Canada's Cosmetic Notification System, a mandatory system under which manufacturers must submit information including composition data on cosmetics prior to first sale in Canada.

Table 2.6 presents reported ranges of aluminum concentrations that may be contained in a wide variety of cosmetic products sold in Canada. However, it should be noted that the data on concentrations are available with respect to reporting categories (< 0.1%, 0.1% to 0.3%, 0.3% to 1.0%, 1% to 3%, 3% to 10%, 10% to 30% and 30% to 100%). Thus the maximum concentration represents an upper limit of a reporting category, and is therefore very likely an overestimate, by a factor of up to 3.3, of the actual maximum concentration in the product category.

Table 2.6 Range of total aluminum concentrations in various categories of cosmetic products sold in Canada

Product Category	**Range of total aluminum concentration (mg/kg)***	**Product Category**	**Range of total aluminum concentration (mg/kg)**
Hair dye	442–300,000	Lipstick	44–300,000
Antiwrinkle preparation	171–333,000	Manicure preparation	44–300,000
Barrier cream	78–10,377	Baby	78–2,349
Toothpaste	1,588–52,930	Skin cleaner	57–529,300
Deodorant and antiperspirant	171–529,300	Skin moisturizer	42–158,790
Eye makeup	42–NA**	Sun	5,293–15,879
Face makeup	44–NA**	Bath	346–10,000
Fragrance	206–30,000	Shaving	57–157,700
Hair conditioner	78–15,879	Shampoo	309–1,588

* Note that the maximum concentration corresponds to an upper limit for a reporting category (see text) and may thereby overestimate the maximum concentration by up to a factor of 3.3)

** Maximum upper bound not available, as the upper limit of reporting category is 100%

2.3.2.8 Vaccines

Most of the vaccines authorized in Canada contain an aluminum salt adjuvant, according to the systematic vaccination schedule used for infants, young children, adolescents and adults (Canada Public Health Agency 2006). Various types of vaccine adjuvants are used by pharmaceutical companies, such as aluminum hydroxide, aluminum phosphate, aluminum sulphate and aluminum potassium sulphate. The quantity of aluminum ranges between 125 µg and 1,000 µg (aluminum hydroxide) per dose, depending on the vaccine. There is no standard or recommendation available in Canada with respect to the maximum quantity of aluminum or aluminum compound that may be used as an adjuvant in vaccines.

2.3.3 Toxicokinetics: human and experimental animals

An overview of the toxicokinetic processes of aluminum was carried out with the goal of highlighting the various factors influencing its pathway from the environment to target organs. Each toxicokinetic process is described below (absorption, distribution and elimination). Aluminum does not undergo phase I and II biotransformation reactions, occurring only in the +3 oxidation state. The metabolism of aluminum is therefore described in relation to its speciation, in the context of the distribution and elimination processes.

2.3.3.1 Absorption

Even at moderately elevated levels in the environment, exposure of aluminum leads to only small increases of aluminum in human tissues due to its low bioavailability through all routes of exposure. Bioavailability refers to the fraction of the total amount of the substance ingested, inhaled or in contact with the skin that reaches the systemic circulation. In this assessment, emphasis is placed on oral bioavailability, as the estimated daily intake (EDI) of the Canadian population shows that ingestion is the major route of exposure (see section 3.2.1); the bioavailability of aluminum with respect to other exposure routes (inhalation and dermal) is also reviewed. Bioavailability estimates for all exposure routes have been summarized in Table 2.7.

2.3.3.1.1 Oral absorption

The interpretation of aluminum oral bioavailability estimates requires the understanding of: (a) the methods used to calculate oral bioavailability, and (b) the physiological and biochemical factors that influence oral absorption. The ingested matrix to which aluminum is bound likely influences its potential absorption, therefore, the oral bioavailabilities of aluminum from drinking water, food and soil are distinguished.

Methods to calculate oral bioavailability

The methods to calculate the oral bioavailability in experimental studies are: (a) mass balance based on intake, and fecal and urinary excretion; (b) comparison of intake with urinary excretion; (c) concentration in a single blood sample and a calculated volume of distribution; (d) aluminum concentration in tissue; and (e) comparison of areas under the plasma concentration-time curve after oral and intravenous administration (Yokel and McNamara 2000). The most common method is comparison of intake with urinary excretion. This method is the simplest and least invasive, and is relatively reliable provided that the collection period is long enough to measure nearly all the aluminum excreted in the urine.

Prior to 1990, aluminum analyses were based on the quantification of the common isotope ^{27}Al ($\approx 100\%$ of the natural isotopes). As ^{27}Al in the environment is ubiquitous, contamination during sampling and analysis may easily occur, leading to overestimation of the tissue concentrations, particularly when the administered amounts of aluminum are near the baseline exposure. The relative contribution from endogenous ^{27}Al is minimized by administering doses that are much higher than the levels encountered in the environment. However, oral absorption may depend on dose. Thus, this approach increases the uncertainty in the estimation of bioavailability of environmental concentrations of aluminum. On this point, the observed relationship between dose and bioavailability is inconsistent: increased

dose of aluminum decreased its bioavailability in the experimental studies of Greger and Baier (1983), Weberg and Berstad (1986), and Cunat et al. (2000) while opposite results were observed in other animal studies (Yokel and McNamara 1985; Ittel et al. 1993).

In recent years accelerator mass spectrometry (AMS) has been used to quantify the isotope ^{26}Al, administered as a tracer (Priest 2004). This analytical technique has allowed researchers to more accurately measure bioavailability of aluminum at levels comparable to the levels to which the general population is actually exposed, since it is possible to distinguish the aluminum in the administered dose (^{26}Al) from the aluminum already in the body (^{27}Al). However the cost and small number of facilities limit the sample analyses, which can result in the diminishing of the precision of the estimation and the information concerning the intra-individual variability (Yokel and McNamara 2000).

Factors influencing oral absorption

The principal mechanism of absorption of ingested aluminum seems to be a passive diffusion through the paracellular pathway (Zhou and Yokel 2005). This diffusion occurs predominantly in the small intestine (duodenum and jejunum) and, to a lesser extent, through the gastric mucosa in stomach (Powell and Thompson 1993; Walton et al. 1994). In addition to passive diffusion, Cunat et al. (2000) suggested that absorption of aluminum may occur by a transcellular and saturable route, which may explain the possible dependency of absorption on the dose level.

The rate of uptake, and consequently the cumulative absorption of aluminum, has been shown to vary depending on physiological and chemical factors. Krewski et al. (2007) summarized factors based on findings in both human and animal studies, including:

- Solubility: absorption is greater with more soluble aluminum compounds;
- Gastric pH: absorption is greater at pH 4 compared to pH 7, probably due to the generation of more soluble aluminum compounds;
- Carboxylic acids: increased absorption in the presence of carboxylic acids, particularly citrate that is naturally present in many foods and fruit juices;
- Silicon compounds: decreased absorption in the presence of silicon-containing compounds in the dietary intake, due to a possible formation of hydroxyaluminosilicate.

Among the factors cited above, particular attention has been given to the significant impact of citrate during the ingestion of aluminum. Oral bioavailability has been found to increase by a factor of 5 to 150 when aluminum is ingested with citrate solution, as verified with studies employing the same aluminum complex and under the same experimental conditions (Weberg and Berstad 1986; Yokel and McNamara 1988; Froment et al. 1989; Priest et al. 1996; Drueke et al. 1997; Schönholzer et al. 1997). Citrate probably facilitates the absorption by opening the tight junction between intestinal cells (Froment et al. 1989; Zhou and Yokel 2005). Zhou et al. (2008) recently explored the influence of citrate in drinking water at a similar molar concentration to aluminum. The researchers did not observe a

significant enhancement of aluminum absorption for an Al:citrate molar ratio of 1:1, and suggested that aluminum absorption may depend on citrate dose.

The principal biochemical explanation for how the factors listed above influence absorption is the nature of the ligand to which the ion Al^{3+} is associated in the gastrointestinal fluid. In vitro studies using Caco-2 cells derived from the human lower intestine show differences between ligands in the uptake rate of aluminum; aluminum citrate and aluminum nitrilotriacetate were absorbed more rapidly than aluminum lactate (Alvarez-Hernandez et al. 1994) and the uptake rate of aluminum fluoride was higher than that of, in decreasing order, Al^{3+}, aluminum maltolate, aluminum citrate and aluminum hydroxide (Zhou and Yokel 2005). Results from in vivo studies provided evidence for significant differences in the oral bioavailability calculated for different ingested aluminum complexes (Yokel and McNamara 1988; Froment et al. 1989). Cunat et al. (2000) concluded that the organic ligands enhance aluminum absorption, in comparison to the inorganic ligands (citrate > tartrate, gluconate, lactate > glutamate, chloride, sulphate, nitrate), based on the results of a study in which rat intestines were locally perfused with aluminum.

The pH of the exposure media may play an important role in the absorption of aluminum, as it affects aluminum speciation. In aluminum sulphate-treated water with low pH, the aluminum sulphate and Al^{3+} (very soluble) are the predominant forms while, when increasing the pH from 6.3 to 7.8, the predominant complex is aluminum hydroxide (likely insoluble). At pH above 7.8, the solubility in water increased due to the presence of the negative ions of aluminum hydroxyl (Walton et al. 1994). As mentioned in section 2.3.2.2.2, while treatment with aluminum sulphate may reduce the total aluminum concentration in finished water as compared to the untreated water source, through the removal of suspended solids containing aluminum, there is evidence that treatment with aluminum salts also increases the concentration of low-molecular-weight, dissolved aluminum species (Health Canada 1998b).

The low pH of the gastric fluid creates a high potential for transformation of the ingested aluminum complex. This led Reiber et al. (1995) to argue that the aluminum in drinking water would not be more readily assimilated than other forms of aluminum, and that regardless of the form in which the aluminum is consumed, a substantial portion of it will likely be solubilized to monomolecular aluminum in the stomach. Other researchers, however, consider this to be an oversimplication, in light of the observed differences in the oral absorption of different aluminum compounds (Krewski et al. 2007).

Concurrent absorption of aluminum with other dietary nutrients has been shown to influence the intestinal absorption of this metal. For example, the presence of vitamin D likely favours the absorption of aluminum (Adler and Berlyne 1985; Ittel et al. 1988; Long et al. 1991; Long et al. 1994) and the consumption of folic acid supplementation is expected to diminish aluminum absorption and/or its accumulation in various organs (bone, kidney and brain) by a possible formation of folate-Al complex (Baydar et al. 2005). Domingo et al. (1993) investigated the effects of various dietary constituents, such as lactic, malic and succinic acids, on the levels of absorption and distribution of aluminum in drinking water and in the diet of mice, where they observed an enhanced absorption with these concurrent ingestions.

A few studies have been conducted to examine whether food composition or the presence of food in the stomach affect oral aluminum bioavailability, and the results have been mixed. The nature of the contents in the stomach influenced the absorption of aluminum in the study of Walton et al. (1994) in which adult Wistar rats were exposed to water treated with aluminum sulphate along with various beverages and foods. The aluminum concentrations in serum increased when the aluminum sulphate treated drinking water was taken with orange juice; the same phenomenon was observed, but to a lesser extent, with coffee. The authors note that the low levels of aluminum in these two beverages would not have contributed to this increase in aluminum levels. In comparison, when aluminum sulphate treated water was given with beer, tea or cola (beverages that may contain appreciable levels of aluminum) the serum concentration did not markedly rise. Meat and carbohydrate/cereal products decreased aluminum absorption. Drüeke et al. (1997) performed a study in rats using ^{26}Al to examine the effect of silicon contained in drinking water as well as solid food, on the absorption of aluminum. In their study, high Si concentrations in the drinking water failed to depress the ^{26}Al fraction absorbed, as estimated on the basis of skeletal accumulation and urinary excretion. In addition, absorption of ^{26}Al was approximately 15 times higher in the fasted state than in the non-fasted state. As part of a study conducted in rats with ^{26}Al, Yokel et al. (2001a) tested the hypothesis that the stomach contents affect aluminum absorption. According to the authors, although stomach contents delayed aluminum absorption, it did not significantly alter the extent of ^{26}Al absorption.

Estimation of the oral bioavailability of aluminum in drinking water

Experimental data for oral bioavailability of aluminum from drinking water, obtained in studies conducted in humans and animals, and based on varying calculation and quantification methods, were evaluated.

The compilation of central values (mean or median) of the results of different studies in humans results in a range of 0.010% to 0.52% for oral bioavailability of aluminum in drinking water, based on experiments involving more than one volunteer. The lower value is the mean value obtained from the data of two volunteers exposed to ^{26}Al-hydroxide in Priest et al. (1998). This experimental study observed the higher value of 0.52% as well when these two volunteers were exposed to ^{26}Al-citrate. In a much larger study with 29 subjects consuming an aluminum-controlled diet, the oral bioavailability from aluminum sulphate-treated municipal drinking water was estimated at 0.36% to 0.39% (Stauber et al. 1999).

As for the central values for the oral bioavailability for experimental animals, a range of 0.04% to 5.1% is reported in experimental studies with the isotope ^{26}Al, whereas the range based on ^{27}Al is 0.01% to 4.56%. The maximum central value of 5.1% for the animal experiments using ^{26}Al was obtained following ingestion of a concentrated solution of citrate (Schönholzer et al. 1997). The second highest value is 0.97%, based on the exposure to aluminum chloride (Zafar et al. 1997). The maximum central value of 4.56% for ^{27}Al was obtained for aluminum citrate ingested by rats with renal failure (Yokel and McNamara 1988). If only healthy animals had been considered, the maximum value would have been 2.18% for ^{27}Al-citrate.

Krewski et al. (2007) proposed a range for the oral bioavailability of aluminum in drinking water of 0.05% to 0.4% for rats and rabbits, and 0.1% to 0.5% for humans, with a most likely value of 0.3%. The approximate correspondence between the ranges and the most likely estimates in humans and animals for bioavailability from drinking water suggests that there is little interspecies difference in this respect.

Estimation of the oral bioavailability of aluminum in food

In spite of the important contribution of food in the total exposure to aluminum, the database for oral bioavailability of aluminum in food is limited. In an early investigation into the potential for the absorption of aluminum accumulated in food, Jones (1938) demonstrated that a large percentage of aluminum in bread made with aluminum-based baking powder was soluble in the gastric juice of dogs. Several decades later, Yokel and Florence (2006) confirmed that some aluminum from biscuits made with baking powder containing acidic ^{26}Al-sodium aluminum phosphate (SALP) reaches the systemic circulation. In this study, about 0.12% of the ingested aluminum crossed the gastrointestinal tract of exposed rats. Using the same experimental method,[10] Yokel et al. (2008) estimated oral bioavailabilities of ~ 0.1% and ~ 0.3% for basic ^{26}Al-SALP incorporated into cheese at concentrations of 1.5% and 3%, respectively.

The oral bioaccessibility[11] of aluminum encountered in different foods was measured by Lopez et al. (2002) and Owen et al. (1994). It is not possible, however, to directly compare their results, since their methodologies differed. Moreover, the bioaccessibility estimates, ranging from 0.3% to 0.9% by Owen et al. (1994) and 0.85 to 2.15% by Lopez et al (2002), cannot be directly used to estimate the oral bioavailability of aluminum, as the in vitro-in vivo relationship has not been established (Ruby et al. 1999). Nonetheless these bioaccessibility studies do provide evidence that oral bioavailability is low and may change according to the nature of consumed foods. For example, the aluminum in bread, jam and tea appeared to be about 2.7 times more soluble than the aluminum in sponge cake (Owen et al. 1994). It is expected that the actual oral bioavailability of aluminum in food is lower than these bioaccessibility values, as solubility in the intestinal tract would not be the only factor limiting absorption.

The oral bioavailability of aluminum in food has also been estimated based on the comparison of aluminum intake in the general population with the urinary excretion and/or the body burden of aluminum (Ganrot 1986; Priest 1993, 2004; Powell and Thompson 1993; Nieboer et al. 1995). These estimates range from 0.1% to 0.8%. Note that the oral bioavailability estimate of 0.12% of Yokel (2006) for rats fed aluminum-containing biscuits

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[10] Bioavailability is determined by comparing the areas under the serum concentration x time curve (AUC) for the ^{26}Al given orally and the ^{27}Al administered intravenously (Yokel et al. 2008).

[11] The oral bioaccessibility is the soluble fraction of the substance in the gastrointestinal system that is available for absorption (Ruby et al. 1999).

falls in this range, as does the estimate of 0.53% by Stauber et al. (1999), based on a controlled diet in humans.

Bioavailability of aluminum in antacids (aluminum hydroxide) has been estimated in three studies in humans, measured alone or in combination with citrate, orange juice, bicarbonate, or calcium acetate (Mauro et al. 2001; Haram et al. 1987; Weberg and Berstad 1986). These measured bioavailabilities, ranging from 0.001% to 0.2% were generally comparable to the bioavailabilities measured in food.

The limited data concerning the oral bioavailability of aluminum from foods do not allow for the determination, with good predictive value, of the potential absorption of aluminum in food. For the purpose of comparison with other media (Table 2.7), the interval of 0.1% to 0.8% is retained, with a most likely range of 0.1% to 0.3%, based on the recent work of Yokel and Florence (2006) and Yokel et al. (2008).

Estimation of the oral bioavailability of aluminum in soils

Another factor of importance in the human exposure assessment for aluminum is the oral bioavailability of aluminum in ingested soil, as soil ingestion is a significant exposure pathway for the toddler group (see section 3.2.1). No bioavailability data on soil were identified. Limited data, however, were found for the bioaccessibility of aluminum in soil, which, as noted above, is an in vitro measure of the soluble fraction of the substance available for absorption.

Shock et al. (2007) estimated the bioaccessibility of aluminum in different tundra soil samples contaminated by mining waste dust, by simulating gastric fluid in an in vitro experiment. The estimated values varied from 0.31% to 4.0%, according to the grain size and to the solid:fluid ratios used in the experiment. As expected, aluminum in the soil with small sized grains size had the greatest absorption.

As is the case for the bioaccessibility data of aluminum in food, these bioaccessibility estimates for aluminum in soil need to be tied to the *in vivo* bioavailability estimates from appropriate *in vivo* models (Ruby et al. 1999). Even if the experimental protocols used to measure food and soil aluminum bioaccessibility differed slightly, the data of Shock et al. (2007) suggest that the bioaccessibility of aluminum in soil is similar to that in food. In the absence of more relevant data, the range for the oral bioavailability of aluminum in soil is therefore assumed to be similar or less than that of food. The relative oral bioavailability of aluminum in soil is considered to be a major source of uncertainty for this exposure pathway; however, bioavailability from soil is expected to be low.

2.3.3.1.2 Dermal absorption

Utilization of antiperspirant with aluminum would contribute to the body burden if aluminum passes through the skin barrier. There is some evidence from case studies, described below, that small amounts of aluminum do reach the systemic circulation. However, to date, no data for dermal bioavailability are available from controlled studies of more than one or two individuals.

In the study of Flarend et al. (2001), ^{26}Al-chlorohydrate (aluminum complex in antiperspirant) was applied to a single underarm of one man and one woman. The cumulative urinary excretion after 43 days following the application accounted for 0.0082% (male) and for 0.016% (female) of the applied dose. After correcting this fraction for the aluminum not excreted in urine (15% of the absorbed dose), this application was estimated to result in a dermal bioavailability of about 0.012%. On the basis of these data, the authors estimated that the amount of aluminum absorbed from regular use would be 0.25 μg/d.

Guillard et al. (2004) reported on one clinical case in which a woman who used an antiperspirant cream with aluminum chlorohydrate over four years showed elevated levels of aluminum in plasma and urine (10.47 μg/dL in plasma[12]). When the woman discontinued use, concentrations in her urine and plasma dropped to reported normal values after the third and eighth months, respectively.

2.3.3.1.3 Inhalation absorption

The ambient air of multiple occupational environments, such as the aluminum production industry and welders' factory (Priest 2004), may have high levels of aluminum. The higher urinary excretion of aluminum in exposed workers, compared to the general population, demonstrates that some inhaled aluminum can reach the systemic circulation (Sjogren et al. 1985; Sjogren et al. 1988; Pierre et al. 1995). This absorption depends on the form of aluminum in the ambient air (adsorbed to PM, vapour condensation fumes and flakes) and, in the case of particulate matter, also depends on the distribution of the sizes of the aerodynamic diameter of PM ($PM_{2.5}$ versus PM_{10}).

Priest (2004) estimated a deposited pulmonary fraction of 1.9% in a study of two volunteers who inhaled ^{26}Al-oxide adsorbed to particles with a mass median aerodynamic diameter (MMAD) of 1.2 μm. The last value is supported by animal studies showing a deposition of fly ash of aluminum into the lungs from 2% to 12% (Krewski et al. 2007). As well, Yokel and McNamara (2001) have proposed an absorption fraction of about 1.5% to 2%, on the basis of the relationship between the urinary excretion of aluminum-exposed workers and the concentrations of airborne soluble aluminum measured in their environment.

An investigation in New Zealand rabbits exposed via the nasal-olfactory pathway (sponge soaked in aluminum solutions inserted into nasal recess for four weeks) provided evidence that inhaled aluminum in the olfactory tract can cross the nasal epithelium to reach the brain directly through axonal transport (Perl and Good 1987). While an analytical protocol for quantifying the amount of aluminum transported along this pathway under environmental exposure conditions has been described (Divine et al. 1999), further experimental work is required to document transport of aluminum via this pathway to the olfactory bulb, and subsequently to other regions of the brain.

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[12] Guillard et al. (2004) indicated that the normal range of aluminum in blood plasma would be < 1.0 μg/dL.

2.3.3.1.4 Parenteral administration

Intravenous injection of aluminum-containing products (e.g., intravenous feeding solutions) results in complete availability of the aluminum to the systemic circulation (Yokel and McNamara 2001; Priest 2004). In the case of intramuscular injection of aluminum species (e.g., via vaccination), potentially all of the aluminum injected may be absorbed into the bloodstream. However, the uptake rate from the muscle to blood circulation differs according to the aluminum complex. Evidence of this was provided in an experimental study, in which rabbits were injected with ^{26}Al-hydroxide and ^{26}Al-phosphate, two common vaccine adjuvants, at standard dose levels. After 28 days, 17 % of the aluminum hydroxide and 51% of the aluminum phosphate were absorbed (Flarend et al. 1997). The authors estimate that this dose, when administered in humans, would represent an increase of 0.4 μg/dL in plasma (see section 2.3.3.2 on distribution, for estimates of normal plasma concentrations).

2.3.3.1.5 Summary of estimates of aluminum bioavailability

The estimates of aluminum bioavailability presented for the different exposure routes in sections 2.3.3.1.1 to 2.3.3.1.4 are summarized in Table 2.7. The information available to generate these estimates varies considerably depending on the exposure route, and should be considered in any application of these estimates in risk assessment.

Table 2.7 Ranges of estimated aluminum bioavailability for various routes of exposure in humans and/or animals

Route of exposure		Bioavailability (%)
Oral	Drinking water (a)	0.0086 to 0.65 (H) 0.01 to 5.1 (A) Proposed likely estimate: 0.3
	Food (b)	0.10 to 0.80 (H) 0.02 to 0.3 (A) Proposed likely range: 0.1 to 0.3
	Antacids (c)	0.001 to 0.20 (H)
	Soil ingestion (d)	Equal or less than food (default assumption)
Dermal (e)		0.012 (H)
Pulmonary (f)		1.5 to 2.0 (H)
Parenteral (g)		100.0

(H) = data from experimental studies conducted in humans
(A) = data from experimental studies conducted in animals

(a) Ranges based on a compilation of the central values of estimates of the oral bioavailability of aluminum from drinking water, obtained in numerous experimental studies conducted in humans and animals. Proposed likely estimate based on experimental work of Stauber et al. (1999) in humans and the critical review of experimental animal data in Krewski et al. (2007).

(b) Based on comparisons of estimates of aluminum intake and urinary excretion in humans and experimental animal data. The estimate of bioavailablility of aluminum in food is associated with greater uncertainty than

that of drinking water, because of the limitations of the database. Proposed likely range based on Yokel and Florence (2006) and Yokel et al. (2008).
(c) Based on human data reported in three studies for the bioavailability of aluminum in antacids alone or in combination with citrate, orange juice, bicarbonate, or calcium acetate.
(d) Assumed to be similar to that in food as a default value in the absence of bioavailability data from soil ingestion; considered to be of low predictive value.
(e) Based on experimental results reported in one study following a dermal exposure in two individuals.
(f) Proposed absorption fraction by Yokel and McNamara (2001) on the basis of the results from two studies in aluminum-exposed workers.
(g) Includes both intravenous (IV) and intramuscular (IM) injection.

2.3.3.1.6 Integrating bioavailability in human health risk assessment

As discussed in previous sections, the generally low oral absorption of aluminum (< 1%) is well recognized. Nonetheless, there is considerable uncertainty associated with differences in oral bioavailability, in relation to:

- the bioavailability of aluminum in different environmental media (soil, different types of food, drinking water, air, dermal application);
- the bioavailability of aluminum in humans versus experimental animal species;
- the influence of dose and dosing regime (bolus dose versus repeated exposure via drinking water or food).

In the characterization of human health risks, relative bioavailability rather than absolute bioavailability is the parameter of greatest interest. Relative bioavailability for a substance may, for example, refer to the ratio of absorbed fractions via two different exposure pathways, or it may refer to the ratio of total absorption by humans (all pathways considered) as compared to the total absorption in experimental animals in the critical study or studies.

Relative bioavailability can be established by directly measuring two absorption fractions and taking the ratio of the two, or potentially indirectly through the measurement of in vitro bioaccessibility and then by comparing in vitro bioaccessibilities (e.g., the fraction of a substance that is extracted through a weak acid solution simulating gastric fluid). In the case of aluminum, bioaccessibility would considerably overestimate bioavailability, as the available evidence indicates that only a fraction of the species dissolved in the stomach is eventually absorbed. However, to the extent that bioaccessibility is proportional to bioavailability, relative bioaccessibility will be approximately equivalent to relative bioavailability.

In the previous sections, experimental data were reviewed with respect to both bioavailability and bioaccessibility of aluminum salts in various media, in humans, and experimental animals. The discussion that follows reconsiders these data from the perspective of relative bioavailability.

The most comprehensive data concerns the bioavailability of aluminum dissolved in drinking water, as measured in both human and animal studies. In humans, measurements of oral absorption of aluminum (citrate, chloride, hydroxide or lactate complexes) generally

varies between 0.01% and 0.65%, while in experimental animals the range of reported values is 0.01% to 5.1%. The ranges largely overlap and do not provide evidence for differences between humans and animals in the bioavailability of aluminum in drinking water. The proposed likely estimate for aluminum bioavailability in both humans and animals is 0.3% (see Table 2.7).

The data on bioavailability of aluminum in food are much more limited, both for humans and animals. Section 2.3.3.1.1 proposes a range of 0.1% to 0.8% for the bioavailability of aluminum salts in food (humans) and 0.02 to 0.3 in animals. These ranges have a high level of uncertainty because of the limited database, but do not provide evidence for differences between humans and animals in the bioavailability of aluminum in food.

The bioaccessibilities of aluminum in soil and food were also compared in section 2.3.3.1.1. These very limited data do not provide evidence for a difference in the amount of aluminum available for absorption of aluminum from these two media, and hence do provide a basis for concluding that there are differences in bioavailability between soil and food.

In comparing the bioavailability of aluminum in drinking water and food, in both animals and humans, the ranges of experimental values largely overlap, and the proposed likely value for drinking water is at the upper end of the proposed likely range for food. Thus the available data are insufficient for identifying a difference in bioavailability of aluminum in drinking water and food.

With regard to inhalation absorption of aluminum, there is again significant variability in the available data. These data do indicate that the bioavailability of aluminum from inhalation may be higher than from the oral route; however, since the concentrations of aluminum in ambient and indoor air are low, the absorption factor for the inhalation route would not significantly influence the evaluation of cumulative exposure from soil, air, drinking water, and food.

Although dermal absorption of aluminum salts is thought to be very low, the data is extremely limited (confined to two studies), each involving one or two individuals (see section 2.3.3.1.2). Therefore, no definitive conclusions can be drawn with respect to its relative bioavailability, although the information available suggests that it is lower than for other routes of exposure.

Consideration of bioavailability may considerably influence the conclusions of human health risk characterization if relative bioavailabilities for different salts, different exposure media and different species are greater than or less than one. In this assessment, however, the limited available data did not provide evidence for relative oral bioavailabilities significantly different from one, either with respect to comparisons of humans and experimental animals, or with respect to comparisons of water, food and soil. The bioavailability via inhalation, which is higher than oral bioavailability, would not significantly influence the estimated absorbed dose, because of the low estimated concentrations of aluminum in ambient and indoor air. Dermal exposure, which appears to be associated with a very low absorption, was considered only qualitatively in this assessment. For these reasons, the estimated values of bioavailability

for different media were not explicitly integrated into the estimation of population exposure or the characterization of relative contribution of the three salts to overall exposure.

2.3.3.2 Distribution

Once absorbed into the systemic circulation, much of Al^{3+} is readily associated at the binding sites of transferrin (Tf), the plasma protein for iron transport. Since, under normal conditions, Tf in blood is only one-third saturated with iron, binding sites for the absorbed aluminum are available (Harris et al. 1996). Consequently, the Al-Tf complex is the predominant aluminum species in plasma, accounting for approximately 91% of the total aluminum in plasma (7% to 8% of aluminum is associated with citrate and less than 1% with phosphate and hydroxide) (Martin 1996). As well, Day et al. (1994) reported that, one hour after the ingestion of ^{26}Al-citrate, 99% of the ^{26}Al in blood was measured in plasma of which 80% was bounded to Tf, 10% to albumin and 5% to proteins having low molecular weight; after 880 days, 86% of aluminum in blood was bounded to plasma proteins (mostly to Tf) and the rest was associated with erythrocytes.

The major physiological compartment of aluminum is the skeleton. Krewski et al. (2007) suggest that approximately 58%, 26%, 11%, 3%, 0.95%, 0.3%, 0.25% and 0.2% of the aluminum body burden would be in the bone, lung, muscle, liver, brain, heart, kidney and spleen, respectively. Aluminum measured in the lungs may reflect deposition of airborne particles. In addition, a significant amount of aluminum analyzed in skin may result from unabsorbed aluminum deposited on skin surface (Priest 2004).

The transport of aluminum into the body and its deposition into the tissues and organs have been shown to vary widely (Priest 2004). This variability, yielding different aluminum concentrations in tissues and organs, can be explained by some of the same factors influencing aluminum absorption. For example, the presence of citrate seems to enhance the distribution of aluminum into the tissue before being associated with Tf (Quartley et al. 1993; Maitani et al. 1994). According to Jouhanneau et al. (1997), the concomitant ingestion of citrate increases aluminum absorption, but does not appear to modify the relative distribution of ^{26}Al in bone, brain and liver in comparison with ingestion without citrate.

Experimental studies have reported volumes of distribution (V_d) for aluminum, describing its potential to be distributed in tissues and organs. Most of these studies suggested that the initial V_d is approximately the blood volume (Krewski et al. 2007). However, longer collection periods lead to higher V_d, indicating a possible dependency between elimination rate and blood concentrations of aluminum (Krewski et al. 2007) (see section 2.3.3.3). Calculating the oral bioavailability of aluminum using blood volume, instead of V_d, may consequently lead to an underestimation (see section 2.3.3.1).

As neurological and reproductive/developmental endpoints are of greatest concern with respect to the environmental exposures evaluated in this assessment (see section 3.2.3.2), particular attention is paid to the distribution processes leading to accumulation in the brain and in the foetus. As well, aluminum retention in bone was investigated, as it plays an important role in the kinetics of aluminum. The principal observations with regard to retention