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Increased urinary excretion of aluminium after ingestion of the food additive sodium aluminium phosphate (SALP) – a study on healthy volunteers

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ABSTRACT

Food is an important source of human aluminium (Al) exposure and regular consumption of foods containing Al-based food additives may result in high Al intakes above health-based tolerable intakes. However, some additives are Al salts with low solubility, and little is known about bioavailability of Al in these additives. We investigated urine Al concentrations in healthy adult volunteers (N = 18, women/men) before (base-line) and after 7 days of ingestion of pancakes with a low Al content (median: <0.5 mg Al/kg) and high Al content (median: 860 mg/kg). The high-Al pancakes contained the common additive sodium aluminium phosphate (SALP). The participants did not know if the pancakes contained SALP or not during the experiment. After adjusting for creatinine content of the urine samples, median base-line Al concentrations before pancake ingestion were in the range 30–40 µmol Al/mol creatinine. Urine Al concentrations after ingestion of low-Al pancakes (average intake: <0.042 Al mg/day) did not differ significantly from the base-line levels. After ingestion of high-Al pancakes (72 mg Al/day) the median Al concentration in urine was more than 2-fold higher than at the base-line sampling before the high-Al pancake ingestion. At the end of the experiment the volunteers ingested an Al-containing antacid (Al-OH, 1800 mg Al/day) for 7 days as a positive control of Al absorption. This caused a 10-fold increase in median urine Al concentration compared to base-line. Our results strongly suggest that Al in the form of SALP in a pancake mix is bioavailable for absorption in humans, which should be taken into account in risk assessment of Al in food in countries with a high use of SALP as a food additive.

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Introduction

Food is an important source of human aluminium (Al) exposure. Duplicate diet studies, total diet studies and market basket surveys, from Japan, Australia, North America and Europe, have reported average Al intakes ranging from 2.4 to 13 mg/day for adults (Krewski et al. 2007; EFSA 2008; JECFA 2012). The solubility of Al at neutral pH is low, thus contributing to a low bioavailability for intestinal Al absorption (<1%) (Krewski et al. 2007). Concomitant presence of organic acids in the intestinal lumen, however, increases the solubility and bioavailability of Al for absorption (Krewski et al. 2007). The absorbed fraction is relatively effectively excreted within a few days in the urine, although a part of absorbed Al has a very long half-life (years) (Greger and Sutherland 1997; Priest 2004). Al accumulates and causes neurotoxic effects and bone toxicity in patients with impaired kidney function when exposed to Al in dialysis water (Wills and Savory 1989; Rob et al. 2001). Al neurotoxicity and bone toxicity are suggested problems in preterm infants exposed to Al in intravenous-feeding solutions (Bishop et al. 1997; Poole et al. 2008). The European Food Safety Authority (EFSA) has proposed a tolerable intake of Al in food of 1 mg Al/kg body weight/week (TWI), whereas the Joint FAO/WHO Expert Committee on Food Additives estimated the TWI to 2 mg/kg/w (EFSA 2008; JECFA 2012). The tolerable intake was in both cases based on animal studies showing neuro-toxicity, embryotoxicity, testis-toxicity and toxicity on the developing nervous system. The EFSA expert group concluded that the EFSA TWI is likely to be exceeded by a significant part of the European population (EFSA 2008).

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In 2013 EFSA published a report on human dietary exposure to Al-containing food additives. It was concluded that regular consumption of foods with Al additives would result in Al intakes well above the TWI (EFSA 2013). However, little is known about the bioavailability of Al in additives when present in foods. A study of oral bioavailability of Al in the food additive acidic sodium aluminium phosphate (SALP) in rats fed SALP-containing biscuits reported that bioavailability of Al in SALP (0.1%) was less than bioavailability of Al in drinking water (0.3%) (Yokel and Florence 2006). To our knowledge no study has investigated the degree of intestinal absorption of the food additive Al in human subjects from the general population during regular consumption of Al additive-containing foods. A better knowledge about the Al absorption from additives in such foodstuffs would greatly improve the risk assessment of the use of Al additives.

We have previously shown that Al concentration in urine is a sensitive marker of intestinal Al absorption from an over-the-counter antacid (Al-OH) (Gräske et al. 2000). In the current study we investigated urine Al concentrations in 18 healthy volunteers before and after 7 days of daily consumption of pancakes made of pancake mixes containing no Al additives or an Al additive declared as sodium aluminium phosphate (SALP). The aim was to determine if consumption of Al additive-containing pancakes resulted in increased urine Al concentrations above background, as a measure of Al absorption.

Materials and methods

Study participants

Healthy adult volunteers, 9 women and 9 men (mean age: 44 years, range: 25–60 years) employed by the Swedish National Food Agency and living in the City of Uppsala, Sweden, were recruited for the study. Participants reported in a questionnaire that they had not used medicinal drugs containing Al during 30 days before the experiment started, and did not take drugs that interact with Al. Participants had not been vaccinated at least 2 months before the experiments. The study was approved by the Ethics Committee of the Medical Faculty at Uppsala University, Uppsala, Sweden.

Experimental design

Study participants daily (in the morning) ingested the test meals for 7 days (test period), with periods of no consumption of at least 7 days between test periods (rest periods) (Figure 1). As a positive control of Al exposure, an Al-containing antacid (Al-OH) was also taken daily for 7 days after a rest

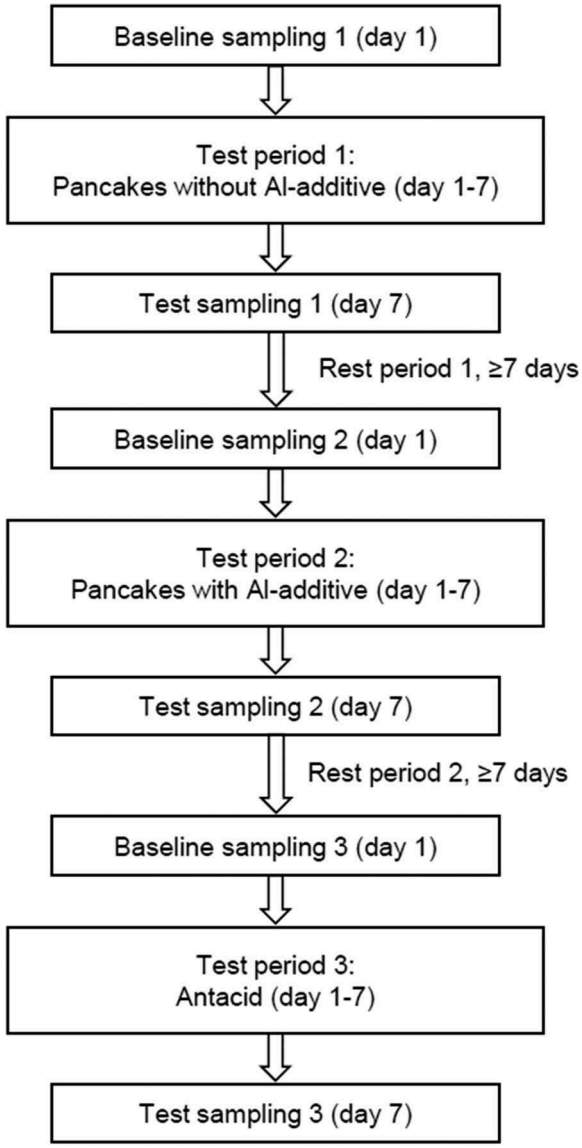

Figure 1. Experimental design. Baseline urine sampling for Al analyses took place in the morning before the start of the 7-day ingestion of pancakes and antacid. Test sampling of urine took place directly after the last ingestion of pancakes and antacid in the morning of the 7th day of ingestion.

period with no pancake ingestion of at least 7 days. The test periods occurred in the sequence pancakes without Al additive (low-Al), pancakes containing Al additive (high-Al) and antacid. The participants did not know if the pancakes contained Al or not during the experiment. Spot urine samples (approx. 15 ml) were taken by the participants before and after each test period. Al-free plastic tubes (Labora, Sollentuna, Sweden) were used. The baseline samples were taken at the first toilet visit in the morning of the first day of the test periods. On day 7 of the test periods a urine sample was similarly taken in the morning after the final ingestion of pancakes or antacid (test sampling). The urine samples were acidified by adding 0.5 ml sub-boiled distilled nitric acid to 10 ml of urine and stored frozen (−20°C) until analysis. Special precautions were taken to prevent extraneous Al contamination.

Pancakes and antacid

Two different types of pancake mixes were used, one for which no Al-containing additives were declared on the package and one for which use of SALP was declared. The content of several packages of each mix were mixed together before preparation of the batter. Pancake batter was prepared as instructed on the packages and pancakes were cooked in a cast iron skillet with indentations to allow for seven small pancakes to be made at once. The median weight of the pancakes was 21 g (range 15–29 g, N = 26). The median Al concentration in the low-Al pancakes was <0.5 mg Al/kg (range:<0.5–4.6 mg/kg, N = 10) and in the high-Al pancakes 860 mg/kg (range: 750–1200 mg/kg, N = 10). Pancakes were randomly sampled for Al analyses, and the remaining pancakes were randomly placed in plastic bags (4 in each) and stored at −20°C until distributed to the study participants. The study participant consumed 4 pancakes per day for 7 days, resulting in an average Al intake of 72 mg/day from high-Al pancakes and <0.042 mg/day from low-Al pancakes.

An over-the-counter antacid was used as a positive control of Al absorption. According to the product data sheet the 10 ml suspension contained 588 mg Al as Al-OH, and users were recommended to take 5–10 ml when necessary during episodes of acid reflux. The study subjects were asked to take 3 doses of 10 ml suspension per day for 7 days, one dose in the morning, at lunch and in the evening. Such a dosing resulted in an Al intake of 1800 mg Al/day

Analyses of urine creatinine and aluminium

Urine creatinine concentrations were determined at the University Hospital, Uppsala, Sweden by an accredited routine laboratory analytical technique. Analyses were performed by a kinetic colorimetric assay on a Hitachi 717 clinical chemistry analyzer, using the HiCo Creatinine (CREA) kit (Boehring Mannheim, Mannheim, Germany).

Aluminium in pancakes and urine were analyzed blinded at ALS Scandinavia AB, Luleå, Sweden, by inductively coupled plasma – sector field mass spectrometry (ICP-SFMS, Element 1, Thermo Finnigan), using modified USEPA Methods 200.7 and 200.8. Pancake samples (0.3–0.5 g) were digested in a commercial microwave oven in capped Teflon vessels using nitric acid (s.*p*, 5 ml) and hydrogen peroxide (0.5 ml). Urine samples (0.5 ml) were diluted with 0.1 ml nitric acid (s.p). Before analysis pancake and urine samples were diluted with Millipore water and an internal standard solution with 5 ppm Lu was added. For both pancakes and urine the sample solutions were compared to certified elemental standard solutions traceable to NIST (National Institute of Standards and Technology). The isotopes Al^{27} and Lu^{175} were monitored in medium resolution mode with six scans of each peak. The quantification limit (LOQ) for Al in pancakes was 0.5 mg Al/kg and in urine 2 μg Al/l. LOQs for both matrices were determined as 10 times the standard deviation of seven method blanks. A method blank was included in the analyses of both the pancake and urine samples, introduced from the first step of the sample preparation. The Al concentration in the urine blank was 1.29 μg Al/l. The concentration in method blank was not subtracted from the measured concentrations in the samples. A reference material, Seronorm (urine, lot 0511545) was analyzed together with the urine samples and the measured concentration was 113 μg Al/l (certified concentration 88–112 ng Al/l). The expected concentration for the reference material was 112 ng Al/l, based on the laboratory´s control card results for the Al analyses in urine. The laboratory participated in QMEQAS (Quebec

Multi-elemental External Quality Assessment Scheme). The z-scores for the laboratory´s results in the three QMEQAS rounds for 2011, when the urine samples were analyzed, ranged between −1.08 to 0.29 (satisfactory).

Calculations and statistics

In the statistical analyses Al concentrations in urine were expressed as µmol Al/mol creatinine. Al concentrations below LOQ were set to ½LOQ. Differences in urine Al concentrations between sampling occasions were tested with the Mann-Whitney U test. Spearman´s correlation coefficients were calculated in the analyses of relations between Al concentrations at different sampling occasions. In this case Al urine data were not transformed. Level of significance was set to $p \leq 0.05$.

Results

Only one urine sample had an Al concentration below LOQ (<2 µg Al/l). The median Al concentration in urine was 7.2 µg/l (range: 2.0–18 µg/l) at the first baseline measurement, 6.9 µg/l (range: 2.7–25 µg/l) after ingestion of low-Al pancakes, 5.7 µg/l (range: <2–18 µg/l) at the second baseline measurement, 14 µg/l (range: 2.7–43) after ingestion of high-Al pancakes, 12 µg/l (range: 2.6–26 µg/l) after the third baseline measurement, and 110 µg/l (range: 28–500 µg/l) after the antacid ingestion.

After adjusting for creatinine content of the urine samples, median base-line Al concentrations after the rest periods were in the range 30–40 µmol Al/mol creatinine (Figure 2). Al concentrations after ingestion of low-Al pancakes did not differ significantly from the base-line 1 concentrations. After ingestion of high-Al pancakes for 7 days the median Al concentration in urine was more than 2-fold higher (67 µmol Al/mol creatinine) than in base-line 2 samples taken in the morning before the start of ingestion of the pancakes (26 µmol Al/mol creatinine) ($p \leq 0.05$) (Figure 2). Antacid dosing for 7 days caused a 10-fold higher median Al concentration in urine compared with the median concentration at base-line 3 ($p \leq 0.05$) (Figure 2).

Creatinine-adjusted Al concentrations in samples from base-line 1 were significantly correlated with concentrations after ingestion of no-Al pancakes (r = 0.64, p = .005), and with concentrations in base-line 2 samples (Spearman´s r = 0.66, p = .003). The correlation between no-Al pancakes concentrations and base-line 2 was weaker (r = 0.39, p = .106), and correlations between base-line 3 and the other background samples varied (r = −0.007–0.48, p = .977–0.045).

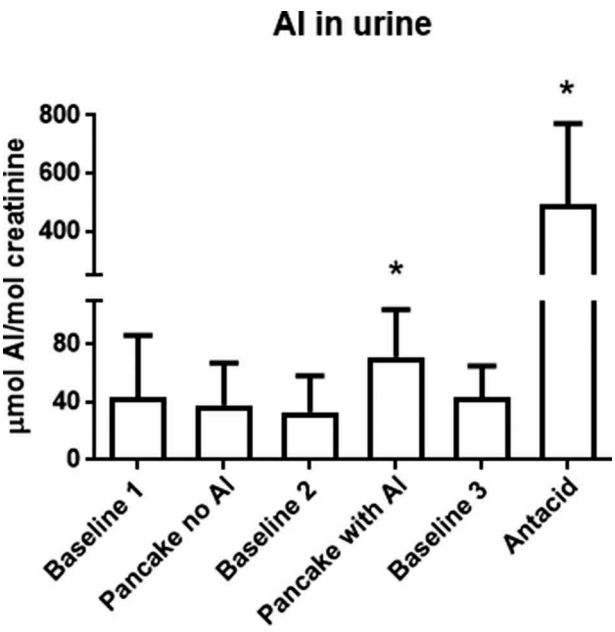

Figure 2. Al concentrations (median, max) in spot urine samples of 18 healthy volunteers. Samples were taken before and after consumption pancakes with no Al additive, pancakes with the Al additive SALP, and an Al-containing antacid for 7 days. Baseline sample 1 was taken in the morning before the start of no Al pancake ingestion. Baseline sample 2 was taken at least 7 days after the end of ingestion of no Al pancakes, in the morning before start of ingestion of pancakes with Al (SALP). Baseline 3 sample was taken after a rest period of at least 7 days, in the morning before start of ingestion of Al-containing antacid. Test samples were taken in the morning directly after the last ingestion of no Al pancakes, Al pancakes and antacid during the test period. *p ≤ 0.05, between baseline 2 and Al pancake samplings, and between baseline 3 and Al antacid samplings (Mann-Whitney U test, N = 18).

Discussion

Our results show that daily consumption of 4 small pancakes containing the Al additive SALP (860 mg Al/kg pancake) by 18 volunteers resulted in a significant increase in urine Al concentrations compared to the base-line Al concentrations in the same subjects before consumption of the pancakes. This shows that the Al intake from the pancakes (72 mg Al/day) was high enough to

cause an increased Al absorption, thus strongly suggesting that the Al in SALP was bioavailable for intestinal absorption.

This is to our best of knowledge the first study to experimentally investigate bioavailability of Al additives in humans consuming food available on the market. The additive in the pancake mix was declared as SALP. This additive is in many countries used either in an acidic form in for instance baking powder for special uses or in a basic form as an emulsifier in processed cheese (Yokel et al. 2008). Although not stated on the pancake mix package, the additive used was most probably the acidic form of the additive, as a component of the leveling agent in the pancake mix. Within the European Union, acidic SALP (E541) is only authorized for use in certain layered sponge cakes with a maximum limit of 400 mg Al/kg in the sponge cake parts, and a recent risk assessment concluded that SALP is of no safety concern in the current authorized use (EFSA 2018). The median Al concentrations in the pancakes containing the Al additive in our study was twice as high as the maximum limit for layered sponge cakes. The mix was produced in the United States (US), where SALP is authorized for a much wider use than within the EU, for instance in self-rising flours and meals (FDA 2018). As a consequence, human exposure to acidic SALP is therefore most probably higher in the US than in Europe. In a US study from 2005, it was estimated that SALP in pancake and waffle mixes could provide up to 180 mg Al per serving (Saiyed and Yokel 2005). In our study, the breakfast with 4 small pancakes (about 80 g) provided on average 74 mg Al per serving, which is less than half of the estimated intakes from a serving of waffles and pancakes (Saiyed and Yokel 2005).

In Europe, total dietary exposure to Al has been estimated as 1.6 to 13 mg/day, corresponding to 0.2 to 1.5 mg/kg body weight per week for adults with a body weight of 60 kg (EFSA 2008). For children the intake is higher due to a higher consumption of food per kg body weight than among adults (EFSA 2008). Duplicate diet studies from Japan, India and Taiwan have indicated similar average daily intakes among adults as in Europe (JECFA 2012). Inter-individual variation of intake may however be large as our study suggests that consumption of pancakes containing SALP may result in a daily intake more than 5-fold higher than the average daily intake. Assuming a body weight of 60 kg, regular consumption of the SALP-containing pancakes for breakfast may contribute about 8 mg Al/kg body weight/week, which is considerably higher than the TWIs published by EFSA and JECFA (1 and 2 mg/kg/w, respectively) (EFSA 2008; JECFA 2012). For children, most likely consuming more pancakes per kg body weight than adults, the intake would be even higher than for adults.

Absorbed Al after ingestion is mainly excreted by the kidneys in humans. Our adult study participants had a median urine Al concentration at base-line 1 and 2, and after ingestion of pancakes with low Al content, of <10 μg/L, with a max of <30 μg/L). Median concentrations are in the same range as recently reported for healthy adults from France and the UK (Morton et al. 2014; Nisse et al. 2017), but lower than reported from the Czech Republic and China (Frankova et al. 2016; Wang et al. 2016; Lu et al. 2016). It is difficult to measure Al in biological samples from humans correctly, due to the high risk of contamination during sampling, sample storage and sample preparation (Michalke et al. 2018), making comparisons between studies difficult. In our study, the similarity of concentrations between the base-line samplings and sampling after ingestion of low-Al pancakes suggests that the study subjects did not intentionally or un-intentionally change their habits in such a way that general Al exposure was significantly affected during the pancake ingestion periods. The subjects were blinded to the Al content of the pancakes, which further assured that the results of the study was not biased by changes in habits by the subjects during pancake ingestion. We observed a relatively strong relation between urine Al concentrations at the 2 first base-line samplings and the sampling after ingestion of low-Al pancakes. This further suggests a stable background Al exposure among participants. The weaker correlations between concentrations in these samples and those in the base-line samples after high Al-pancake ingestion period may be due to a remaining influence of Al ingestion on urine concentrations in some subjects after the relatively short rest period (minimum 7 days).

Oral bioavailability of different forms of Al has in animal experiments been determined to be 0.025–1.5% (Willhite et al. 2014). In humans, using ^{26}Al methodology, oral bioavailability ranged from 0.002% to 1% (Priest 2004). A study of bioavailability of ^{26}Al in rats fed ^{26}Al-SALP-containing biscuits (1–2% SALP) reported a ^{26}Al bioavailability of 0.1% (Yokel and Florence 2006). In 2011 EFSA evaluated a study of bioavailability of ingested ^{26}Al-labelled Al and Al compounds in the rat, made available by the industry (EFSA 2011). Bioavailability was studied by determining the ratio of the fraction of ^{26}Al left in the carcass 7 days after oral administration of the ^{26}Al-labelled compound over the fraction of carcass ^{26}Al left 7 days after intravenous administration (iv) of ^{26}Al-labelled aluminium citrate. In the study, the fraction of absorption was estimated to range from 0.025% (Al hydroxide) to 0.21 (Al sulphate). For SALP bioavailability was <0.024% (EFSA 2011).

The design of our study did not make it possible to determine the oral bioavailability of Al from SALP. We can only do a rough calculation of the percentage of Al excreted in urine after ingestion of SALP, which was estimated to be about 0.04% of the daily Al dose from the high-Al pancakes. This estimate is based on the assumption that the creatinine-adjusted Al concentrations in the spot urine samples are representative of concentrations in 24-h urine samples. The median 24-h Al urinary excretion after the 7-day consumption the high-Al pancakes was estimated to be approximately 0.9 μmol Al, using the median spot urine Al concentration (67 nmol/mmol creatinine) after high-Al pancake ingestion and average 24-h creatinine excretion in adults of approximately 13 mmol (average for men and women) (Bingham et al. 1988; Alexandrov et al. 2018). After subtraction of the average base-line Al excretion (0.34 μmol/24 h), and assuming that about 50% of the absorbed Al dose is excreted within 24 h (Talbot et al. 1995), the excretion of 0.56 μmol Al/24 h during 2 days (1.1 μmol Al) represents approximately 0.04% of the daily Al dose from the pancakes (2.7 mmol).

At the end of the study period the participants ingested an over-the-counter antacid containing Al-hydroxide for 7 days, resulting in an Al dose of 1800 mg/day (66 mmol). After this exposure the average urine Al concentration was about 10 times higher than at the background samplings, showing a large increase in Al absorption. In an earlier study (Gräske et al. 2000) healthy adults took the same antacid dose daily for 6 weeks, resulting in median concentrations of Al in urine after 2, 4, and 6 weeks of 334–419 nmol/mmol creatinine, which was similar to the median concentration found in the present study after 1 week of Al antacid dosing (440 nmol/mmol creatinine). This suggests a stabilization of Al excretion already after 1 week of antacid dosing. Using the same assumption as in the calculations of bioavailability of Al in SALP, urinary excretion of antacid Al was estimated to about 0.017% of the daily Al dose from the antacid.

In Sweden, and most probably also in many other countries, Al antacids are regarded as safe for treatment of heartburn during pregnancy. Heartburn is common in pregnancy and symptoms may persist for several months from the end of the first trimester (Richter 2005). Al antacids are commonly taken in connection to meals and there are components in food, such as low-molecular-weight organic acids, that substantially increase the bioavailability of Al from antacids (Slanina et al. 1986; Walker et al. 1990). Taken together, our results and the results from animal studies regarding transfer of Al from the mother to the fetus (Domingo et al. 2000), strongly suggest that long-term use of Al antacids during pregnancy may increase the risk of Al accumulation in the growing fetus. Since studies have shown that gestational Al exposure of animals causes developmental effects of the offspring, and that Al antacids can be used by pregnant women without professional medical control, the safety of Al antacids during pregnancy can be questioned (Reinke et al. 2003). Riihimäki and Aitio (Riihimaki and Aitio 2012) proposed an action limit for urine Al of 80 μg/L in occupational workers, based on reports of impaired cognition in Al welders with many years of exposure. This action limit is lower than the median Al concentrations observed among our healthy volunteers taking the antacid as recommended on the package.

Conclusion

Our study shows that daily ingestion of pancakes containing the food additive SALP for a week causes an increased Al excretion in urine, strongly

suggesting that Al in SALP is bioavailable for intestinal absorption. Long-term daily consumption of products containing similar levels of SALP as in the pancakes may thus cause an increased Al accumulation in the body above background. Since background exposure to Al is close or above currently accepted tolerable intakes, this additional exposure is of concern. An even higher concern is the availability of over-the-counter drugs with a very high Al content, especially if used over an extended time period by women during pregnancy.

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Disclosure statement

The authors reported no potential conflict of interest.

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