into contact with foodstuffs under normal or foreseeable conditions of use must not transfer their constituents to food in quantities which could endanger human health, or bring

about an unacceptable change in the composition of the food, or bring about a deterioration in the organoleptic characteristics thereof.

International technical standards such as EN 601 and EN 602 (EN 601, 2004; EN 602, 2004) are available to characterize the compositions of aluminium and its alloys when used to produce castings and semi-finished products for food contact materials.

3.1.2. Aluminium and aluminium compounds as additives in food contact plastic materials

The use of aluminium as such and of certain aluminium organic and inorganic compounds as additives for food contact plastic materials is permitted under Directive 2002/72/EC (EC, 2002) and amendments relating to plastic materials and articles intended to come into contact with foodstuffs. The following additives are in the positive lists of the substances authorized at the EU level, and relevant provisions include the specific migration limit (SML) for the specified compound in foods.

Table 2. **Aluminium-containing additives authorised for food contact plastic materials**

Ref no	CAS	Name	Restrictions and/or specifications
34475	-	Aluminium calcium hydroxide phosphite, hydrate	
34480		Aluminium fibers, flakes and powders	
34560	021645-51-2	Aluminium hydroxide	
34650	151841-65-5	Aluminium hydroxybis[2,2'-methylenebis(4,6-di-tert.butylphenyl)phosphate]	SML= 5 mg/kg
34690	011097-59-9	Aluminium magnesium carbonate hydroxide	
34720	001344-28-1	Aluminium oxide	
85760	012068-40-5	Silicic acid, lithium aluminium salt (2:1:1)	SML (T) relative to Lithium

The SML for Ref no. 85760 refers to lithium ion. The (T) refers to "Total" limit for lithium.

Aluminium salts of the authorised acids, phenols or alcohols are also indirectly authorised as monomers and/or additives, even if not specifically mentioned, for food contact plastic materials under the Directive 2002/72/EC and amendments.

The use of aluminium and alloys is also specifically regulated in the national legislations in some EU- Member States as well as aluminium organic and inorganic compounds for other food contact materials.

3.2. Authorised food additives containing aluminium according to Directive 95/2/EC on food additives other than colours and sweeteners

Certain aluminium compounds, namely aluminium sulphate, aluminium sodium sulphate, aluminium potassium sulphate, aluminium ammonium sulphate, sodium aluminium phosphate (SALP, acidic form), sodium, potassium and calcium aluminium silicate, and bentonite are permitted as food additives under Directive 95/2 EC on food additives other than colours and sweeteners. The following provisions apply, in relation to foodstuffs in which the additives are permitted and the maximum levels permitted:

Table 3. **Aluminium-containing food additives (other than colours and sweeteners) authorised for use in the European Union (Directive 95/2/EC modified)**

E No	Name	Foodstuff	Maximum level
E 520	Aluminium sulphate	Egg white	30 mg/kg
E 521	Aluminium sodium sulphate		
E 522	Aluminium potassium sulphate	Candied, crystallized and glacé fruit and vegetables	200 mg/kg, Individually or in combination, expressed as aluminium
E 523	Aluminium ammonium sulphate		
E 541	Sodium aluminium phosphate, acidic	Fine bakery wares (scones and sponge wares only)	1 g/kg expressed as aluminium
E 554	Sodium aluminium silicate	Dietary food supplements	quantum satis
E 555	Potassium aluminium silicate	Foodstuffs in tablet and coated tablet form	quantum satis
E 556	Calcium aluminium silicate		
E 559	Aluminium silicate (Kaolin)	Rice	quantum satis
		Sausages (surface treatment only)	quantum satis
		Confectionery excluding chocolate (surface treatment only)	quantum satis
		Seasonings	30 g/kg
		Tin-greasing products	30 g/kg
		Dried powdered foodstuffs (including sugars)	10 g/kg
		Salt and its substitutes	10 g/kg
		Sliced or grated hard, semi-hard and processed cheese	10 g/kg
		Sliced or grated cheese analogues and processed cheese analogues	10 g/kg
		Chewing gums	
E 555	Potassium aluminium silicate		In E 171 titanium dioxide and E 172 iron oxides and hydroxides (max 90 % relative to the pigment)
E 558	Bentonite	As carriers:	Colours, max. 5 %
E 559	Aluminium silicate (Kaolin)		Colours, max. 5 %
E 1452	Starch aluminium octenyl succinate	Encapsulated vitamin prepartions in food supplements as defined in Directive 2002/46/EC	35 g/kg in food supplements

3.3. Authorised food colours containing aluminium according to Directive 94/36/EC on colours for use in foodstuffs

Directive 94/36/EC currently authorises the use of aluminium metal (E173) for the external coating of sugar confectionery and for decoration of cakes and pastries (at quantum satis).

In addition, aluminium lakes* can also be prepared from a number of colours listed in the annex I to Directive 94/36/EC and used in various applications. The aluminium lakes are prepared by reacting food colours with alumina (aluminium trioxide) under aqueous conditions, resulting in a water-insoluble colour which has advantages for use in e.g. food products containing oils and fats, or products lacking sufficient moisture to dissolve the water-soluble colours.

According to the data provided on lakes from natural colours there is quite a large variation in the dye contents from approximately 2.5% to 50% and also in their aluminium contents; aluminium content in the lakes range from 0.01 to 18 % w/w depending on the lake.

Aluminium lakes are used at a level up to 950 mg/kg in confectionery and fine bakery wares mostly in decorations, icing, coatings and fillings (CIAA, 2007).

3.4. Specific purity criteria concerning food additives

Specifications for the aluminium-containing food additives listed above are included in Directive 96/77/EC. In addition, Commission Directive 95/45/EC, which lays down specific purity criteria concerning colours for use in foodstuffs, provides general specifications for the aluminium lakes of permitted food colours such as Ponceau 4R, Sunset Yellow and Quinoline Yellow. The purity criteria for the original food colour also apply to the aluminium lake. In addition, the aluminium lake should contain no more than 0.5% HCl-insoluble material and no more than 0.2% ether-extractable material under neutral conditions. There are no additional specification requirements for the aluminium lakes (Directive 95/45/EC). However, it is noted that according to the definition of aluminium lakes unreacted aluminium may also be present in the final product.

3.5. Use of Aluminium in water for human consumption

Aluminium compounds (e.g. aluminium sulphate, aluminium polychloride) are used as flocculating agents in the treatment of water intended for human consumption. In the Council Directive 1998/83/EC (Quality of water for human consumption) aluminium ion is one of the indicator parameters that must be monitored among the Quality Standards set by the Article 5. The parametric value is 200 µg/l (Annex I, part C): the value is fixed only for monitoring purposes and for the fulfilment of the obligations imposed in Article 8 of the above directive.

There is no limit value for aluminium ion in the mineral water regulation (Directive 2003/40/CE).

* general definition of lakes

3.6. 3.6 Miscellaneous uses

Aluminium compounds are used in over-the-counter medicinal products and in the manufacture of topically applied products such as antiperspirants. Aluminium and aluminium compounds also have many uses in manufacturing industry. While this opinion focuses on exposure from food sources, other sources of exposure must also be taken into account, and it is recognised that users of aluminium-containing medications are exposed to (much) higher doses than those resulting from aluminium in their diet. Similarly, industrial workers may be exposed to high levels of aluminium. Based on limited data, daily occupational aluminium exposure can range from <1 mg to 40 mg per 8-h shift.

4. Dietary Exposure

The major route of exposure to aluminium for the general population is through food, both as a consequence of the natural occurrence of aluminium in food (e.g. fruit, vegetables, cereals, seeds and meat), and the use of aluminium and aluminium compounds in food processing, packaging and storage, and not least the use of aluminium compounds as food additives. Aluminium in drinking water represents a minor source of exposure. The Panel noted that additional exposures may arise from the use of aluminium compounds in pharmaceuticals and consumer products, such as antiperspirants, and through occupational exposure (see 3.6).

Studies from Germany, France, UK, Ireland, and Spain have shown that most unprocessed foods typically contain less than 5 mg aluminium/kg. Higher concentrations (mean levels 5 to 10 mg/kg) were often found in breads, cakes and pastries (with biscuits having the highest levels), some vegetables (with mushrooms, spinach, radish, swiss chard, lettuce and corn salad having the highest levels), glacé fruits, dairy products (with soft cheese having the highest level), sausages, offals, shellfish, sugar-rich foods, baking mixes, and a majority of farinaceous products and flours. Foods with very high mean concentrations included tea leaves, herbs, cocoa and cocoa products, and spices. It should be stressed that large variations were seen in the aluminium content of the individual food types between and within the various countries, probably reflecting differences in local background levels of aluminium and differences in use patterns of aluminium-containing food additives and food contact materials. Due to the design of the human dietary studies and the analytical methods used, which only determine the total aluminium content in food, and not the individual aluminium compounds or species present, it is not possible to conclude on the specific sources contributing to the aluminium content of a particular food, such as the amount inherently present, the contributions from use of food additives, and the amounts released to the food during processing and storage from aluminium-containing foils, containers, or utensils.

Aluminium migration from food contact materials seems to depend on several factors such as the duration and temperature of heating, the composition and the pH-value of food, and the presence of other substances (e.g. organic acids, salt and other ions). Under normal and typical conditions the contribution of migration from food contact materials would represent only a small fraction of the total dietary exposure. However, the Panel noted that in the presence of acids and salts, the use of aluminium-based pans, bowls, and foils for foods such as apple puree, rhubarb, tomato puree or salted herring could result in increased aluminium concentrations in such foods. Also, the use of aluminium vessels and trays for convenience and fast food might moderately increase the aluminium concentrations, especially in foods that contain tomato, different types of pickles, and vinegar.

Total dietary exposure to aluminium from all sources has been estimated from duplicate diet studies (the Netherlands, Hungary, Germany, Sweden, and Italy), and market basket and total diet studies (UK, Finland, and France). Duplicate diets can be considered as the most accurate approach for measuring the real exposure of an individual. However, this approach requires a considerable commitment from the participants and during the survey there is a risk of a change in the pattern of food consumption. Market basket and total diet studies allow the estimation of the population dietary exposures to aluminium based on the analytical determination of the content of aluminium established in food groups or food items as consumed by the population surveyed.

In the above mentioned European countries non-occupationally exposed adults have an estimated mean dietary exposure between 1.6 and 13 mg aluminium per day from food. This range correspond to a dietary exposure from 0.2 to 1.5 mg/kg bw /week in a 60 kg adult. Large variations in mean dietary exposure were found between the different countries and, within a country, between different surveys. It is not always clear if the contribution of drinking water is included in these estimates, but the dietary exposure to aluminium from treated drinking water might be relatively low (up to 0.4 mg/day). Large individual variations in dietary exposure can occur as a consequence of differences in living areas and soil composition, individual dietary patterns and consumption of foods with aluminium-containing food additives.

In France and UK results of total diet studies were also used to assess upper percentiles of exposures by combining analytical results with raw data, including individual body weight, from national dietary surveys. Children generally have a higher food intake than adults when expressed on a body weight basis, and therefore represent the group with the highest potential exposure to aluminium per kg body weight. In children and young people the potential estimated exposure at the 97.5th percentile ranged from 0.7 mg/kg bw/week for children aged 3-15 years in France to 2.3 mg/kg bw/week for toddlers (1.5-4.5 years) and 1.7 mg/kg bw/week for those aged 4-18 years in the UK. A duplicate diet study conducted in 1988 in the former West Germany indicated that 10% of children aged 5-8 years had an exposure higher than 0.38 mg/kg bw/week. For adults the highest potential estimated dietary exposure (97.5th percentile) was 0.4 mg/kg bw/week in France and 0.94 mg/kg bw/week in the UK. In the elderly living in care in the UK these estimates were slightly higher (1.14 mg/kg bw/week).

In infants aged 0-3, 4-6, 7-9 and 10-12 months potential dietary exposures from infant formulae and other foods manufactured specially for infants were estimated to be respectively 0.10, 0.20, 0.43 and 0.78 mg/kg bw/week in a study by FSA (2006) based on maximum recommended amounts of foods from manufacturer's example menus. Due to the study design, these potential dietary exposures might be overestimated since wastage of food was not considered. On the other hand these estimates did not include any contribution from home-made (baby) food or from breast milk and no account was made of the possible contribution from water used to reconstitute dried or concentrated infant food and formulae. Moreover, brand loyalty was not considered.

The aluminium content of infant formulae varies according to their formulation with higher levels being found in soya-based formulae.

Potential exposure to aluminium for infants from a variety of formulae (including water used in the reconstitution) was estimated by the Panel based on analytical determination performed by Navarro-Blasco & Alvarez-Galindo (2003) in products available on the Spanish market. Average concentration values ranged from 0.24 mg/l to 0. 69 mg/l in reconstituted milk-based formulae and was 0.93 mg/l in reconstituted soya-based formulae. Estimated average dietary exposure based on the consumption of 0.7 l per day day in a 3-month infant weighting 6.1 kg ranged from 0.2 to 0.6 mg/kg bw/week in milk-based formulae and was 0.75 mg /kg bw/week for soya-based formulae. Estimated dietary exposure based on the high consumption of 1 l per

day ranged from 0.3 to 0.9 mg/kg bw/week in milk-based formulae and was 1.1 mg /kg bw/week for soya-based formulae.

The Panel noted that in the study of Navarro-Blasco and Alvarez-Galindo (2003) the highest reported aluminium concentration for both soya-based formulae and milk-based formulae was around 4 times higher that the mean concentrations estimated above, leading to a 4 times higher potential exposure in brand-loyal infants.

Potential exposure in breast-fed infants was estimated to be less than 0.07 mg/kg bw/week based on the daily high consumption of 1 l per day and assuming a body weight of 6.1 kg.

Soybean can naturally accumulate aluminium and also aluminium impurities in other basic components of the soya-based formulae or contamination during processing might be reasons for such high aluminium levels (Navarro-Blasco & Alvarez-Galindo, 2003).

To evaluate aluminium exposure in more detail, information on important sources in the diet is needed. Total diet studies (TDS) can provide insight into these sources. However, due to the food sampling methodology (e.g. high aggregation level of food groups in some TDS), the results sometimes provide only rough indications. From studies in the UK and France, cereals and cereal products (including buns, cakes, pastries, biscuits, breakfast cereals, rice, bread and other cereal products), vegetables, and beverages appeared to be the main contributors (>10%) to the dietary aluminium exposure. As mentioned before, it should be kept in mind that it is not possible to distinguish between the specific sources of aluminium. Therefore, these contributions also may reflect partly the use of aluminium-containing food additives which are permitted for use, for instance in some bakery products, and aluminium from food colours used as aluminium lakes. To the knowledge of the Panel, no analytical studies in Europe have focused on the aluminium content of food that contains permitted aluminium-containing food additives.

5. Biological and toxicological data

Studies on the absorption, distribution and elimination of aluminium in humans and experimental animals as well as studies on the toxicological properties of aluminium compounds in experimental animals are summarised below.

The Panel noted that most of the biochemical and toxicological studies did not measure the "normal" aluminium content of the basal diet fed to the animals, and therefore the stated dose in such studies is likely to be an underestimate of the total aluminium exposure. Thus, rat diets have been reported to contain 110 (Kandiah and Kies, 1994), 100 (Gupta et al., 1986), 5 (Glynn *et al.*, 1995), and 51 mg aluminium/kg (Yokel et al., unpublished results cited by IAI, 2007), mouse diet to contain 131 and 64.5 mg aluminum/kg (Dlugaszek et al., 2000 and Fosmire et al., 1993 as cited by IAI, 2007), guinea pig diet to contain 47 (Golub et al., 1996a) and 60 mg aluminium/kg (Owen et al., 1994), and rabbit diet to contain 297, 1215 and 335 mg Al/kg (Fulton & Jeffery, 1990, Yokel and McNamara, 1985, and Yokel et al., unpublished results, as cited by IAI, 2007). As an example, for a rat diet containing aluminium at a concentration of 100 mg/kg, applying the default conversion factors indicates base-line doses of aluminium equivalent to 15 mg/kg bw for mice and 10 mg/kg bw for rats. On the other hand, the actual level of Al^{3+} in test solutions of aluminium compounds for toxicological studies could be dramatically lower than the nominal level if the procedure used for adjusting pH, filtering, and measuring the remaining aluminium in the preparations were not adequately controlled.

5.1. Absorption, distribution and excretion

It has been suggested that acid digestion in the stomach would solubilise most of the ingested aluminium compounds. In acidic aqueous solutions with pH <5, the aluminium ion exists mainly as Al^{+3}, e.g. hydrated Al^{3+} ($Al(H_2O)_6)^{3+}$). By passing from the stomach to the intestines the increase in pH results in the formation of complexes of aluminium with hydroxide and finally the formation of insoluble aluminium hydroxide at neutral pH. Therefore, as the pH is neutralised in the duodenum the aluminium ion is gradually converted to aluminium hydroxide and the majority is then expected to precipitate in the intestine, with subsequent faecal excretion, leaving only a minor fraction available for absorption.

Although the water solubility of aluminium compounds appears to be one of the major factors affecting their bioavailability, it is not possible to extrapolate from solubility in water to bioavailability. Additionally, due to available dietary ligands that may either increase (e.g. citrate, lactate, and other organic carboxylic acid complexing agents, fluoride), or decrease the absorption (such as phosphate, silicon, polyphenols) the bioavailability of any particular aluminium compound can be markedly different depending on the presence or absence of particular food and beverages in the intestines.

Available studies indicate that the oral bioavailability of aluminium in humans and experimental animals from drinking water is in the range of 0.3%, whereas the bioavailability of aluminium from food and beverages generally is considered to be lower, about 0.1%. However, considering the available human and animal data, it is likely that the oral absorption of aluminium from food can vary at least 10-fold depending on the chemical forms present in the intestinal tract.

Except for sodium aluminium phosphate (SALP), acidic, none of the aluminium compounds authorised as food additives in the EU have been studied for bioavailability. The bioavailability of aluminium from SALP, acidic, when incorporated in a biscuit, was found to be about 0.1 % in the rat. However, the Panel noted that in the FEEDAP opinion on Zeolite, a form of sodium aluminium silicate used in animal feed, it was stated that sodium aluminium silicate may be partly hydrolysed in the digestive tract, mainly in the abomasum (because of the low pH value) resulting in release of aluminium and silicate ions. Thus, in an unpublished study in cows, an increase of the aluminium serum level from 13 µg/l before treatment to 85 µg/l during a three-week administration of 600 g Zeolite per day was reported.

This finding on sodium aluminium silicate in cows is in line with the suggestion by some authors that acid digestion in the stomach would solubilise most of the ingested aluminium compounds to the monomolecular species Al^{+3} (e.g. hydrated $Al(H_2O)_6)^{3+}$). The Panel therefore noted that other insoluble aluminium-containing food additives that previously have been considered not to be absorbed from the gut can be expected to behave similarly.

After absorption, aluminium distributes unequally to all tissues in humans and accumulates in some. The total body burden of aluminium in healthy human subjects has been reported to be approximately 30–50 mg/kg bw. Normal levels of aluminium in serum are approximately 1–3 µg/L. About one-half of the total body burden of aluminium is in the skeleton, and about one-fourth is in the lungs (from accumulation of inhaled insoluble aluminium compounds). Reported normal levels in human bone tissue range from 5 to 10 mg/kg. Aluminium has also been found in human skin, lower gastrointestinal tract, lymph nodes, adrenals, parathyroid glands, and in most soft tissue organs. In rats accumulation of aluminium was higher in the spleen, liver, bone, and kidneys than in the brain, muscle, heart, or lung. It has also been reported that aluminium can reach the placenta and fetus and to some extent distribute to the milk of lactating mothers. Aluminium levels have been found to increase with ageing in a number of tissues and organs (bone, muscle, lung, liver, and kidney) of experimental animals.

The main carrier of Al^{3+} in plasma is the iron binding protein transferrin. Studies have demonstrated that about 89% of the Al^{3+} in plasma is bound to transferrin and about 11% to citrate. Cellular uptake of aluminium in organs and tissues is believed to be relatively slow and most likely occurs from the aluminium bound to transferrin by transferrin-receptor mediated endocytosis. There are two routes by which aluminium might enter the brain from the blood: 1) through the blood brain barrier (BBB) and 2) through the choroid plexuses into the cerebrospinal fluid of the ventricles within the brain and then into the brain. Aluminium has been shown to rapidly enter the brain extracellular fluid and the cerebrospinal fluid, with smaller concentrations in these than in the blood.

The distribution of aluminium may be modulated by several factors. Although citrate and fluoride have been shown to reduce tissue accumulation of aluminium and increase its renal excretion in experimental animals, this only occurs when the aluminium concentration exceeds the transferring metal binding capacity. This will seldom happen in humans. The iron status is negatively correlated with aluminium accumulation in tissues and animal experiments have shown that calcium and magnesium deficiency may contribute to accumulation of aluminium in the brain and bone.

Following ingestion in humans, absorbed aluminium from the blood is eliminated primarily by the kidneys, presumably as the citrate, and excreted in the urine. Unabsorbed aluminium is excreted in the faeces. Excretion via the bile constitutes a secondary, but minor route. The two most recent studies in humans that had normal renal function, did not consume any specific diet, took no medications containing aluminium, and had no other special exposure to aluminium, reported urine levels of aluminium of 3.3 (median) and 8.9 µg/l (mean), respectively.

Multiple values have been reported for the elimination half life of aluminium in humans and animals, suggesting that there is more than one compartment of aluminium storage from which aluminium is eliminated.

Within the first day after receiving a single injection of ^{26}Al citrate, approximately 59% of the dose was excreted in the urine of six subjects. At the end of 5 days, it was estimated that 27% of the dose was retained in the body. However, when ^{26}Al levels were monitored for more than 3 or 10 years in a single subject that received the injection, half-lives of approximately 7 years and 50 years were estimated.

Initial half-lives of 2 – 5 hours were reported in rats, mice, rabbits and dogs after intravenous injection of soluble aluminium salts. When the sampling time was prolonged the half-life of aluminium in rabbits was estimated to be 113, 74, 44, 42, 4.2 and 2.3 days in spleen, liver, lung, serum, kidney cortex, and kidney medulla, respectively. A second half-life in the kidney greatly exceeded 100 days. In rats, the whole organism elimination half-life was estimated to be 8 to 24 days in serum, kidney, muscle, liver, tibia and spleen.

Aluminium persists for a very long time in the rat brain following intraveneous injection of very small doses of 26Al. A half-life of 150 days has been reported. However, this estimate is not expected to have a high degree of accuracy as brain samples were not obtained for at least 3 half-lives. Based on calculations for offspring of rats that were given 26Al injections daily from day 1 to 20 postpartum and thereafter examined on days 40, 80, 160, 320 or 730 postpartum, elimination half-lives of approximately 13 and 1635 days in the brain were suggested. Half-lives of 7 and 520 days were suggested for parietal bone. For liver and kidneys half-lives were suggested to be 5 and 430 days and 5 and 400 days, respectively. In blood the values were 16 and 980 days.

There is little published information on allometric scaling of aluminium elimination rates that can be used to extrapolate these results from the rat to the human. For aluminium in the brain

150 days is approximately 20% of, and 1365 days exceeds, the rat's normal life span. For comparison, the whole-body half-life of aluminium in the human was estimated to be 50 years.

5.2. Acute toxicity

The acute oral toxicity of a number of inorganic aluminium salts has been evaluated in rats and mice, and shows a wide range of LD_{50} values from 162 to 750 mg aluminium/kg bw in rats and 164 to 980 mg aluminium/kg bw in the mouse for different compounds. However, the range of available LD_{50} data obtained after intraperitoneal administration (25-82 mg aluminium/kg bw in rats and 40-133 mg aluminium/kg bw in mice) is much narrower than that for oral administration, indicating that the toxicity is dependent on the systemic aluminium exposure. The range of different potencies following oral administration is therefore likely to be dependent upon the bioavailability. The difference between the oral and intraperitoneal LD_{50} values suggests that the extent of absorption for different aluminium salts is in the following order: Aluminium bromide > nitrate > chloride > sulphate.

5.3. Subchronic toxicity

In rats, aluminium nitrate in the drinking water for 28 days produced mild histopathological changes in the spleen and liver at 104 mg aluminium/kg bw per day, with a NOAEL of 52 mg aluminium/kg bw per day. However, in another study using a similar dosage regimen the same researchers reported that 261 mg aluminium/kg bw per day for 100 days produced decreased body weight gain but no histopathological changes. The NOAEL for decreased body weight in this study was 52 mg aluminium/kg bw per day.

Some poorly reported studies in rats given aluminium sulphate ($Al_2(SO_4)_3$) or potassium aluminium sulphate ($KAl(SO_4)_2$) by oral gavage for 21 days reported mild histopathological effects in the kidney and liver at the lowest dose of 17 mg aluminium sulphate/kg bw per day. The severity of the effects increased with dose and effects on nerve cells, testes, bone and stomach were also reported at higher doses. However, the total doses in these studies are unclear because the dietary content of aluminium was not taken into account.

Studies involving dietary administration of aluminium hydroxide ($Al(OH)_3$) and sodium aluminium phosphate (SALP) to rats for 28 days resulted in no effects at the highest tested doses, which were in the region of 140-300 mg Al/kg bw per day.

Dietary administration of acidic SALP, to groups of beagle dogs for 26 weeks produced no toxicologically relevant effects on haematological or clinical chemistry parameters, ophthalmological examination, urine analysis, faecal occult blood tests, organ weights or histopathological observations. Based on food consumption data, the highest dietary concentrations equalled 88 and 93 mg aluminium/kg bw per day for males and females respectively. These were not corrected for the basal aluminium content of the diet.

In contrast, in another study, dietary administration of SALP, basic, to beagle dogs for 26 weeks resulted in decreased food consumption, decreased body and testis weight and histopathological changes in liver and kidney of male dogs after 75 mg aluminium/kg bw per day. No effects were seen in females. The NOAEL was 27 mg aluminium/kg bw per day in the male dogs.

5.4. Genotoxicity

Aluminium compounds were non-mutagenic in bacterial and mammalian cell systems, but some produced DNA damage and effects on chromosome integrity and segregation *in vitro*. Clastogenic effects were also observed in *vivo* when aluminium sulphate was administered at high doses by gavage or by the intraperitoneal route. Several indirect mechanisms have been proposed to explain the variety of genotoxic effects elicited by aluminium salts in experimental systems. Cross-linking of DNA with chromosomal proteins, interaction with microtubule assembly and mitotic spindle functioning, induction of oxidative damage, damage of lysosomal membranes with liberation of DNAase, have been suggested to explain the induction of structural chromosomal aberrations, sister chromatid exchanges, chromosome loss and formation of oxidized bases in experimental systems. The Panel noted that these indirect mechanisms of genotoxicity, occurring at relatively high levels of exposure, are unlikely to be of relevance for humans exposed to aluminium via the diet.

5.5. Carcinogenicity

The International Agency for Research on Cancer (IARC) has concluded that "the available epidemiological studies provide limited evidence that certain exposures in the aluminum production industry are carcinogenic to humans, giving rise to cancer of the lung and bladder." However, the aluminium exposure was confounded by exposure to other agents including polycyclic aromatic hydrocarbons, aromatic amines, nitro compounds and asbestos. There is no evidence of increased cancer risk in non-occupationally exposed persons and IARC did not implicate aluminium itself as a human carcinogen.

Overall the database on carcinogenicity of aluminium compounds is limited. The majority of available studies are old and reports contain little experimental detail. Dose levels of aluminium were generally low and the Panel concluded that it was not possible to reach a conclusion on the carcinogenicity of aluminium from these studies. In a poorly reported oral drinking water study in rats exposed to aluminum potassium sulphate a significantly increased incidence of gross tumours were reported in male rats. The types of tumours were not specified further. The same authors reported that this aluminium compound produced a significantly increased incidence of gross tumours and "lymphoma leukemia" in treated female mice.

The recent, more robust study of Oneda and co-workers in the B6C3F1 mouse did not however indicate any carcinogenic potential of aluminium potassium sulphate at levels of up to 850 mg Al/kg bw/day in the diet. The Panel also noted the absence of epidemiological evidence for carcinogenicity of aluminium compounds used therapeutically, and the conclusion of IARC that aluminium itself is unlikely to be a human carcinogen, despite the observation of an association between inhalation exposure to aluminium dust and aluminium compounds during production/processing and cancer in workers.

Overall the Panel concluded that aluminium is unlikely to be a human carcinogen at exposures relevant to dietary intake.

5.6. Reproductive and developmental toxicity

Several studies have been performed on the reproductive and developmental toxicity of aluminium compounds. Two studies in male mice using either intraperitoneal or subcutaneous administration of aluminium nitrate or chloride clearly demonstrated the ability of aluminium to produce testicular toxicity, decreased sperm quality and reduced fertility in male mice.

However, no effects on male fertility were observed in one rat study where aluminium nitrate was administered by gavage. Unfortunately no data were reported on histological examination of testes, as it is well known that male rats maintain fertility even after severe testicular lesions. This also means that they may be less sensitive to this effect than humans.

Reduced testicular weight and impaired semen quality have also been observed in male rabbits after daily administration by gavage of 34 mg/kg bw of aluminium chloride (corresponding to 6.4 mg aluminium/kg bw/day), the only dose applied, for 16 weeks. In male beagle dogs, dietary administration for 26 weeks of basic sodium aluminium phosphate (SALP), at a level corresponding to 75 mg aluminium/kg bw/day produced a decrease of testicular weight and degeneration of germinal epithelium. The NOAEL was 27 mg aluminium/kg bw/day.

Only two studies are available on reproductive toxicity in females. No effects on female fertility was seen in rats after exposure for two weeks before mating and during gestation to aluminium nitrate by gavage or dissolved in drinking water.

None of the aluminium compounds authorised as food additives in the EU have been tested for reproductive toxicity. However, the Panel noted that when SALP, acidic, was tested in dogs using a protocol similar to that used for SALP, basic, no testicular effects were reported after doses up to 88 mg aluminium/kg bw/day for 26 weeks.

The potential of aluminium to produce embryotoxicity and teratogenicity has been demonstrated in rats given intraperitoneal injections of 0, 75, 100, or 200 mg aluminium chloride/kg bw/day on days 9 -13 or 14 -18 of pregnancy, corresponding to 15, 20, or 40 mg Al/kg bw/day. However, after oral administration, only one study has reported congenital malformations (cleft palate) in mice after gavage exposure to 627 mg aluminium lactate/kg bw/day. In this study 166 mg aluminium hydroxide/kg bw per day had no effect. In general, high doses of aluminium nitrate, chloride or lactate given by gavage were able to induce some signs of embryotoxicity in mice and rats, in particular, reduced fetal body weight or pup weight at birth and delayed ossification. The lowest LOAEL was reported for aluminium nitrate at a daily dose corresponding to 13 mg aluminium/kg bw/day in the rat. After dietary exposure of rats to aluminium chloride and lactate the lowest NOAEL was 100 mg aluminium/kg bw/day, respectively. Gavage administration of aluminium hydroxide at doses providing up to 264 mg aluminium/kg bw/day was without embryotoxic effects in rats.

5.7. Neurotoxicity and developmental neurotoxicity

The neurotoxicity of aluminium in humans was discovered in patients undergoing dialysis, where insufficiently purified water was used, and the patients were therefore exposed parenterally to high concentrations of aluminium, whereas data from healthy humans are insufficient to draw conclusions. The mechanism of action is not known. It has been suggested that aluminium is implicated in the aetiology of Alzheimer's disease and an association of aluminium with other neurodegenerative diseases in humans has also been postulated. These hypotheses are still controversial. Some epidemiology studies of aluminium in water suggest an association and others do not. The studies mainly adopt assumptions about exposure based on concentrations of aluminium in the water supply and do not include estimates of additional dietary exposure. The Panel concluded that these studies are not informative for a safety assessment of aluminium from dietary intake.

The Panel also noted that the German Federal Institute for Risk Assessment (BfR, 2007) in an updated statement on aluminium and Alzheimer's disease concluded that "so far no causal relationship has been proven scientifically between elevated aluminium uptake from foods including drinking water, medical products or cosmetics and Alzheimer's disease. Amyloid

deposits in the brain are typical for Alzheimer's. However, an above-average frequency was not observed either in dialysis patients or in aluminium workers – two groups of individuals who come into contact with aluminium on a larger scale". Similar conclusions were reported by the French food safety Agency (AFSSA, 2003). On the basis of the available scientific data the Panel does not consider exposure to aluminium via the food to constitute a risk for developing Alzheimer's disease.

Aluminium is a neurotoxicant in experimental animals. However, most of the animal studies performed have several limitations.

Behavioural impairment has been observed in the absence of overt encephalopathy or neurohistopathology in rats and mice exposed to soluble aluminium salts (e.g. lactate, chloride) in the diet or drinking water generally at doses of 200 mg aluminium/kg bw per day or higher. Effects involved impairment of performance on passive and conditioned avoidance responses. Because these studies were designed specifically to investigate behavioural effects and other potential endpoints were incompletely evaluated, a possible role of organ toxicity (kidney, liver, immunological) cannot be discounted. In a study in male Swiss Webster mice where aluminium was given in the diet as aluminium lactate no consistent behavioural effects were seen after doses equivalent to 100 mg/kg bw/day.

In rats of different ages given daily doses of aluminium chloride in the drinking water for periods of 30, 60, or 90 days, a LOAEL of 52 mg aluminium/kg bw/day and a NOAEL of 30 mg aluminium/kg bw/day was reported for effects on the vestibulo-ocular reflex.

Effects of oral aluminium exposure (as lactate or chloride) on brain development have been studied in mice. Effects recorded in more than one study in immature animals included impaired performance of reflexes and simple behaviours. Post-natal mortality and growth were also affected at the higher doses in some of these studies. Adult rats and mice have also been assessed for brain function after developmental exposures. Reduced grip strength and startle responsiveness were found to persist up to 150 days of age. There was no effect on reactions to the light avoidance task in rats after gestational or postnatal exposure. In these studies, LOAELs were identified that ranged from maternal doses of 50 to 500 mg aluminium/kg bw/day.

From the study in mice where the lowest LOAEL of 50 mg aluminium/kg bw/day, given as lactate, was reported for neurodevelopmental effects in the offspring, NOAELs of 10 mg aluminium/kg bw/day in the mother during pregnancy and 42 mg/ kg bw/day during lactation could also be identified. However, it should be noted that, in another study performed by the same group of researchers, with administration of aluminium lactate from conception throughout the whole lifespan at 100 mg/kg bw/day no clear signs of neurotoxicity were observed in the same strain of mice.

6. Discussion

The major route of exposure to aluminium for the general population is through food. Aluminium in drinking water represents a minor, source of exposure. Non-food exposures may arise from the use of aluminium compounds in pharmaceuticals and consumer products.

Total dietary exposure to aluminium from all sources has been estimated for various European countries from duplicate diet studies and market basket and total diet studies. Mean dietary exposure from water and food in non-occupational exposed adults showed large variations between the different countries and, within a country, between different surveys. It ranged from 1.6 to 13 mg aluminium per day from food in 60 kg adult. Large individual variations in dietary

exposure to aluminium can occur. Children generally have higher food intake than adults when expressed on a body weight basis, and therefore represent the group with the highest potential exposure to aluminium per kg body weight In children and young people the potential estimated exposure at the 97.5th percentile ranged from 0.7 mg/kg bw/week for children aged 3-15 years in France to 2.3 mg/kg bw/week for toddlers (1.5-4.5 years) and 1.7 mg/kg bw/week for those aged 4-18 years in the UK.

Due to the design of the studies, which only determine the total aluminium content in the food, and not the individual aluminium compounds or species present, it is not possible to conclude on the specific sources contributing to the aluminium content of a particular food, such as the amount inherently present, the contributions from use of food additives, and the amounts released to the food during processing and storage from aluminium-containing foils, containers, or utensils. Such information would require that the individual EU Member Countries initiate studies on background levels of aluminium in food and obtain information on the use of aluminium-containing food additives, namely what compounds are used, in which foods, and at what levels.

In UK and France cereal and cereal products, including buns, cakes, pastries and biscuits, and bread, vegetables, and (hot) beverages appeared to be important contributors to dietary aluminium exposure. As mentioned before, it should be kept in mind that it is not possible to distinguish between the specific sources of aluminium. Therefore, these contributions also may reflect partly the use of aluminium-containing food additives which are permitted for use, for instance in some bakery products, and aluminium from food colours used as aluminium lakes.

The aluminium content of soya-based formulae is generally relatively high. Mean potential exposure to aluminium for infants consuming soya-based formulae might be higher (~1.07 mg/kg bw/week) than for infants fed on adapted starter formulae (~0.30 mg/kg bw/week) and particularly in comparation with breast fed children (less than 0.07 mg/kg bw/week).

Studies on the acute toxicity in rats and mice showed similar potency with respect to the dose of the aluminium ion of several aluminium salts after intraperitoneal administration, whereas studies using oral administration showed marked differences in potencies. This strongly suggests that oral toxicity of any aluminium compound is dependent on the absorption of the aluminium ion.

It has been suggested that acid digestion in the stomach would solubilise most of the ingested aluminium compounds to the monomolecular species Al+3, even the insoluble salts. Findings on sodium aluminium silicate in cows is in line with this suggestion, and the Panel therefore noted that other insoluble aluminium-containing food additives that previously have been considered not to be absorbed from the gut can be expected to behave similarly. As the pH is neutralised in the duodenum the aluminium ion is gradually converted to aluminium hydroxide and the majority is then expected to precipitate in the intestine, with subsequent faecal excretion, leaving only a minor fraction available for absorption.

The water solubility of an aluminium compound appears to increase the bioavailability of the aluminium ion and the presence or absence in the intestines of dietary ligands may either increase (e.g. citrate, lactate, and other organic carboxylic acid complexing agents, fluoride), or decrease the absorption (e.g. phosphate, silicon, polyphenols).

The oral bioavailability of aluminium in humans and experimental animals from drinking water has been estimated to be in the range of 0.3%, whereas the bioavailability of aluminium from food and beverages generally is considered to be lower, about 0.1%. However, it is likely that the oral absorption of aluminium from food can vary at least 10-fold depending on the chemical forms present.

Due to these complex interactions, predictions of the actual absorption of the aluminium ion from a given aluminium compound are difficult to make.

After absorption, aluminium distributes to all tissues in animals and humans and accumulates in some, in particular bone. The main carrier of Al3+ in plasma is the iron binding protein, transferrin. It has been reported that aluminium can enter the brain and reach the placenta and fetus and to some extent distribute to the milk of lactating mothers. Aluminium levels have been found to increase with ageing in a number of tissues and organs (bone, muscle, lung, liver, and kidney) of experimental animals.

Aluminium is eliminated primarily by the kidneys, presumably as the citrate, and excreted in the urine. Unabsorbed aluminium is excreted in the faeces. Excretion via the bile constitutes a secondary, but minor route.

Aluminium persists for a very long time in various organs and tissues of experimental animals and humans. Multiple values have been reported for the elimination half life of aluminium, ranging from hours, days, and months to years, suggesting that there is more than one compartment of aluminium storage from which aluminium is eliminated. Although retention times for aluminium appear to be longer in humans than in rodents, there is little information on allometric scaling of aluminium elimination rates that can be used to extrapolate these results from rodent to the human.

Except for sodium aluminium phosphate (SALP), acidic, none of the aluminium compounds authorised as food additives in the EU have been studied for their toxicological properties. In general, the more soluble aluminium salts, such as the chloride, nitrate, sulphate, lactate, and citrate have been used. Most of these studies were not conducted in accordance with the guidelines for regulatory submissions, and for many of them the study designs and reporting do not allow NOAELs and LOAELs to be identified. Furthermore, there was little consistency in the effects and effective dose levels observed in different studies.

In addition, most of the biochemical and toxicological studies did not measure the “normal” aluminium content of the basal diet fed to the animals, and therefore the stated dose is likely to be an underestimate of the total aluminium exposure. As an example, for a rat diet containing aluminium at a concentration of 100 mg/kg, applying the default conversion factors indicates base-line doses of aluminium equivalent to 15 mg/kg bw/day for mice and 10 mg/kg bw/day for rats. On the other hand, the actual level of Al3+ in test solutions of aluminium compounds for toxicological studies could be dramatically lower than the nominal level if the procedures used for adjusting pH, filtering, and measuring the remaining aluminium in the preparations were not adequately controlled.

Dietary administration of SALP, acidic, to groups of beagle dogs for 26 weeks produced no toxicologically relevant effects. The NOAELs equalled 88 and 93 mg aluminium/kg bw per day for males and females, respectively. In contrast, dietary administration of SALP, basic, to beagle dogs for 26 weeks resulted in decreased food consumption, decreased body and testis weight and histopathological changes in liver and kidney of male dogs after 75 mg aluminium/kg bw per day. No effects were seen in females. The NOAEL was 27 mg aluminium/kg bw per day in the male dogs.

Aluminium compounds were non-mutagenic in bacterial and mammalian cell systems, but some produced DNA damage and effects on chromosome integrity and segregation in vitro. Several indirect mechanisms have been proposed and the Panel noted that these indirect mechanisms of genotoxicity, occurring at relatively high levels of exposure, are unlikely to be of relevance for humans exposed to aluminium via the diet.

Overall the database on carcinogenicity of aluminium compounds is limited. In the most recent study no indication of any carcinogenic potential was obtained in mice given aluminium potassium sulphate at high levels in the diet. Overall the Panel concluded that aluminium is unlikely to be a human carcinogen at exposures relevant to dietary intake.

Studies on the reproductive toxicity in male mice (using either intraperitoneal or subcutaneous administration of aluminium nitrate or chloride) and rabbits (using gavage administration of aluminium chloride) have demonstrated the ability of aluminium to produce testicular toxicity, decreased sperm quality and reduced fertility. No reproductive toxicity was seen in females administered aluminium nitrate by gavage or dissolved in drinking water.

In general, high doses of aluminium nitrate, chloride or lactate given by gavage were able to induce some signs of embryotoxicity in mice and rats, in particular, reduced fetal body weight or pup weight at birth and delayed ossification. In rats, the lowest LOAEL was reported for aluminium nitrate at a daily dose corresponding to 13 mg aluminium/kg bw/day. After dietary exposure of rats to aluminium chloride and lactate, the lowest NOAEL for reproductive toxicity was 100 mg aluminium/kg bw/day for both compounds. Gavage administration of aluminium hydroxide at doses providing up to 264 mg aluminium/kg bw/day was without embryotoxic effects in rats.

The neurotoxicity of aluminium in humans has been shown in patients undergoing dialysis where insufficiently purified water was used, and the patients were therefore parenterally exposed to high concentrations of aluminium. It has been suggested that aluminium is implicated in the aetiology of Alzheimer's disease and associated with other neurodegenerative diseases in humans. However, these hypotheses remain controversial. Based on the available scientific data, the Panel does not consider exposure to aluminium via the food to constitute a risk for developing Alzheimer's disease.

Aluminium is neurotoxic in experimental animals, however, most of the studies performed have several limitations. The Panel noted that the results reported in a series of studies in mice by one laboratory were inconsistent with respect to effects on neurotoxicity and neurodevelopment. The limited number of dose levels used, especially in the low dose range makes it difficult to determine a NOAEL and to observe any dose-response relationships. In the studies on neurodevelopmental toxicity, information is lacking on what has been done to reduce effects related to the variability between litters and in most of the studies no corrections were made for differences in birth weight and preweaning pup weights between the groups while controlling for litter size. The intake of aluminium in most of the studies was estimated based on the aluminium content of an assumed figure for food consumption rather than calculated based on the actual food intake.

Studies where aluminium was given by gavage should not be included in the evaluation of the neurodevelopmental toxicity because the toxicokinetics, which includes the fetal exposure to aluminium, will differ in this type of study from that after dietary administration. Given that placental transfer will be via the blood, it is serum rather than tissue levels that will be critical in determining the magnitude of fetal exposure. Following a bolus administration, serum aluminium levels would be elevated before redistributing to the tissue compartments. In contrast, serum aluminium levels would be much less elevated following dietary exposure and better resemble the situation after human dietary exposure. Also a study in mice where small doses of aluminium chloride was given in drinking water was not included due to several methodological problems in the study.

The animal studies performed on the neurotoxicity and neurodevelopmental toxicity have several limitations in their design and conduct. Behavioural impairment has been observed in rats and mice exposed to soluble aluminium salts (e.g. lactate, chloride) in the diet or drinking

water generally at doses of 200 mg aluminium/kg bw per day or higher. In a study in male mice where aluminium was given in the diet as aluminium lactate no consistent behavioural effects were seen after doses equivalent to 100 mg/kg bw/day. In rats given daily doses of aluminium chloride in the drinking water for periods up to 90 days, a LOAEL of 52 mg aluminium/kg bw/day and a NOAEL of 30 mg aluminium/kg bw/day was reported for effects on the vestibulo-ocular reflex.

Effects of oral aluminium exposure (as lactate or chloride) on brain development have been studied in mice. LOAELs for impaired performance of reflexes and simple behaviours in the offspring ranged from maternal doses of 50 to 500 mg aluminium/kg bw/day. In one study, NOAELs of 10 mg aluminium/kg bw/day in the mother during pregnancy and 42 mg/ kg bw/day during lactation could also be identified. However, it should be noted that, in another study performed by the same group of researchers, with administration of aluminium lactate from conception throughout the whole lifespan at 100 mg/kg bw/day no clear signs of neurotoxicity were observed in the same strain of mice.

7. Conclusions

The Panel noted that several compounds containing aluminium have the potential to produce neurotoxicity (mice, rats) and to affect the male reproductive system (dogs). In addition, after maternal exposure they have shown embryotoxicity (mice) and have affected the developing nervous system in the offspring (mice, rats). The Panel also noted that there are very few specific toxicological data for food additives containing aluminium. Thus the Panel considered it prudent to take the above-mentioned effects into account when setting a tolerable intake for all dietary sources. The available studies have a number of limitations and do not allow any dose-response relationships to be established. The Panel therefore based its evaluation on the combined evidence from several studies in mice, rats and dogs that used dietary administration of aluminium compounds. In these studies the lowest LOAELs for effects on neurotoxicity, testes, embryotoxicity, and the developing nervous system were 52, 75, 100, and 50 mg aluminium/kg bw/day, respectively. Similarly, the lowest NOAELs for effects on these endpoints were reported at 30, 27, 100, and for effects on the developing nervous system, between 10 and 42 mg aluminium/kg bw per day, respectively.

When the Panel used the lower end of the LOAELs of 50 mg aluminium/kg bw per day for neurodevelopmental toxicity in mice a tolerable daily intake (TDI) of 0.17 mg aluminium/kg bw per day could be established. The Panel used the default uncertainty factor of 100 to allow for inter- and intra-species variations and an additional factor of 3 for using a LOAEL instead of a NOAEL. The Panel noted that in the case of the study providing this LOAEL, another study performed by the same group of researchers with administration of aluminium lactate from conception throughout the whole lifespan, a dose level of 100 mg/kg bw/day in the same strain of mice, showed no clear signs of neurotoxicity. The Panel concluded therefore that the additional factor of 3 used for using a LOAEL instead of a NOAEL.is sufficiently large.

When the Panel used the lowest NOAEL of 10 mg aluminium/kg bw per day for neurodevelopmental toxicity in mice, a tolerable daily intake (TDI) of 0.10 mg aluminium/kg bw per day could be established. The Panel used the default uncertainty factor of 100 to allow for inter- and intra species variations.

The Panel noted several deficiencies and uncertainties in the overall database. The aluminium dose delivered to the fetus is dependent on the level in the maternal blood of the mother. Whether maternal blood would be at or near steady state, is determined by the half-life of aluminium. In the animal studies this will be determined by the dosing regimen whereas

humans would be expected to be at a steady state. The available data do not permit a direct comparison of the half-lives for aluminium in the blood of humans and rodents, but the Panel considered that the default uncertainty factor for inter-species differences in toxicokinetics would not adequately cover potential differences between humans and animals, the half-life being longer in humans than in mice. On the other hand, the bioavailability of aluminium from aluminium lactate or aluminium chloride, used in the pivotal studies, is considered to be generally higher than the bioavailability of aluminium from the aluminium compounds used as food additives and the forms in which aluminium occurs naturally in food. Overall, The Panel considered that an additional uncertainty factor was not needed for uncertainties in the database. In view of the cumulative nature of aluminium in the organism after dietary exposure, the Panel considered it more appropriate to establish a tolerable weekly intake (TWI) for aluminium rather than a TDI. When the LOAEL approach is used this would result in a TWI of 1.2 mg/kg bw/week, whereas the use of the NOAEL approach would result in a TWI of 0.7 mg/kg bw/week. However, given the lack of clear dose-response relationships from the available studies and the consequent uncertainties in defining reliable NOAELs and LOAELs for the toxicity of aluminium, the Panel concluded that a value of 1 mg aluminium/kg bw/week, representing a rounded value between the TWIs provided by the LOAEL and NOAEL approaches, should be established as the TWI.

In infants aged 0-3, 4-6, 7-9 and 10-12 months potential dietary exposures based from infant formulae and other foods manufactured specially for infants were estimated to be respectively 0.10, 0.20, 0.43 and 0.78 mg/kg bw/week.

Potential exposure to aluminium in 3-month infants from a variety of infant formulae was estimated by the Panel: at the mean it was up to 0.6 mg/kg bw/week for milk-based formulae and was 0.75 mg /kg bw/week for soya-based formulae; at high percentiles of exposure it was up to 0.9 mg/kg bw/week in milk-based formulae and was 1.1 mg /kg bw/week for soya-based formulae.

The Panel noted that in some individual brands of formulae (both milk-based and soya-based) the aluminium concentration was around 4 times higher that the mean concentrations estimated above, leading to a 4 times higher potential exposure in brand-loyal infants.

Potential exposure in breast-fed infants was estimated to be less than 0.07 mg/kg bw/week.

Mean dietary exposure from water and food in non-occupational exposed adults showed large variations between the different countries and, within a country, between different surveys. It ranged from 1.6 to 13 mg aluminium per day, corresponding to an exposure of approximately 0.2 to 1.5 mg/kg bw/week from water and food in a 60 kg adult. Children generally have higher food intake than adults when expressed on a body weight basis, and therefore represent the group with the highest potential exposure to aluminium per kg body weight. In children and young people the estimated exposure at the 97.5th percentile in the UK and France ranged from 0.7 to 2.3 mg aluminium/kg bw/week.

The TWI of 1 mg/kg bw/week is therefore likely to be exceeded in a significant part of the European population. Cereals and cereal products, vegetables, beverages and certain infant formulae appear to be the main contributors to the dietary aluminium exposure.

Aluminium in drinking water represents a minor, source of exposure. Additional exposures may arise from the use of aluminium compounds in pharmaceuticals and consumer products.

Due to the design of the human dietary studies and the analytical methods used, which only determine the total aluminium content in food, and not the individual aluminium compounds or species present, it is not possible to conclude on the specific sources contributing to the aluminium content of a particular food, such as the amount inherently present, the contributions

from use of food additives, and the amounts released to the food during processing and storage from aluminium-containing foils, containers, or utensils. Thus a detailed breakdown by exposure source is not possible.