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Systematic review of potential health risks posed by pharmaceutical, occupational and consumer exposures to metallic and nanoscale aluminum, aluminum oxides, aluminum hydroxide and its soluble salts

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Abstract

Aluminum (Al) is a ubiquitous substance encountered both naturally (as the third most abundant element) and intentionally (used in water, foods, pharmaceuticals, and vaccines); it is also present in ambient and occupational airborne particulates. Existing data underscore the importance of Al physical and chemical forms in relation to its uptake, accumulation, and systemic bioavailability.

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The present review represents a systematic examination of the peer-reviewed literature on the adverse health effects of Al materials published since a previous critical evaluation compiled by Krewski et al. (2007).

Challenges encountered in carrying out the present review reflected the experimental use of different physical and chemical Al forms, different routes of administration, and different target organs in relation to the magnitude, frequency, and duration of exposure. Wide variations in diet can result in Al intakes that are often higher than the World Health Organization provisional tolerable weekly intake (PTWI), which is based on studies with Al citrate. Comparing daily dietary Al exposures on the basis of “total Al” assumes that gastrointestinal bioavailability for all dietary Al forms is equivalent to that for Al citrate, an approach that requires validation. Current occupational exposure limits (OELs) for identical Al substances vary as much as 15-fold.

The toxicity of different Al forms depends in large measure on their physical behavior and relative solubility in water. The toxicity of soluble Al forms depends upon the delivered dose of Al^{+3} to target tissues. Trivalent Al reacts with water to produce bidentate superoxide coordination spheres $[Al(O_2)(H_2O_4)]^{+2}$ and $Al(H_2O)_6^{+3}$ that after complexation with $O_2^{\bullet-}$, generate Al superoxides $[Al(O_2^{\bullet})](H_2O_5)]^{+2}$. Semireduced AlO_2^{\bullet} radicals deplete mitochondrial Fe and promote generation of H_2O_2 , $O_2^{\bullet-}$ and OH^{\bullet} . Thus, it is the Al^{+3} -induced formation of oxygen radicals that accounts for the oxidative damage that leads to intrinsic apoptosis. In contrast, the toxicity of the insoluble Al oxides depends primarily on their behavior as particulates.

Aluminum has been held responsible for human morbidity and mortality, but there is no consistent and convincing evidence to associate the Al found in food and drinking water at the doses and chemical forms presently consumed by people living in North America and Western Europe with increased risk for Alzheimer’s disease (AD). Neither is there clear evidence to show use of Al-containing underarm antiperspirants or cosmetics increases the risk of AD or breast cancer. Metallic Al, its oxides, and common Al salts have not been shown to be either genotoxic or carcinogenic. Aluminum exposures during neonatal and pediatric parenteral nutrition (PN) can impair bone mineralization and delay neurological development. Adverse effects to vaccines with Al adjuvants have occurred; however, recent controlled trials found that the immunologic response to certain vaccines with Al adjuvants was no greater, and in some cases less than, that after identical vaccination without Al adjuvants.

The scientific literature on the adverse health effects of Al is extensive. Health risk assessments for Al must take into account individual co-factors (e.g., age, renal function, diet, gastric pH). Conclusions from the current review point to the need for refinement of the PTWI, reduction of Al contamination in PN solutions, justification for routine addition of Al to vaccines, and harmonization of OELs for Al substances.

Keywords

Alzheimer’s disease; antiperspirants; aluminum nanoparticles; breast cancer; encephalopathy; microcytic anemia; minimal risk level; osteomalacia; parenteral nutrition; reactive oxygen; threshold limit value; tolerable weekly intake; vaccine adjuvants

Introduction

The adverse neurologic, hematopoietic, skeletal, respiratory, immunologic, and other effects associated with excessive aluminum (Al) exposures are well known (reviewed in ATSDR 2008, Nordic Expert Group 2011, Willhite et al. 2012). Controversy over what constitutes “safe” Al exposure began at least 100 years ago (Gies 1911) and questions persist concerning the role of Al in AD (Campdelacreu 2012, Exley et al. 2012, Tomljenovic 2011, Solfrizzi et al. 2011, Walton 2012a) and other disease states (AFSSAPS 2011). Over the past two decades, a number of regulatory guidelines and limits on Al have been adopted and revised. To appreciate these changes in Al guidance and regulation, it is important to keep in mind that the physical and chemical nature of the particular Al form can be far more important to health outcomes than exposure to Al per se.

Krewski et al. (2007) summarized exposure and toxicity data for approximately 100 different Al forms and found that health risks to humans related to excessive Al exposure include:

- Osteomalacia and microcytic anemia after exposure from dialysate and/or gastric antacids or Al phosphate binders in people with compromised kidney function;
- Encephalopathy/dementia after exposure from dialysate and/or Al phosphate binders in patients with impaired renal function;
- Contact allergy and local irritation/adverse reactions to vaccines with Al adjuvants;
- Pneumoconiosis after long-term inhalation of Al dusts or powders.

Krewski et al. (2007), like Sorenson et al. (1974), observed that most healthy adults tolerate comparatively large repeated daily oral Al exposures (up to 3500–7200 mg/day from antacids and buffered aspirin) without any adverse effect, but that other people (notably pre-term infants, young children, and those with reduced kidney function) can be at serious risk for systemic Al intoxication even at much lower daily doses. Because Al gastrointestinal uptake varies from essentially non-detectable for hydrated Al silicates (Afriyie-Gyawu et al. 2005, Wiles et al. 2004), to 0.1–0.3% for sodium Al phosphates in foods, to 0.2% for $AlCl_3$ to much higher values (> 2.0%) after ingestion of organic Al (EFSA 2011, Krewski et al. 2007), exposures expressed as “total Al” are problematic for human health risk assessments.

The present review compiles recent environmental and occupational Al exposures, evaluates recent Al health effects data, and compares those outcomes with existing Al exposure standards and guidelines.

Sources of information

A systematic approach was undertaken to update the evidence for adverse health effects in humans of metallic Al, Al oxides, and Al hydroxide considered by Krewski et al. (2007). The search strategy was designed to identify recently published studies that examined acute toxicity, irritation/corrosion, sensitization, mutagenicity/genotoxicity, carcinogenicity,

repeated dose toxicity including neurotoxicity, reproduction and developmental toxicity associated with oral, inhalation, dermal, and intramuscular exposures to these Al substances. The Ovid MEDLINE, Ovid EMBASE and Toxline databases were searched to ensure that the database remained current during the conduct of the hazard assessments. The search strategy was first developed to cover the Ovid MEDLINE and the Ovid EMBASE and then adapted to cover the Toxline database. Search terms were grouped according to the Boolean operators OR and AND to develop the search profile. The titles and abstracts of all articles identified in the primary search were independently examined by two reviewers to determine the potential eligibility of each study for inclusion. No language exclusion criteria were applied at the screening stage in an effort to compensate for potential publication bias. Following the primary screening, the full articles were obtained and the inclusion/exclusion criteria applied. Only publications appearing in peer-reviewed sources (including book chapters and regulatory evaluations) were included; conference proceedings and abstracts were excluded. Where only abstracts of full studies could be located, or further details were required particularly relating to data reporting, the corresponding author was contacted to ascertain the particulars of the study. Where multiple publications on the same issue or data were identified, only the most relevant study was retained.

After all of the relevant studies were identified, the same two reviewers independently extracted data and entered the study results into a standard data abstraction form. The collected data related to referencing, Al compound(s) tested, subject selection/animal species/test system, study design, and results. The same two reviewers then independently assessed the methodological quality of all included studies. The quality of individual in vivo and in vitro studies was assessed using criteria developed by Klimisch et al. (1997) and Schneider et al. (2009). The overall methodological quality of individual epidemiological studies was assessed using a set of relevant check points used in the EU risk assessment of metals (EC 2005) and the Wells et al. (2003) and Bradford-Hill (1965) guidance. Differences in quality assessment of individual studies were resolved by consensus. No attempt was made to blind the reviewers to the authorship of the original publications. Consistency/concordance or lack of concordance between results of comparable human studies, between results in studies of different genders, species and strains in comparable animal studies and between results of different in vitro assays designed to measure similar endpoints were taken into account.

Using our search algorithm, 3820 studies were identified since publication of the Krewski et al. (2007) monograph and of those 469 are included here. Publications dated prior to 2007 are cited where they contribute to understanding the more recent data. The more informative studies are discussed below whereas others deemed less so are summarized in tables.

Environmental and occupational exposure

Krewski et al. (2007) tabulated the major sources of Al exposure in humans. Daily exposures range from as little as less than 0.06 mg/day as a result of inhaling PM₁₀ particulates in ambient air with 0.6–7.0 µg Al/m³ to as high as 3500–5200 mg Al/day as a result of consuming Al antacids.

Dietary

Yokel (2012) found that daily dietary Al contributed only a fraction (0.07–0.2%) of that received from gastric antacids. Depending upon regional preferences, beverages can constitute a major source of ingested Al. Cao et al. (2010) measured Al in 17 fermented and 19 raw teas grown near Puerh City, China; the Al concentration in fermented tea (794 ± 140 mg/kg) was somewhat higher than that in raw tea (594 ± 129 mg/kg) and based on the tea consumption rates among 110 Puerh City and 109 Kuming City residents, mean daily Al doses from tea were 99 and 60 $\mu\text{g}/\text{kg}\cdot\text{day}$, respectively. Consumption of tea infusions can account for up to 50% of one's daily Al exposure (Yokel 2013).

Aluminum concentrations in eight different infant formulas purchased in the United Kingdom ranged from 176 to 700 $\mu\text{g}/\text{L}$ and the Al content in eight different reconstituted formulas ranged from 333 to 629 $\mu\text{g}/\text{L}$. For a (50th percentile) five-month-old boy weighing 7.63 kg or a (50th percentile) 12 -and-a half- month-old 10.46 kg boy (CDC 2000), these concentrations correspond to daily Al consumption between 27–78 and 19–57 $\mu\text{g}/\text{kg}\cdot\text{day}$, respectively (Burrell and Exley 2010). Those values are consistent with or generally less than those reported for Australian, Canadian, and French children (FSANZ 2011, Health Canada 2007, Rose et al. 2010).

Aluminum concentrations present in formula can vary by location, over time and with product type. Dabeka et al. (2011) calculated current mean total Al concentrations in Canadian ready-to-use milk- and soy-based formulas as 440 and 730 mg/L, respectively. Compared to their previous study (Dabeka and McKenzie 1990) that found 130 and 1980 μg Al/L in similar products, mean Al levels in formula ranged from 72 $\mu\text{g}/\text{L}$ in fat supplements to 510 $\mu\text{g}/\text{L}$ in a whey-based formula. Lactose-free formula had a somewhat higher Al content than the standard milk-based formula, but the highest concentration (3442 $\mu\text{g}/\text{L}$) was found in a milk-based iron-fortified ready-to-use formula.

Dabeka et al. (2011) collected levels of Al in formula measured in Britain, the European continent, Nigeria, Spain, Saudi Arabia, and the United States. Aluminum concentrations as low as 6 $\mu\text{g}/\text{L}$ to as high as 1152 $\mu\text{g}/\text{L}$ (particularly for soy-based, lactose-free, and hypoallergenic formula) have been reported. However, the contemporary data all show Al levels far lower than the highest recorded (5900 mg/kg) for a dry formula purchased in the United Kingdom (Ministry of Agriculture, Fisheries and Food 1999). Assuming an infant consumed only commercial formula, Dabeka and McKenzie (1990) calculated that daily ingestion of a soy-based (high Al) formula by a 1- to 3 month-old baby corresponded to 363 $\mu\text{g}/\text{kg}\cdot\text{day}$ amounting to ~700 times the daily Al dose received by an infant consuming only cow's milk (0.5–2.0 $\mu\text{g}/\text{kg}\cdot\text{day}$).

As with infant formula, the Al concentrations in milk vary by source, location, and local practice. Al-Ashmawy (2011) found differences in Al concentrations in raw cow's milk (0.004 ± 0.001 mg/L), 'small market' milk (0.081 ± 0.010 mg/L), powdered milk (0.732 ± 0.270 mg/L) and processed cheese (0.027–5.7 mg/kg). The differences in Al concentrations between raw milk and "small market" milk were attributed to boiling raw milk in Al pans. Processed Egyptian cheese wrapped in Al foil had higher Al concentrations (1.62 ± 0.32 mg/kg) than processed cheese packed in glass containers (1.14 ± 0.55 mg/kg).

Based on those results, Al-Ashmawy (2011) calculated maximum estimated daily intakes (MEDI) for consumption of 200 ml Egyptian bulk farm milk or market milk per day or 45 g (~1.5 ounces) processed cheese per day provided 0.029, 0.612, and 4.282 mg Al/kg-day, respectively. For a 60-kg Egyptian adult, the milk MEDI contributed 6 µg/kg-day and consumption of processed Egyptian cheese (mean Al = 1.1–1.6 mg Al/kg) contributed 2.2–4.28 mg Al/kg-day or 15–30 mg Al/kg-week, equivalent to 15 times the 2 mg/kg-week PTWI (Benford et al. 2012). Assuming a 60-kg adult consumes 200 ml of cow's milk per day, the daily Al dose varied from 0.23 to 13.1 µg/kg-day (Arnich et al. 2012, Fernandez-Lorenzo et al. 1999, Franzmann et al. 1976, Garcia et al. 1999, González-Weller et al. 2010; Hermansen et al. 2005). The Al concentrations in processed cheese reported by Al-Ashmawy (2011) are less than those reported in American cheese (411–695 mg/kg), in Swiss, cheddar, and bleu cheese (3.83–14.1 mg/kg) and in processed cheese (297 mg/kg) by Pennington (1987), Schenk et al. (1989) and Greger et al. (1985). The Al in processed cheese is related to the addition of anti-caking additives including sodium aluminosilicate (Saiyed and Yokel 2005, Schenk et al. 1989, Stahl et al. 2011).

A number of Al dietary exposure assessments considered fish and shellfish. As part of the 2006–2007 French national dietary survey, Arnich et al. (2012) found the highest Al concentrations in molluscs and crustaceans (21.09 mg/kg). Fish and its products had the highest Al levels of all French foods sampled, with mean levels in shrimp (25.5 mg/kg) and mussels (42.9 mg/kg) that were 7–10 times those found in salmon (4.57 mg/kg) and other smoked or fried fish. Those results were generally consistent with those by Millour et al. (2011) who found Al at up to 116 mg/kg in shellfish. Employing microwave digestion and ICP-MS, Guerin et al. (2011) found a mean 1.35 mg Al/kg in the edible portions of 159 species of saltwater organisms collected from four French coastal areas. The highest levels were present in sea urchin (88.4 mg/kg), gurnard (9.68 mg/kg), eel, anchovy and pollock (2.53–3.59 mg/kg). Those data were similar to the results for commercially important species from Agah et al. (2009), Erkan et al. (2009), Kelly et al. (2008), Leblanc et al. (2005), and Mahalakshmi et al. (2012). The levels reported by Agah et al. (2009), Kelly et al. (2008), and Leblanc et al. (2005) in fresh seafood do not account for the increased Al after baking or grilling in Al foil or other Al kitchenware (Ranau et al. 2001) or after addition of alum as a firming agent during canning (Wong et al. 2010).

Braganca et al. (2011) measured Al concentrations in commercial Brazilian grape, peach, mango, passion fruit, and guava juice. Depending upon the manufacturer, Al concentrations in grape juice ranged from less than 0.1 to 0.19 mg/L, peach ranged from 0.15 to 0.31 mg/L, mango varied from less than 0.1 to 0.25 mg/L, passion fruit from less than 0.11 to 0.37 mg/L and Al concentrations in guava juice ranged from less than 0.19 to 0.3 mg/L. Those levels were consistent with the mid-range Al concentrations (0.05–1.1 mg/L) in Spanish fruit juice (González-Weller et al. 2010) and taken together with the daily Al contributions from drinking water and soft drinks, the mean Spanish (non-alcoholic) beverage consumption amounted to 156 µg Al/person or 2.6 µg/kg-day for a 60-kg adult. Thus, the Al associated with consumption of fruit juice represented only a small fraction (1.5%) of the total daily Al intake by Spanish adults (González-Weller et al. 2010).

Tariba (2011) tabulated the (total) Al concentrations in wines from Argentina (0.017–0.018 mg/L), the Czech Republic (0.132–1.67 mg/L), Croatia (0.244–0.81 mg/L), Hungary (0.01–1.5 mg/L) and Greece (0.36–9.5 mg/L). The major source of Al in wine is bentonite/montmorillonite clay added during manufacture as a clarifying agent to reduce suspended proteins, polypeptides, and other particulates (McKinnon et al. 1992). Tariba (2011) pointed to the organic acids in wine as facilitating Al uptake from the gut, but neglected to note that the hydrated Al silicates (e.g., bentonite) in wine have no measurable oral bioavailability (Wiles et al. 2004).

Ohno et al. (2010) measured Al in Japanese rice, cereals and potatoes, sweets, oils and fats, legumes, fruit, green and yellow vegetables, seaweed, alcohol and other beverages, seafood, meat and poultry, dairy and seasonings. For most Japanese the highest Al daily exposure (1.1 g/person) was associated with drinking 550 g of alcoholic beverages. The mean total daily dietary Al consumed by a 50-kg Japanese adult was 3.6 ± 1.3 mg/day (25.2 mg/week or 70 $\mu\text{g}/\text{kg}\text{-day}$) or approximately 25% of the 285 $\mu\text{g}/\text{kg}\text{-day}$ PTWI (Benford et al. 2012). Ogimoto et al. (2012) conducted a similar survey and found that scones (0.37 mg/g), pound cake (0.36 mg/g), and salted jellyfish (0.90 mg/g) had the highest Al concentrations. Sato et al. (2014) found the highest Al concentrations in processed Japanese confections (21.73 mg/kg) and the lowest in rice (0.32–0.43 mg/kg).

The mean total daily Al dietary consumption (including alcoholic and non-alcoholic beverages, coffee, soups, and broth made with potable drinking water) by French adults and children (40 and 62.2 $\mu\text{g}/\text{kg}\text{-day}$; 95% UCI = 69 and 119 $\mu\text{g}/\text{kg}\text{-day}$, respectively) (Arnich et al. 2012) was somewhat less than Al consumed by Japanese. Of the foods included in the 2011 French national dietary survey, pastries contained Al at up to 24 mg/kg, biscuits contained Al at up to 10 mg/kg and dark chocolate contained Al at up to 54 mg/kg (Millour et al. 2011). At customary French consumption rates, coffee and vegetables (excluding potatoes) accounted for 24% of total daily dietary Al for an adult and pasta, pastries, cakes, and dairy products accounted for 19% of a child's daily Al consumption. For residents of the Canary Islands, the estimated total daily dietary Al intake was 10.2 mg/day (170 $\mu\text{g}/\text{kg}\text{-day}$ for a 60 kg adult) where the naturally occurring levels of Al in fruit were a major source (González-Weller et al. 2010).

Rose et al. (2010) found UK consumers received their highest Al dietary dose from cereals and that the highest Al levels provided adults and toddlers with 144 and 345 $\mu\text{g}/\text{kg}\text{-day}$, respectively. Compared to the 2 mg/kg-week PTWI (Benford et al. 2012) [equivalent to 120 mg/week for a 60-kg woman or 285 $\mu\text{g}/\text{kg}\text{-day}$], the average daily Al doses for UK residents aged 4–18 were less than the PTWI while those for residents 1.5–4.5 years consuming the highest Al levels were 20% greater than the PTWI.

Total dietary Al intakes vary with location

Country	Mean adult exposure ($\mu\text{g}/\text{kg}\text{-day}$)	Mean child exposure ($\mu\text{g}/\text{kg}\text{-day}$)	References
Australia	36	44	FSANZ (2011)
Japan	70	NR*	Ohno et al. (2010)

	43	64–123	Sato et al. (2014)
Hong Kong	86	NR	Wong et al. (2010)
Canada	56	64	Health Canada (2007)
Western Europe	28.6–214	NR	EFSA (2008)
France	40.3	62.2	Arnich et al. (2012)
Italy	60	NR	Turconi et al. (2009)
United Kingdom	71	187	Rose et al. (2010)
Canary Islands	124–204	NR	González-Weller et al. (2010)

*NR not reported

Stahl et al. (2011) calculated Al consumption by German adults (70 kg) and children (30 kg). Of all German foods considered, cocoa powders consistently had the highest mean Al (165 mg/kg) and chocolate had a mean 48 mg Al/kg. Based on average yearly cocoa consumption, the German child received 4% and the adult received 2% of the PTWI; chocolate provided up to 12% of the adult and 30% of the child's PTWI.

Yokel (2013) compiled typical median Al concentrations found in United States beer (0.16 mg/L), coffee (0.24 mg/L), fruit juice (0.18–0.67 mg/L), wine (0.90 mg/L), soft drinks (0.25–0.41 mg/L) and distilled spirits (0.42 mg/L). The highest Al concentrations were present in powdered non-dairy creamers (38–170 mg/kg), in paprika (92 mg/kg) and in single-serving packets of table salt (180 mg/kg). In general, current total Al dietary exposures in the United States are somewhat less than those measured during the 1990s when mean total daily adult dietary intake was 7–9 mg/day (ATSDR 2008, Pennington and Schoen 1995), an intake equivalent to 116–128 µg Al/kg-day for a 60-kg adult. Thus, dietary Al exposures for most Americans represent about 50% of the PTWI. Assuming ingestion of five EU-approved Al food additives at their maximum permitted levels, the EFSA (2013) calculated Al doses for toddlers (11.3–156.2 mg/kg-week), children (26.9–286.8 mg/kg-week) and adults (2.3–100.4 mg/kg-week). All of the calculated values were greater than the PTWI.

Consumer products

Two studies found that certain metallic and ceramic products can leach considerable quantities of Al. Bolle et al. (2011) found 0.07–3.5 mg Al/L in aqueous citric acid (1 g/L at pH 2.7 to simulate commercial lyophilized teas with lemon) extracts (30 min on a heated hotplate) from traditional Indian and Moroccan brass teapots. Demont and associates (2012) measured Al migration from glazed ceramic pots at up to 90 mg/L into pH 2.37–3.63 aqueous citric, acetic or maleic acids at 22° C.

Aluminum migration from glass bottles into electrolyte and glucose solutions and into infant formula has been recognized for many years (Bohrer et al. 2001, 2003, Koo et al. 1988). Fekete et al. (2012) investigated Al leaching from glass, ceramic, and stainless steel utensils as well as from Al plates and foil. Aluminum migration from these articles depends on temperature (20–180° C), contact time (30–142 min), pH (2.2–7), and salt concentration (0–9.6 g/L) of the extractant (cream, tomato sauce, black tea, or salted lemon juice). Extreme temperature, low pH and prolonged contact times caused complete disintegration of Al foil

and plates. When pH 4.5 tomato sauce with 5 g/L salt was used as the extractant, Al leaching from glass and stainless steel was less than the analytical limit of detection; daily Al doses depend not only on kitchenware and food type, but frequency of Al utensil use in food storage and preparation.

Verbeken et al. (2011) examined Al migration from the food-grade Al foil used in hospital cryo preservation of human skin. They found 1.4 mg Al/L in pooled cryo preservation media (30% v/v glycerol in physiological saline) for seven skin samples that had been frozen for 10 years.

Aluminum is present at 0.37% in tobacco and at 0.4% in marijuana (Exley et al. 2006). Intentional inhalation of glue (Akay et al. 2008), cocaine, and/or heroin ('Chasing the Dragon') can lead to Al exposure when Al-bound drug vaporizes after heating on Al plates, cans, or foil (Boto de los Bueis et al. 2002, Pechansky et al. 2007), where Al can enter the brain via olfactory pathways (Perl and Good 1987, Divine et al. 1999, Exley et al. 1996, Yokel 2002). Aluminum concentrations in heroin (42–2280 ppm) increase as a result of its synthesis at elevated temperature in Al cookware (Bora et al. 2002). These exposures are such that elevated urinary Al can be measured after repeated heroin use either after it is inhaled off Al foil or after intravenous injection (Exley et al. 2007a). Intentional abuse of oral methadone delivered by intravenous injection has also been held responsible for Al intoxication (Friesen et al. 2006).

Da Silva et al. (2010) measured Al concentrations in 14 different calcium (Ca) dietary supplements and gastric antacid capsules or chewable tablets. These supplements were made of synthetic carbonate/phosphates, carbonate/citrate, carbonate malate/succinate/glutamate or crushed oyster shell, and the antacids were comprised of Ca carbonate compounded with MgO, Mg stearate, aspartame, sucrose, powdered cellulose, and/or Na hexametaphosphate. Aluminum concentrations generally ranged from 0.24 to 0.65 mg/g Ca, but one antacid (sold under the tradename AntSyn2 with H₂MgO₂, C₃₆ H₇₀MgO₂, corn starch and dextrose) contained 1.22–1.25 mg Al/g Ca. All the chewable tablets had higher Al concentrations than any of the capsules; those chewable tablets provide 2–12 mg Al/day or 33–200 µg Al/kg-day for a 60-kg adult. Assuming consumption of a chewable daily Ca dietary supplement sufficient to provide 1500–3000 mg Ca/day represents 11–70% of the current 285 µg/kg-day PTWI (Benford et al. 2012).

Prescription of Al-based phosphate binders has been discontinued in large part in North America and in the United Kingdom due to cases of Al-induced microcytic anemia, seizures, and osteomalacia (National Kidney Foundation 2003), but it remains common in Australia, New Zealand, Germany, Italy, and Spain (Mudge et al. 2011). Except in rare cases of equipment failure (CDC 2008) or inadvertent introduction of Al into dialysate (Berend et al. 2001), elevated serum Al and risk of dialysis encephalopathy have for all practical purposes been eliminated by controlling Al concentrations in dialysate to less than 10 µg/L (ANSI/AAMI 2004, CAN/CSA-ISO 2011) and substituting Al phosphate binders with Ca acetate, Ca carbonate, sevelamer, or lanthanum. Abnormally high plasma and serum Al levels can result after daily consumption of the customary approximately 4 g of Al-based phosphate chelators even with regular clinical monitoring (Arenas et al. 2008, Cárdenas et al. 2010,

Gault et al. 2006). Those observations contrast with Jimenez et al. (2011) and Mudge et al. (2011) who concluded Al-based phosphate chelators are not only economical and effective, but they have a high rate of patient compliance without undue health risk. In this regard, Mudge et al. (2011) presented Australian patient costs for Al(OH)₃ (currently A72¢/day) compared to A\$10.80/day for sevelamer and A\$13.20/day for lanthanum (equivalent to an annual A\$262, A\$3942, and A\$4818, respectively).

Cárdenas and associates (2010) compared serum Al in 63 patients on renal dialysis (21–89 years of age) with that of 20 healthy referents (24–73 years of age). The dialysis water had less than 2 µg Al/L and the mean serum Al in healthy people (8.05 ± 4.3 µg/L) was less than the serum Al in those with kidney disease (26.5 ± 8.0 µg/L). Given the very low Al concentration in dialysis water, Cárdenas et al. (2010) concluded that consumption of Al(OH)₃ to mitigate hyperphosphatemia was the primary source of elevated serum Al.

Kan et al. (2010) confirmed the on-going problem with elevated Al among HD patients. Pepper et al. (2011) evaluated serum Al using ICP-MS and measured Al body burdens using the 48-h low-dose (500 mg) DFO challenge test in 39 HD patients with a history of chronic (1–73 months) Al(OH)₃ ingestion. Those patients were 56.5 ± 2.4 years of age, consumed on average a total of 1.2 kg (0.07–7.15 kg) of Al(OH)₃ over 23 months and the mean time since Al(OH)₃ dosing ceased until evaluation was 12.9 months. Serum Al concentrations for 37 of the 39 subjects were less than 1.0 µmol/L (27 µg/L) and the remaining two (who consumed 1.36–1.85 kg of Al(OH)₃) had serum Al less than 3.0 µmol/L (80 µg/L). Although serum Al increased significantly after DFO challenge, none of these patients experienced an increase higher than 3 µmol/L. No confirmatory bone biopsy data were presented to support the contention that these doses of Al(OH)₃ represent low risk. As there was no significant correlation ($p = 0.10$) between cumulative Al dose and post-DFO serum Al concentration, Pepper et al. (2011) suggested that Al exposure from phosphate binders “is likely to be dwarfed by other sources such as drinking water and foods.” Pepper et al. (2011) offered no empirical comparisons to support that interpretation whereas Krewski et al. (2007) noted mean daily Al intake from food (7.2–8.6 mg) and drinking water (0.16 mg) were substantially less than the customary 4000 mg Al/day used by patients on kidney dialysis.

Evaluations of Al(OH)₃ or other Al-based phosphate binders in routine management of patients with compromised kidney function are problematic (Jimenez et al. 2011). Hou et al. (2010) measured serum Al in 319 patients on chronic (41.5 ± 34.9 months) HD (166 men and 153 women aged 21–89 years) compared to 62 young (23.9 ± 3.7 years) healthy students and 81 patients (57.9 ± 15.2 years) with renal failure who were not on dialysis. Those on HD had significantly higher serum Al (3–443 µg/L) than renal patients not on dialysis (2–237 µg/L) or the healthy students (1–14 µg/L). There was no indication of gender-related differences at any age, but serum creatinine levels were inversely correlated ($p < 0.0001$) with serum Al. Older dialysis patients (67–89 years) had significantly higher serum Al than younger (21–43 years) dialysis patients. Out of the 319 HD patients, 14 patients used oral Al(OH)₃ to control serum phosphate and three had serum Al higher than 250 µg/L. Ingested Al(OH)₃ is not the only source of Al that Bohrer et al. (2009) found for patients with kidney disease, because injectable drugs (notably insulin, EPO, and Fe) were also significant Al sources. Jimenez et al. (2011) concluded that Al-based phosphate binders

could be used but in light of the risks for adynamic bone disease other measures (reduced dietary phosphate and increased dialysis duration) should be exhausted prior to considering use of Al-based phosphate binders.

After reviewing the history of $\text{Al}(\text{OH})_3$ to control serum phosphate in patients with kidney disease, Mudge et al. (2011) calculated that at customary doses, $\text{Al}(\text{OH})_3$ reduced serum phosphate 0.3 mmol/L and that reduction is equivalent to a 10–15% reduction in cardiovascular mortality for these patients. Mudge et al. (2011) reported success with $\text{Al}(\text{OH})_3$ (as compared with Ca carbonate) and pointed out that there are no controlled prospective randomized clinical trials that have examined the safety and efficacy of different phosphate binders. Mudge et al. (2011) made no mention of restrictions to control dietary acids (e.g., ascorbate, citrate, and lactate) that enhance Al uptake from ingested $\text{Al}(\text{OH})_3$ (Coburn et al. 1991, Priest et al. 1996, Weberg and Berstad 1986). The experience described by Mudge et al. (2011) contrasts with the dose-dependent increase in serum Al and/or Al-induced bone disease after oral $\text{Al}(\text{OH})_3$ among renal patients with no history of dialysis (Andreoli et al. 1984, Felsenfeld et al. 1982), who either all received identical Al exposures during dialysis (Cannata et al. 1983) or who were never exposed to excessive Al in dialysis fluid, but who used Al-based phosphate binders (Andress et al. 1986, Jenkins et al. 1989, Salusky et al. 1991).

Drinking water

Health Canada (2010) reported mean Al concentrations of 20–174 $\mu\text{g}/\text{L}$ in finished municipal tap water. Frankowski et al. (2011) measured Al in potable water using three analytical techniques (GFAAS, ICP-MS, and ICP-AES) and found the chemical forms depended upon water source pH, temperature and the concentrations of organic carbon and the nature of the suspended particulates. At lower Al concentrations and at pH 5.5–6.5, the fluorides (AlF_2^+ , AlF_3^0 , and AlF_4^-) and sulfates (AlSO_4^+ , and $\text{Al}(\text{SO}_4)_2^-$) predominated, but at higher Al concentrations and at neutral pH, the hydroxides (AlOH^{2+} , $\text{Al}(\text{OH})_2^+$, and $\text{Al}(\text{OH})_4^-$) and Al organics (e.g., fulvic and humic acids) were the major species.

Al-Ashmawy (2011) considered drinking water contributed approximately 1.2% of a typical Egyptian's daily Al intake, a conclusion that was consistent with Ohno et al. (2010) who found that adults living in six Japanese cities who consumed 2 liters of water each day received $80 \pm 7 \mu\text{g Al/day}$ or 2.2% of their total mean daily Al dietary intake ($3600 \pm 1370 \mu\text{g/day}$). Assuming a 50-kg Japanese adult consumes 2 liters of drinking water per day, water accounts for $1.6 \mu\text{g Al/kg-day}$ or 0.6% of the $285 \mu\text{g Al/kg-day}$ PTWI (Benford et al. 2012). Those concentrations are consistent with historical data from the United States where a median Al concentration in finished municipal drinking water (0.112 mg/L) corresponded to a daily ingested dose (assuming consumption of 1.4 l/day) of $160 \mu\text{g Al/kg}$ or about 1% of the amount contributed by food for a 70-kg adult (ATSDR 2008, Krewski et al. 2007). Those estimates are lower than the 4% value put forward by WHO (2010) after assuming drinking water contained 0.1 mg Al/L.

Workplace air

The air inside Al smelters, foundries, and remelting plants can contain appreciable concentrations of Al oxides and Na_3AlF_6 (Nordic Expert Group 2011, Westberg et al. 2001).

Weinbruch et al. (2010) used SEM and energy-dispersive X-ray microanalysis (EDX) to define the size, morphology, and composition of 543 Söderberg and 176 Prebake potroom aerosol particles (> 500 nm); particles smaller than 500 nm were composed primarily of sodium Al fluorides. The highest mean inhalable particle mass concentration ($6800 \mu\text{g}/\text{m}^3$) was found in Prebake potrooms. Total and respirable Al dust concentrations in workers' breathing zones during routine operations were 0.08 – $2.1 \text{ mg}/\text{m}^3$ and $0.03 \text{ mg}/\text{m}^3$, respectively. The Al oxides present in these dusts generally constitute approximately 25–44% of the total Al. On average, the Söderberg particles were composed of 60% soot, 7.2% Al oxides, and cryolite (NaAlF_6) mixtures, 0.7% pure oxides, 12% silicates, 14% Ca sulfates and lesser amounts (3%) of Ca fluorides. The Prebake particles were primarily (56%) mixtures of Al oxides and cryolite, 36% soot, 1% silicates, 0.6% Ca fluorides, and 2.8% other materials. No pure cryolite particles were seen in either process. Under humid conditions (as in the respiratory tract) all these aerosols developed thin films of water over their surfaces and the Al oxides/cryolite particles agglomerated into larger water droplets. These observations are important because up to 10% of the airborne HF and 1% of the airborne SO_2 dissolved into those liquid aerosols and their physical properties facilitated transfer of these acids into the deeper (alveolar) regions of the lung than when workers are exposed to the airborne acid alone. At the present time, however, it is not known if these factors increase the risk of local pulmonary irritation, edema, and hemorrhage or contribute to occupational respiratory disease (Weinbruch et al. 2010).

Lewis et al. (2011) compiled workplace area (> 120 min) and breathing zone (> 30 – 543 min) measurements of Al_2O_3 and Al_2S_3 in dust generated during handling of a powdered catalyst (zeolite with trace elements) used in crude oil fractionation. No efforts were expended to determine particle size distributions, but the literature sources suggested the mean diameter was 70–80 nm. Personal and workplace area samples found the highest total dust ($540 \text{ mg}/\text{m}^3$) and Al oxide ($2.1 \text{ mg}/\text{m}^3$) concentrations during catalyst loading, but airborne Al_2S_3 concentrations were always less than the analytical limit of detection.

Alumina and Al silicate nanoparticles (2–3 nm diameter) are used in pigments and cosmetics, fine polishing powders, and in microelectronics production. Al nanoparticles are generated during friction stir, flame, and solid-state welding on Al (Curwin and Bertke 2011, Dash and D'Arcy 2008, Gomes et al. 2012a, 2012b, Pfefferkorn et al. 2010), sanding painted surfaces (Koponen et al. 2010) and in electric arc thermal sprays (Bémer et al. 2010). The extent of Al nanoparticle exposure during welding depends on work practices, the temperature of the weld (as a function of electrical current) and operator distance to the welding front (Gomes et al. 2012). While concerns have been expressed over carcinogenic potential and other aspects of toxicity associated with occupational and environmental exposures to engineered nanospheres or nanodots, short- and long nanobelts, nanorods, nanowires, or nanotubes (Borm et al. 2006, Byrne and Baugh 2008, Nel et al. 2006, NIOSH 2011), it has proven complicated to assess health risks of nanoscale materials because the

physiochemical properties and particle behavior can differ from those of ultrafine or bulk materials of the same chemical composition.

Ambient air

Boullemant (2011) compared collection methods used to capture total particulate matter ($PM_{total} = PM > 0.3 \mu m$ plus condensables), PM_{10} and $PM_{2.5}$ in Al smelter emissions (e.g., anode baking furnace exhaust, potroom scrubber stacks, and potroom roof vents). Two primary Al smelters (both using prebake technologies) with different production rates (190 and 420 kt/year) were studied. The uncontrolled roof vents were responsible for 85% of all smelter emissions and accounted for 71% of all smelter $PM_{2.5}$. Aluminum comprised the majority of the $PM_{2.5}$ mass fraction regardless of whether the sample was from ambient air (1.74–4.05%) or from stacks at the gas treatment center (13%). Scanning electron microscopy/energy dispersive X-ray analyses confirmed these Al particles were related to those generated in the electrolytic bath (chiolite, cryolite, $NaAlF_4$, and fluorinated alumina).

Naturally occurring Al nanoforms are prominent in volcanic ash (Wada 1987) and in the fine fractions of clay soils (Li et al. 2012a, Theng and Yuan 2008). 1–100 nm Al nanoplatelets, nanowires/nanotubes and/or nanodots are abundant in allophane (where nanotubes exist as individual 3.5–5.0 nm particles 30–50 Å in diameter), halloysite, hectorite, kaolinite and montmorillonite (Childs et al. 1990, Floody et al. 2009, Hall et al. 1985, Karube et al. 1996, Theng et al. 1982) and these materials are present in the dust suspended in ambient air.

Absorption, distribution, and elimination

Ingestion

Krewski et al. (2007) described the influence of Al chemical form and the influence of citrate and other carboxylic acids on oral absorption of Al. Ingested Al is absorbed primarily from the duodenum and small intestine via passive diffusion, pinocytosis, and transferrin/vitamin D-dependent active transport (summarized in Crisponi et al. 2012). Parathyroid hormone (PTH) increases intestinal Al uptake by stimulating renal synthesis of 1, 25-dihydroxycholecalciferol (1, 25-DHC) (Azik et al. 2011, Malluche and Faugere 1985). Dietary constituents that reduce Al uptake from the gut include phosphates that combine with Al to yield insoluble dialuminum triphosphate and Fe that competes for transferrin; dietary factors that enhance Al uptake include citric and other organic acids. Following absorption, Al^{3+} in serum is bound primarily (~90%) to transferrin and the remaining fraction is bound to low molecular weight molecules including citrate, phosphate, and citrate-phosphate complexes of which Al-citrate predominates (7–8%) (Yokel and McNamara 2001).

Mujika et al. (2011b) studied the interaction between Al^{3+} and Fe^{3+} with serum transferrin. Iron bound to serum transferrin is normally released from the protein's closed conformation N-lobe to the transferrin receptor 1 in peripheral (e.g., neurons, glial and blood-brain barrier) cells where it is internalized by endocytosis. The process is pH-dependent in that the endosomal pH 5.5 is significantly less than serum pH (7.4). Trivalent Al does not compete

effectively with ferric iron for serum Fe-binding sites. The successive stability constants for Fe^{3+} binding to transferrin ($\log K_1 = 22.7$ and $\log K_2 = 22.1$) are much higher than those for Al^{3+} ($\log K_1 = 12.9$ and $\log K_2 = 12.3$). As 70% of serum metal binding sites are normally unoccupied by Fe^{3+} , the transferrin protein can accommodate two Al^{3+} ions—first one binding at the C-lobe and the second at the N-lobe. Additional studies of serum transferrin Al^{3+} binding and release by Mujika et al. (2012a) revealed that only under conditions where Tyr188 is protonated do transferrin's conformational hinge-bending and hinge-twisting changes permit Al^{3+} release (Mujika et al. 2012a).

Citrate is important not only because it increases gastrointestinal Al bioavailability (Krewski et al. 2007, Priest 2004, 2010a, 2010b, Wu et al. 2012b) and 7–8% of the Al in plasma is bound to citrate (Chen et al. 2010b, Krewski et al. 2007), but it has been suggested that Al-citrate is also taken up by the monocarbonate transporter (MCT) and that it might serve as a substrate for the organic anion-transporting polypeptide (OATP) enabling brain brain influx (Crisponi et al. 2012, Yokel 2006), where it constitutes approximately 90% of the Al in cerebrospinal fluid (Yokel and McNamara 2001). Based on Al citrate uptake into immortalized rat cells in the presence of ligands for the sodium-independent L-glutamate/L-cysteine exchanger system Xc^- , Nagasawa et al. (2005) suggested that system may also mediate Al citrate uptake into the brain.

The EFSA (2011) reviewed the Al gastrointestinal bioavailability results by Priest (2010a). This study examined Sprague-Dawley rats given a single oral 50-mg intubation of ^{26}Al citrate (1.47 ng ^{26}Al), AlCl_3 , $\text{Al}(\text{NO}_3)_3$, or $\text{Al}_2(\text{SO}_4)_3$ in water or 17 mg of $\text{Al}(\text{OH})_3$ or 23 mg of Al_2O_3 in carboxymethylcellulose or 6.9 mg metallic Al particles in honey. At 7 days after intubation, whole body (WB) ^{26}Al retention (following removal of the pelt, gut, paws, tail and head in an effort to reduce external contamination) after an oral dose was compared to that after iv injection of 0.19 ng ^{26}Al citrate. The mean ^{26}Al fraction remaining at 7 days after iv Al citrate ($0.079 \pm 0.006\%$) was substantially less than the 0.3–1.49% gastrointestinal uptake reported previously for rats (Froment et al. 1989, Schönholzer et al. 1997, Yokel et al. 2001). It is possible this difference is due to Al elimination during the 7 days after administration. Among the salts $\text{Al}_2(\text{SO}_4)_3$ had the highest oral absorbed fraction ($0.21 \pm 0.079\%$) and $\text{Al}(\text{OH})_3$ had the lowest ($0.025 \pm 0.041\%$). Retention of ^{26}Al after an oral dose of metallic Al ($< 0.015\%$) was less than the analytical limit of detection.

Yokel and associates (2008) measured gastrointestinal uptake of ^{26}Al by fasted male F344 rats from 1 g of processed cheese containing 1.5% or 3% basic sodium aluminum phosphate (SALP). Comparing the area under the serum concentration: time curve after 60-h intravenous infusion with 100 μg Al/kg-h (as $\text{AlK}(\text{SO}_4)_2$) to the serum ^{26}Al concentrations after feeding cheese, peak circulating Al was achieved at 8.0–8.6 h and the highest concentration was seen in rats that consumed the lower (1.5%) SALP cheese. Total oral Al bioavailability was 3 times greater in rats consuming cheese with the higher Al content than in those consuming the lower Al level cheese. Yokel and Florence (2008) then compared oral bioavailability (to 60 h) of ^{26}Al in F344 rats using serum concentration: time profiles after an intravenous infusion of $\text{AlK}(\text{SO}_4)_2$ at 100 μg Al/kg-hr over 14 h. Total gastrointestinal uptake of Al from tea was 0.37% (Flaten 2002, Yokel and Florence 2008), a

value higher than the Al uptake measured in rats fed cheese containing SALP (0.10–0.29%) or after rats were fed acidic SALP in baked goods (0.12%) (Yokel and Florence 2006).

Poirier et al. (2011) compared the relative oral Al uptake and distribution after repeated 7 or 14 days oral gavage with 30 mg/kg-day of either Al citrate, $\text{Al}_2(\text{SO}_4)_3$, AlCl_3 , $\text{Al}(\text{OH})_3$, or $\text{Al}(\text{NO}_3)_3$ dissolved in deionized water ($< 2 \mu\text{g Al/L}$) in rats. Whole blood Al concentrations were similar at Day 7 for all Al forms. Whole blood Al concentrations declined on Day 14 compared to those measured on Day 7 despite the continued daily oral dosing. The highest Al concentrations were present in liver, kidney, and bone.

The Poirier et al. (2011) conclusions with $\text{Al}_2(\text{SO}_4)_3$ and $\text{Al}(\text{OH})_3$ contrast with the relative WB Al bioavailability (0.025–0.21%) after a single oral 50-mg intubation in groups of six adult female Sprague-Dawley rats with ^{26}Al labeled $\text{Al}_2(\text{SO}_4)_3 > \text{Al citrate} > \text{AlCl}_3 > \text{Al}(\text{NO}_3)_3 > \text{Al}(\text{OH})_3$ (EFSA 2011). The comparatively low value ($0.025 \pm 0.041\%$) listed by EFSA (2011) for $\text{Al}(\text{OH})_3$ is perhaps due to the smaller 17 mg dose given as a suspension in carboxymethylcellulose which may alter uptake compared to the aqueous vehicle used for the other congeners.

The factors relating to bioavailability and tissue accumulation of Al citrate are complicated. Mujika et al. (2012b) examined Al^{+3} binding with citrate and determined four pKa values (2.9, 4.3, 5.6, and 11.6/14.4). Citrate binds Al^{+3} at three coordination sites and three labile water molecules occupy the remaining positions in an octahedron. Depending on pH, unprotonated citrate binds Al^{+3} at two terminal carboxylic and one alkoxy group; as pH increases, a second then a third ionization of carboxyl then alkoxy groups commences and Al^{+3} binding shifts the citrate pKa values. This binding and deprotonation of the trivalent Al-citrate coordination complex contributes to its high uptake from the gut. Binding and deprotonation also contribute to Al interaction with MCT and OATP transporters, Al sequestration in different intracellular compartments and to Al efflux from the central nervous system (Crisponi and Nurchi 2011, Yokel 2002).

The bioavailability of ingested Al depends in large measure on the aqueous solubility of the particular physical and chemical form. Krewski et al. (2007) concluded that gastrointestinal bioavailability of $\text{Al}(\text{OH})_3$ is 0.1% or less and that Al uptake from foods ranges between 0.1 and 0.3%. The data from Poirier et al. (2011) and Priest (2010a) support the conclusion that ingested citrate enhances Al uptake from the gut.

Percutaneous

Krewski et al. (2007) concluded that topical Al penetration into intact skin “is very shallow”. This conclusion was based in part on the data by Flarend et al. (2001), who found 0.012% of a single topical ^{26}Al -labeled ACH dose applied to the underarm of two volunteers was absorbed.

Mayeux et al. (2012) inspected Al deposition patterns in the stratum corneum following 1 or 7 days repeated application of aqueous 5% AlCl_3 on the forearms of volunteers. A total of 37 volunteers of both genders (aged, 21–59 years) participated. The AlCl_3 solution was applied on skin of the volar aspect of the forearm and after air drying, biometrological

measurements were performed at rest and after a moderate 10-min physical exercise on a cycloergometer. The AlCl_3 -treated skin was documented using two ultraviolet light-emitting cameras to record subtle variations or changes related to AlCl_3 deposition and/or local effects. After a single application of AlCl_3 , Al deposits on skin were observed predominantly inside the microrelief lines and at their crossings. After daily applications of AlCl_3 for 1 week, Al deposits were evident within the plateaus delimited by the microrelief lines. No information regarding local irritation following single or repeated applications of AlCl_3 or after physical exercise compared with the resting condition was provided.

The Mayeux protocol also included corneoxenometry to predict local AlCl_3 irritation (Goffin et al. 2000, Piérard-Franchimont et al. 2010). Briefly, CSSS were dipped into AlCl_3 solutions at 5, 20, and 40% for 2 h and these samples were then dried and stained with toluidine blue and basic fuchsin for 3 min. After rinsing, the color of the samples was measured and the staining intensity of the stratum corneum was calculated. No significant differences in the median or range of staining intensity were detected at any concentration compared to the concurrent water control. Mayeux et al. (2012) suggested these data were indicative of low irritant potential for AlCl_3 under the conditions of their study. Among the limitations of this study are: little information was available on the study participants, test compound (chemical characteristics and purity), no information regarding pH of the administered AlCl_3 solutions, or the pH of the skin after exposure and the report provided no details on the application technique (e.g. duration of contact, occlusion condition).

Yanagishita et al. (2012) studied localization of Al in palm skin after topical 20% AlCl_3 treatment for palmar hyperhidrosis. The study included 127 patients (no other details available) who received a daily solution without occlusion (once each day) for one month. No mention was made of the pH of the solution or whether any of the participants complained of local irritation or other clinical signs. The mean rate of sweat production after 30 days of AlCl_3 applications was reduced significantly. Hematoxylin-eosin staining of the stratum corneum found that prior to AlCl_3 treatment the eccrine sweat ducts were intact, but after treatment those ducts were filled with an amorphous polysaccharide/cytokeratin-containing cast. Histologic study of 5 μm sections of treated palm skin found that an Al complex was present on the surface of the stratum corneum and in casts that accumulated in the sweat duct. There was no evidence of Al accumulation in either the eccrine sweat duct or in the sweat gland.

In a report that measured Al retention beneath the epidermis, Guillard et al. (2012) measured Al in a dermatofibrosarcoma taken from a 45-year-old woman at 5–12 years after im injection of an $\text{Al}(\text{OH})_3$ adjuvant-containing vaccine. Skin Al (768 mg/kg dry weight) was elevated compared to that in the skin of two untreated volunteers (40–44 mg/kg dry weight). However, the high Al concentration was traced to the Al-containing tattoo paste (35 mg Al/kg) used to mark the biopsy site.

Pineau et al. (2012) used Franz[®] diffusion cells to measure Al transdermal movement from topical ACH at 37°C for 6–24 h. Abdominal skin biopsies (513 μm thick) from five healthy Caucasian (29–52 years) volunteers were treated with either a 14.5% ACH emulsion (8 mg), a 21.2% ACH “stick” (4.5 mg) or a 38.5% ACH aerosol base (2.6 mg). The mean thickness

of the materials applied to the skin was $1402 \pm 348 \mu\text{m}$. Blanks applied to tape-stripped skin were of similar thickness. Because of its high viscosity, a higher dose of the aerosol base could not be applied to the test cells. After incubation, the superficial horny layer was removed and the skin was dissected to separate epidermis and dermis. Regardless of the ACH formulation, the highest mean Al concentration ($2.24\text{--}4.43 \mu\text{g}/\text{cm}^2$) was present in the horny layer. The epidermis had the highest mean Al concentration ($9.42 \pm 7.82 \text{mg}/\text{cm}^2$) after it was in treated with the 21.2% “stick”. The most salient observation was the fact that the Al concentrations in the Franz[®] receptor fluid were less than $0.1 \mu\text{g}/\text{cm}^2$ and corresponded to only 0.012% (1/10,000) of the applied Al. The Pineau et al. (2012) in vitro assays used abdominal skin and the experimental conditions were such that personal habits and conditions (e.g., frequent repeated underarm shaving) and individual rates of Al application (e.g., diaper rash, prickly heat, insect stings, *Tinea pedis*) (reviewed in Krewski et al. 2007) could not be taken into account.

One case of systemic hyperaluminemia (plasma Al = $104.7 \mu\text{g}/\text{L}$) presenting with complaints of bone pain after 4 years of daily ACH deodorant application has been described (Guillard et al. 2004). In light of that report, Yokel (2012) calculated the highest systemic Al uptake after routine topical application of a commercial 20% Al zirconium glycine or a 25% ACH deodorant was no more than $0.1 \text{mg}/\text{kg}\text{-day}$.

Inhalation

Aluminum workers can encounter a mixture of Al fumes and inhalable (aerodynamic diameter $\approx 100 \mu\text{m}$), thoracic ($< 28 \mu\text{m}$), and respirable ($< 10 \mu\text{m}$) Al particulates in the occupational environment. These materials can be deposited in the respiratory tract where a fraction is absorbed from the lung and above 95% is eliminated in urine (reviewed in ATSDR 2008, Krewski et al. 2007). The magnitude of these exposures and their associated Al urinary concentrations depend upon the particular industrial operations (such as bauxite mining, Al refining, reduction, casting, fettling, slagging, welding, and AlF_3 production) and the Al forms encountered. Krewski et al. (2007) estimated that inhalation of Al dust and fume by refinery workers and welders yields a daily intake on the order of $6 \times 10^{-3} \text{mg}/\text{kg}\text{-day}$.

Intramuscular injection

Systemic uptake of Al from a vaccine depot in skeletal muscle depends upon the chemical form of the Al adjuvant (Flarend et al. 1997, Verdier et al. 2005). Krewski et al. (2007) examined Al absorption and distribution profiles of $\text{Al}(\text{OH})_3$ (present as poorly crystallized $\text{AlO}(\text{OH})$) and AlPO_4 (present as HAlO_5P) (Hem and White 1995, Shirodkar et al. 1990) and concluded that 100% of the injected Al is eventually absorbed. This conclusion was based in part on results by Verdier et al. (2005) who found that Al concentrations in muscle at 3–6 months after a single im injection of $\text{AlO}(\text{OH})$ in macaques were 4-fold higher than after equivalent injection of AlPO_4 . Muscle Al concentrations declined to less than the analytical limit of detection ($< 25 \mu\text{g}/\text{g}$) within 12 months.

Intramuscular $\text{AlO}(\text{OH})$ is more rapidly taken up into rabbit blood than AlPO_4 . Within 1 h of a single im injection of 0.85mg Al as $^{26}\text{Al}(\text{OH})_3$ plasma ^{26}Al peaked at $2 \text{ng}/\text{ml}$ (Flarend

et al. 1997). The maximum Al concentration represented approximately 7% of the normal Al level in rabbit plasma (30 ng/ml). Total ^{26}Al uptake from the injection ranged from 13 to 22% and was distributed to all organs examined (kidney > spleen > liver > heart > lymph nodes > brain). The initial plasma ^{26}Al concentrations after AIO(OH) injection were thrice those after equivalent injection of AlPO_4 , but by 28 days mean peripheral tissue ^{26}Al concentrations were 3-fold greater in rabbits given AlPO_4 compared to those in rabbits given AIO(OH). Aluminum uptake from the depot continued for more than 28 days at which time only 6% of the injected ^{26}Al had been eliminated in urine compared to 22% of the injected $^{26}\text{AlPO}_4$. Flarend et al. (1997) extrapolated the rabbit plasma concentration:time profile to humans and concluded that the Al dose associated with a single im adjuvant injection represented 0.8% or lesser increase above the normal (2.7–6.2 $\mu\text{g Al/L}$) range (Krewski et al. 2007).

Mechanisms of action

Understanding mechanism of action and compound-specific bioavailability is key to the evaluation and interpretation of the health risks posed by exposure to the many different physical and chemical forms of Al. Mechanistic studies with the soluble Al salts point to Al^{+3} as the entity responsible for tissue damage whereas studies with the non-reactive Al oxides demonstrate adverse effects of particulates that are separate and distinct from the actions of ionized Al. Under some conditions (e.g., Al welding, fettling, refining) mixed exposures to soluble, sparingly soluble, and insoluble Al forms occur.

Fraga et al. (1990), Gutteridge et al. (1985), Savory et al. (1999), Tomljenovic (2011) and Zatta et al. (2002) concluded that elevated Al^{+3} concentrations induce cytotoxicity as a result of oxidative damage. Mailloux et al. (2011) traced the biochemical events contributing to (soluble) Al-induced toxicity in cultured HepG2 cells and advanced the hypothesis that disruption of “mitochondrial metabolism is the main site of the toxicological action of Al” due to interference with “Fe-dependent redox sensitive enzymes in the tricarboxylic acid (TCA) cycle and oxidative phosphorylation”. Initial changes (apparently initiated via Al^{+3} binding with protein and competition for Fe-binding sites) include depletion of mitochondrial Fe and generation of H_2O_2 , $\text{O}_2^{\cdot-}$ and OH^{\cdot} . These changes result in a cellular metabolic shift from oxidative ATP production to anaerobic glycolysis (seen with the increased activity of LDH, pyruvate kinase, and glyceraldehyde-3-phosphate dehydrogenase) resulting in increased α -ketoglutarate and succinate and reduced L-carnitine due to diversion of α -ketoglutarate to scavenging ROS. These changes are reflected in reduced fatty acid β -oxidation that further facilitates increased peroxidation.

Data from cultured murine primary cortical astrocytes treated with Al glycinate do not necessarily support the hypothesis that mitochondrial membranes are the primary Al^{+3} target. Aremu et al. (2011) found no indication of mitochondrial-mediated apoptosis after astrocyte incubation with 0.1 mM Al glycinate for 12–24 h (followed by maintenance in fresh media for 7 days) or after culture with 0.1 or 1.0 mM Al glycinate for 48 h. Not only were there no detectable alterations in *Bcl2*, *Bax*, or *Bcl2* binding component 3/p53 (*Bbc3/PUMA*) expression, but there was no influence on cytochrome *c* release. Aluminum

treatment up-regulated Ire1 β , a response that was considered indicative of stress within the endoplasmic reticulum (Aremu et al. 2011).

Trivalent Al is a promoter of Fe-mediated (Gutteridge et al. 1985, Lemire and Appanna 2011) and non-Fe superoxide radical anion-mediated biological oxidation (Exley 2004, Kong et al. 1992, Mendez-Alvarez et al. 2002). Several theories advanced the concept that Al⁺³ binding with phospholipids leads to peroxidation and altered membrane fluid dynamics as responsible for Al toxicity. Ghribi et al. (2001a, 2001b, 2002) suggested the primary site of Al damage was within the endoplasmic reticulum leading to cytochrome *c* release from mitochondria and activation of apoptotic demise. Free energy calculations and the physical chemistry of trivalent Al in water and its complex with O₂^{•-} demonstrate displacement of a water molecule [Al(H₂O)₆⁺³ + O₂^{•-} → [Al(O₂[•])(H₂O)₅]⁺² + H₂O] to produce bidentate superoxides (Mujika et al. 2011a). Thus, reaction of Al⁺³ with its first microsolvation shell generates an Al⁺³ superoxide semireduced radical [AlO₂[•]]⁺² via [Al(H₂O)₆]⁺³. Formation of these radicals, together with Al⁺³ potentiation of Fe⁺²/Fe⁺³ redox and non-heme-mediated OH[•] formation, appear to account for the oxidant activity of Al⁺³ in biological systems.

Some the earliest genomic changes induced by Al⁺³ appear to involve increased p53 (Johnson et al. 2005) followed by *Bax* translocation, increased *Bax* reactivity in the endoplasmic reticulum (Ghribi et al. 2001a), reduced endoplasmic reticulum (Ghribi et al. 2001a, 2001b), and mitochondrial (Ghribi et al. 2001c) *Bcl-2* and perturbation of the *Bcl-2/Bax* ratio (Savory et al. 1999). These events are followed by activation of caspase-3 (Ghribi et al. 2001a) and caspase-12 (Ghribi et al. 2001b). The intrinsic apoptotic pathway responds to oxidative stress and this is apparent in the Al⁺³—induced release of mitochondrial cytochrome *c* (Ghribi et al. 2001a, 2001c) into the cytosol. The initial oxidative changes that lead to DNA fragmentation (Ghribi et al. 2001c) and the genomic response that occur at the lowest Al⁺³ concentration and at the earliest key metabolic juncture responsible for cytotoxicity remain to be confirmed (Crisponi et al. 2012).

Unlike the soluble salts, insoluble Al materials elicit dose-dependent pulmonary damage as a consequence of accumulation of nonreactive particles. At neutral pH the Al oxides and oxyhydroxides are chemically stable. After 60 days incubation of 565 mg/L Al₂O₃ in pH 5.3–8.2 deionized or saline water at room temperature, Batten and Lafayette (undated) found the concentration of soluble Al⁺³ undetectable. Pauluhn (2009a) reported pulmonary inflammation after rats inhaled γ -AlO(OH) for 4 weeks. There was no evidence for either Al translocation from the lung or increased urinary Al. Those data are consistent with the observations by de Kom et al. (1997) who found no significant difference in serum Al among bauxite (gibbsite [Al(OH)₃], boehmite [γ -AlO(OH)], and diaspora [α -AlO(OH)]) miners compared to wood workers. Prolonged inhalation of bauxite dust increased the risk of simple and complex pneumoconiosis (Shaver's disease) (Beach et al. 2001, Donoghue et al. 2014, Friesen et al. 2009, Gartner 1952, Taiwo 2014). These conditions are related to inert particle accumulation and lung overload (Oberdörster 1995).

Organ systems and function

Nervous system

The AD and AI literatures remain linked in reports from some researchers (Bondy 2010, Campdelacreu 2012, Tomljenovic 2011, Walton 2012b) yet others conclude factors distinct from AI are responsible for AD (reviewed in Lidsky 2014, Willhite et al. 2012). A primary feature of AD pathogenesis is β -amyloid precursor protein (APP) catabolism by the actions of α - and β -secretase that yield the amyloid β -peptides ($A\beta$). While $A\beta$ is constitutively produced from APP, normally it is degraded immediately; failing that, $A\beta$ polypeptides can mis-fold and self-aggregate in the brain leading to insoluble 'senile' plaques.

$A\beta_{1-40}$ is the major form present in biological fluids and $A\beta_{1-42}$ is the major insoluble form present in neuronal plaques. These plaques consist of an amorphous core surrounded by amyloid adjacent to degenerating neurons and glial cells. The plaques accumulate, neurofibrillary tangles develop, intraneuronal (argyrophilic) granulovacuolar lesions appear and progressive atrophy (shrinkage) of the brain follows. The amyloid cascade hypothesis seeks to explain the excessive $A\beta$ accumulation and it is believed the relative rates of $A\beta$ generation and degradation are key to AD. The AI/AD hypothesis has three distinct aspects: AI participation in $A\beta$ aggregation (perhaps via cross-linking hyperphosphorylated protein); AI induction of $A\beta$ integration into β -sheet proteins found in the cores of senile plaques and AI-mediation of abnormal Fe-catalyzed oxidation, increased free radical generation, increased lipid peroxidation (LPO), inflammation and neuronal apoptosis.

At least four physiological factors contribute to the increased susceptibility of the brain to oxidative insult: its high rate of O_2 consumption, the abundance of polyunsaturated fatty acids, its elevated Fe content and its relatively low antioxidant capabilities. Aluminum binds to phospholipids (Verstraeten et al. 1997a), stimulates Fe-initiated LPO (Toda and Yase 1998, Xie and Yokel 1996) and it reacts with O_2^- to form $Al-O_2^-$ that increases oxidation of amino acids leading to generation of protein carbonyls (Exley 2004, Sánchez-Iglesias et al. 2009, Yokel 2000). These reactions reduce the activity of antioxidant enzymes (e.g., glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase) (Chaitanya et al. 2012, Shrivastava 2012, Verstraeten et al. 1997b, Yuan et al. 2012).

It is well known that Al^{+3} and other metal ions (notably Cu^{+2} , Fe^{+3} and Zn^{+2}) can bind proteins including $A\beta$ and that those reactions (at least in vitro) can lead to conformation changes, reduced $A\beta$ solubility and can promote spontaneous $A\beta$ (1–42) Al^{+3} oligomerization, aggregation, and precipitation. Zinc⁺² and Cu^{+2} accelerate amorphous $A\beta$ aggregation whereas Al^{+3} and Fe^{+3} tend to promote $A\beta$ fibril and oligomer formation (Kawahara 2005, Kawahara and Kato-Negishi 2011, Ricchelli et al. 2005). SanMartín et al. (2012) interpreted the elevated concentrations of Al, Cu, Fe, and Zn in human neurofibrillary tangles and senile plaques along with their in vitro acceleration of $A\beta$ fibril and amyloid β oligomer formation as consequences of oxidative stress.

Data on the presence and accumulation of AI in amyloid fibers and AD plaques vary. A number of reports (e.g., Bjertness et al. 1996, Landsberg et al. 1992, Makjanic et al. 1998) failed to find AI accumulation in either whole AD brain or neuritic cores and neurofibrillary

tangles. Strozzyk et al. (2009) found no correlation between A β and A β ₄₂ in the cerebrospinal fluid of AD patients. In contrast, Yumoto et al. (2009) used EDX spectroscopy to measure A β in amyloid fibers of senile AD plaques in the human hippocampus and temporal lobe. Identification of senile plaque cores by TEM found A β peptides in senile plaque cores where A β , P and Ca co-located. The Yumoto et al. (2009) findings are consistent with earlier data by Good et al. (1992) and Perl and Moalem (2006) who found A β in tangle-bearing neurons of the AD hippocampus, but none of those data defined whether the presence of A β occurs as a result of the AD pathophysiological process or whether elevated A β concentrations initiate or accelerate A β fibril and/or amyloid β oligomer formation.

Kawahara and Kato-Negishi (2011) collated data on A β structural alterations and Thinakaran and Koo (2008) reviewed the human APP³ gene and intracellular proteolytic APP processing. These authors listed 25 + APP mutations considered causal in early onset familial AD (EOFAD) and hereditary cerebral angiopathy. EOFAD is associated with mutations in the presenilin one (PS1) or two (PS2) genes found on chromosomes 14 and 1, respectively. More than 230 APP/PS1/PS2 mutations have been associated with EOFAD; however, EOFAD accounts for less than 1% of all AD cases (Wu et al. 2012d).

For the more common late onset AD (LOAD) the major genetic risk factor identified thus far is the inheritance of the apolipoprotein E4 gene (apoE4) (Verghese et al. 2011). Inheritance of the apoE4 allele has been linked to enhanced aggregation of A β and to reduced A β clearance from the brain (Potter and Wisniewski 2012). From studies with more than 16,000 subjects, four new A β genetic determinants for sporadic late onset AD have been identified and these include the PICALM (phosphatidyl inositol binding clathrin assembly protein), CLU (clusterin), CR1 (complement component receptor 1) and BIN₁ (bridging integrator 1) genes (Harold et al. 2009, Lambert and Amouyel 2011). Results of functional assays suggest that LOAD is associated with impaired clearance of the A β peptide where CR1 participates in A β clearance, PICALM apparently alters synaptic vesicle cycling, BIN₁ appears to alter neuronal membranes and formation of synaptic vesicles and CLU enhances amyloid plaque formation. Together with apoE, CLU influences the structure and accumulation of A β . Of the many recent reports concerning A β neurotoxicity, those judged more informative are described below.

Neurotoxicity in humans—Exley and House (2011) tabulated literature reports on the A β content of human brain. In general the normal range is between 0.1 and 4.5 μ g/g dry wt. with the higher values (> 2 μ g/g dry wt.) measured in brains of non-demented elderly, AD patients (up to 11.5 μ g/g dry wt.), dialysis encephalopathy (up to 14.1 mg μ g/g dry wt.), congophilic amyloid angiopathy (CAA) (up to 23.0 μ g/g dry wt.) and other encephalopathies (up to 47.4 μ g/g dry wt.).

House et al. (2012) measured A β in the temporal, frontal, occipital, and parietal lobes of brains from older donors ($n = 60$, aged 70–103 years) (described in Wharton et al. 2011). The A β content ranged from 0 (after subtraction of method blank values) to 33 μ g/g dry wt ($n = 713$ tissue digests). The median A β value was 1.02 μ g/g dry wt. and 75% of all values were less than 2.01 μ g/g dry wt. All these A β concentrations were within the “normal” range (0.1–4.5 μ g/g; Exley and House 2011) for aged brain.

Akatsu et al. (2011) studied Al concentrations in the hippocampus and amygdala from people with AD (15 and 18 patients, respectively) or dementia with Lewy bodies (DLB) (11 and 11 patients, respectively) and compared those values to samples from brains of people with no history of dementia. The average Al concentrations in the hippocampus ($n = 12$) and amygdala ($n = 16$) of non-demented people were 2.8 ± 2.0 and 6.0 ± 6.5 μM wet tissue, respectively. The average Al concentrations in the hippocampus ($n = 15$) and amygdala ($n = 18$) from AD patients were 4.4 ± 3.8 and 6.4 ± 5.5 μM wet weight, respectively. The average Al concentrations in the hippocampus ($n = 11$) and amygdala ($n = 11$) from people with DLB were 5.6 ± 6.1 and 6.9 ± 5.9 μM wet weight, respectively. Akatsu et al. (2011) found no significant differences in total Al concentrations in the hippocampus and amygdala between demented and non-demented individuals.

Rusina et al. (2011) measured Al in brains from 29 deceased patients (mean age 79 years, women to men ratio 20:9) with neuropathologically confirmed AD. All these samples fulfilled the National Institute of Aging (Hyman et al. 2012, McKhann et al. 2011) and Reagan Institute (Newell et al. 1999) AD diagnostic criteria. The 27 subjects (12 women and 15 men, mean age 76 years) in the referent group had no signs of AD or other degenerative dementias on autopsy. Different statistical approaches used by Rusina et al. (2011) provided somewhat different results: higher mean Al concentrations in the hippocampus were found in AD patients compared with the healthy individuals (0.357 vs 0.090 $\mu\text{g/g}$; $p = 0.039$) after Box-Cox data transformation, but not after standard logarithmic transformation to correct deviations from normality.

Walton (2010) examined Al in corticolimbic tissue from brains of five deceased older AD patients (4 males and 1 female) compared to five non-demented referents (4 males and 1 female). Autopsy confirmed diagnoses were made according to criteria established by the Neuropathology Task Force of the Consortium to Establish a Registry for Alzheimer's Disease (Mirra et al. 1991). Ten-micron paraffin sections from the corticolimbic region were examined after histological staining for Al (using the modified Walton (2004) method) and immunostaining with anti-PHF1 antibody for hyperphosphorylated tau. Nine of the 10 subjects exhibited pre-tangle cells. The remaining AD subject had extensive CA1 cell loss. The pre-tangle granules did not stain positively for Al; one referent and one AD case had CA1 pyramidal cells with distinctive cytoplasmic pools that stained for both Al and hyperphosphorylated tau. Walton (2010) reported a few NFT development pre-tangle stage 1 (early 1a and late 1b), mature NFT stage 2 and extracellular NFT stage 3 in AD and non-demented subjects. Early pre-tangle (stage 1a) cells contained small cytoplasmic granules that were distributed throughout the cytoplasm that immunostained for hyperphosphorylated tau. These cells were observed frequently in both aged demented and non-demented humans. Late pre-tangle (stage 1b) cells had grainy-textured cytoplasmic pools that stained for Al and hyperphosphorylated tau and these were visible as cytoplasmic filaments. There was no evidence for Al accumulation in cells at the early pre-tangle stage. The presence of early pre-tangle cells was observed in four of the AD cases and in one referent. Walton (2010) suggested that the lack of Al staining during the early stage could indicate either an absence of Al or that Al levels were below the staining threshold. Mature (stage 2) NFTs were observed as densely packed filaments that stained for both Al and hyperphosphorylated tau; in these cases, the nuclei of affected cells were displaced to the cell periphery and in some of

these cells no cytoplasm at all could be seen given the extent of the large NFTs. Mature NFTs were observed in all AD cases and in three of the five referents. Extracellular (stage 3) NFTs stained for both A β and hyperphosphorylated tau; in most of these cases, the glial cells were associated with extracellular NFTs. Stage 3 NFTs were commonly observed in AD cases and less often in the referents. After A β de-staining and re-staining for hyperphosphorylated tau, the A β /hyperphosphorylated tau complexes were evident in the cytoplasm during the late pre-tangle stage, mature and extracellular stages. Overall the Walton (2010) report provides indications of colocalization of A β with hyperphosphorylated tau during NFT formation in the late pre-tangle stage, mature, and extracellular stages. While these observations could be taken as evidence for A β contributions to NFT formation, neither A β levels nor NFT presence show clear relations with AD clinical pathology or pathogenesis (Armstrong 2013, De-Paula et al. 2012, Hamdy 1990, Mizoroki et al. 2007). In spite of the reported sensitivity and specificity of the Walton (2004) method for identifying A β and NFTs in brain, there has been no independent validation of the Walton staining technique.

Ionized Al and other ionized inorganics bind protein and it is not inconsistent that metals (including Cu, non-heme Fe, Zn and Al) are colocalized with A β _{40/42} in cerebral amyloid angiopathy (reviewed in Kawahara and Kato-Negishi 2011). As such, Al is not the only inorganic element implicated in AD (Bolognin et al. 2011, Grasso et al. 2011) and recent studies point to reduced Cu status and elevated AD risk (Schrag et al. 2011). Baum et al. (2010) measured Al and 11 other inorganic elements by ICP-MS in the serum of 44 AD and 41 healthy referent subjects who lacked symptoms of neurologic disease. All AD patients had NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association) diagnosis of probable or possible AD (McKhann et al. 1984). These individuals were recruited from geriatric outpatient clinics ($n = 35$) and long-term care facilities ($n = 9$). The authors administered the Cantonese Mini-Mental Status Examination (MMSE, maximum score 30; Chiu et al. 1994) to 43 AD and one healthy subject (rationale was not given for lack of MMSE assessment for the remaining 40 referents). Three statistical models were tested: (1) one metal at a time with age and sex as additional control covariates; (2) all metals in one model along with age and sex; and (3) a model with variables selected from model (2) by forward stepwise selection ($p = 0.05$, likelihood ratio test). Using the unadjusted comparisons, the AD patients had significantly higher serum Al (905 ± 630 nmol/L or 24 ± 17 μ g/L) (median \pm interquartile range) than healthy referents (580 ± 620 nmol/L or 15 ± 16 μ g/L). Using the unadjusted comparisons, the AD patients had lower ($p = 0.0001$) serum Zn ($10,900 \pm 1600$ nmol/L) than healthy referents ($12,300 \pm 1600$ nmol/L). After adjustment for age and gender (model 1), serum Al was increased ($p = 0.002$) and serum Zn was reduced ($p = 0.0007$) in AD patients compared to their healthy referents. These conclusions depended on statistical procedures; in the simultaneous model adjusted for all metals (Al, As, Be, Cr, Co, Cu, I, Fe, Mn, Ni, Se, and Zn) (model 2), only Cr, Se and Zn were significantly different with only Se and Zn differing after Bonferroni adjustment. In a forward stepwise regression (model 3), only Zn was reduced ($p = 0.005$). Since serum Zn was reduced significantly in all models, Baum et al. (2010) suggested that Zn induced A β aggregation (Bush and Tanzi 2002). The Cantonese MMSE results correlated significantly with serum Al and As concentrations. The

serum Al data show marked variability and those values are elevated for the healthy participants (perhaps associated with Al antacid consumption) compared to the normal median (0.12 μM or 3.2 $\mu\text{g/L}$ with an upper limit of 6 $\mu\text{g/L}$) concentration (reviewed in Krewski et al. 2007). Those observations and the fact that only one healthy referent was subject to MMSE scoring reduce the confidence that can be placed in the authors' conclusions.

Baum et al. (2010) also suggested that the increased serum Al in AD patients might be associated with more efficient uptake of dietary Al in patients with AD, but that the reason(s) for this difference in Al uptake were unknown (Miu et al. 2004, Roberts et al. 1998). The Baum et al. (2010) suggestion that Al gastrointestinal uptake is greater among people with AD than in otherwise healthy people is consistent with Moore et al. (2000), but it is at odds with the results presented by Molloy et al. (2007) who found there was no difference in Al (consumed as $\text{Al}(\text{OH})_3$ with citrate) uptake by AD patients and/or healthy people with apoE alleles compared to that by those who did not carry the apoE $\epsilon 4$ allele. Rather, the differences in serum Al might reflect reduced renal Al clearance as a consequence of declines in kidney function with age.

Following a similar line of inquiry, Exley et al. (2012) compared Al, Fe, and Cu concentrations to the $\text{A}\beta$ content in senile plaques and in areas of amyloid angiopathy in brains from 38 women and 22 men (ages 70–103 years). There was no significant correlation between Al or Fe and senile plaques or amyloid angiopathy. The Exley et al. (2012) data do not support the hypothesis that elevated brain Al is associated with enhanced $\text{A}\beta_{42}$ in senile plaques and/or focal CAA.

A pan-Canadian outbreak of hyperaluminemia occurred during 2005 among patients on peritoneal dialysis (PD). This was traced to a high Al content in dialysate solutions (1.3 $\mu\text{mol/L}$, current maximum recommended < 0.742 $\mu\text{mol/L}$). Yue et al. (2011) examined 83 of those patients exposed to Al-contaminated dialysate and found the mean serum Al was $1.77 \pm 0.74 \mu\text{mol/L}$ (47 $\mu\text{g/L}$) compared to a normal upper limit of 6 $\mu\text{g/L}$ (reviewed in Krewski et al. 2007).

Sandhu et al. (2011) carried out retrospective analyses of quarterly serum Al determinations for 589 HD patients with end-stage renal disease. A total of 5,674 Al measurements for 589 patients were made and of those 32 (0.5%) had Al concentrations 20 $\mu\text{g/L}$ or higher. The overall mean Al concentration was 10 $\mu\text{g/L}$ (range: 2–28 $\mu\text{g/L}$). Out of 589 (4.2%) patients, 25 patients experienced increased serum Al at some point in the study. The reason for increased serum Al was identified for only two of the participants (Al-containing antacids).

In a small clinical study, Elshamaa and associates (2010) found a significant ($p = 0.0001$) correlation between serum Al and EPO dose among 22 boys and 21 girls (11 ± 3.3 years) with end-stage renal disease. These children were on long-term HD and renal dialysate was eliminated as a source of excess Al inasmuch as the filtered deionized water contained 10 μg Al/L or lesser. None were given Al-containing phosphate binders. The HD patients were moderately anemic and weekly subcutaneous EPO injections were given to maintain a 28–31% hematocrit. Serum Al (> 30 $\mu\text{g/L}$) was significantly higher among HD patients than in

healthy referents, but there were no significant differences between HD boys and HD girls and HD duration had no influence on serum Al. There was a significant ($p = 0.0001$) linear correlation ($r = 0.77$) between serum Al and EPO dose. While the data suggest EPO was the source of the elevated Al, Elshamaa et al. (2010) did not quantify Al in the EPO given to these patients. This failure and the facts that the study was relatively small and confined to a single institution detract from the conclusions reached.

Albizzati et al. (2012) compared Al concentrations in blood, urine, and hair for 17 autistic children (ages 6–16 years; mean 11.5 ± 3.2 years; 15 males and 2 females) to those for non-autistic subjects (ages 6–16 years; mean: 10.4 ± 3.2 years; 15 males and 2 females). There were no significant differences in Al between the two groups.

Bakar et al. (2010) evaluated drinking water Al concentrations in relation to cognitive function among residents of the Kirazli region of the Biga Peninsula, northwest Turkey. The Kirazli region was included in the study as it has acidic drinking water and its Al concentration exceeds the WHO (1984, 2004) recommended maximum (0.2 mg Al/L). Of 201 Kirazli inhabitants 73 agreed to participate; the referent group included 164 selected from 921 residents of a Ciplak-Halileli village in the same province. A neurologist administered the MMSE using face-to-face interviews and performed clinical examinations. All subjects obtained their drinking water from groundwater networks in their regions and a total of 237 people from both regions participated in the study. Drinking water collected in both regions revealed higher Al concentrations in Kirazli (13–16 mg/L) than in the referent region (0.005–0.010 mg/L). Despite the differences in Al levels in their drinking water, no significant differences were detected between serum Al levels, the MMSE scores or the incidence of clinical neuropathy between the two regions.

Studies of Akila et al. (1999), Bowler et al. (2003), Flaten et al. (1996), Hanninen et al. (1994), and Riihimaki et al. (2000) described subtle deficits in cognition associated with chronic occupational exposure to Al fume. It is those observations that apparently prompted the reduction in the TLV[®] for Al welding fume (ACGIH 2008). Those observations contrast with Kiesswetter et al. (2007, 2009) who found no changes in neurobehavioral parameters or motor performance compared to production or construction workers of similar average age.

Giorgianni et al. (2012) measured serum Al and performance on the Wechsler Memory Scale, attention matrix test and the color-word (Stroop) test for 86 non-smoking (apparently healthy) male Al welders (38.45 ± 6.34 years). Those results were compared to the results for 90 (38.29 ± 7.14 years) male clerical workers who had no history of occupational Al exposure. Study participants had similar years of formal education and all were employed at the same shipyard for similar durations (mean = 15.5–15.8 years). Employees who used Al-containing antacids, experienced occupational Mn exposure or who had a history of diabetes, kidney disease, or cerebrovascular conditions were excluded. Work station (presumably area sampling) concentrations of airborne Al fume averaged 19.5 mg/m^3 and this was attributed to “soldering operations performed inside large and medium-size hulls with double-bottoms and limited air circulation”. Serum Al among the welders ($24.2 \pm 9.9 \text{ } \mu\text{g/L}$) was four times that in the clerical workers ($6.93 \pm 1.95 \text{ } \mu\text{g/L}$). Performance of welders on the Wechsler and Stroop tests was reduced and older welders displayed reduced attention

spans compared to the office staff; welders with longer employment generally had poorer scores. Giorgianni et al. (2012) concluded that chronic exposure (e.g., 16 years) to Al welding fume not only resulted in markedly elevated circulating Al, but that those concentrations over many years were associated with impaired cognition. The Giorgianni et al. (2012) data were qualitatively consistent with observations made by Akila et al. (1999), Bast-Petterson et al. (1994, 2000), Bowler et al. (2003), Hanninen et al. (1994), Riihimäki et al. (2000), and Sjogren et al. (1990). However, the confined space welding operations, apparent lack of fume control, absence of comprehensive exposure data (including frequency, duration and peak concentrations) taken together with the very high mean airborne Al levels do not permit quantitative comparisons among the different studies.

Kiesswetter et al. (2007) conducted a 4-year longitudinal repeated measures study of 20 Al welders exposed to 5–8 mg/m³ total dust in their breathing zone. There was no relation between symptoms, verbal intelligence, logic, psychomotor performance, memory or attention, and urinary (88–140 µg/g creatinine) or plasma (13–16 µg/L) Al. Kiesswetter et al. (2009) conducted a similar study in a second plant of 92 welders with an average of 11 years Al fume exposure. Personal samples found these men were exposed to 0.5–0.8 mg/m³ total dust and that their urinary Al (23–43 µg/g creatinine) and plasma Al (5–9 µg/L) concentrations were somewhat lower than those measured in the first cohort. There were no differences on neurobehavioral or motor performance tests by these welders compared to those by 50 construction workers of similar age not employed in Al welding. Kiesswetter et al. (2009) concluded, “The repeated measurement models of both studies show no adverse effects of Al welding.”

The review by Riihimäki and Aitio (2012) concluded that workers exposed to fine or ultrafine Al particulates while engaged in MIG/MAG Al welding, production and use of Al powders, plasma cutting, grinding, polishing, and thermal spraying were at risk for Al-induced cognitive deficit. Riihimäki and Aitio (2012) found “The mainstream of studies over the past two decades on workers exposed to fine particles of sparsely soluble aluminum have revealed exposure-related subclinical disturbances of cognitive functions and associated subjective symptoms”. These are mixed exposures in that Al accounted for approximately 30% of the fume generated from AlMg 4.5 Mn welding wire, Mg accounted for 3% and Cu, Mn, Pb, and Zn each represented 0.2% (Riihimäki and Aitio 2012). Results by Buchta et al. (2005), Meyer-Baron et al. (2007), Polizzi et al. (2002), and Riihimäki et al. (2000) differ. Buchta et al. (2005) concluded that their neurobehavioral results with 44 welders who had a mean 11 years exposure to Al fume were no different from those of 37 production workers of similar age who had no opportunity for exposure to Al welding fume. Meyer-Baron et al. (2007) examined 9 studies of 449 workers employed in Al welding, smelting and electrolysis compared to 315 control workers. Although Meyer-Baron et al. (2007) concluded that urinary Al less than 135 µg/L “might have an effect on cognitive performance” measured using six different neuropsychological tests with 10 variables (including the symbol-digit and digit span forward/backward tests), when one of the nine studies with uncertain Al exposure was omitted from their meta-analysis there was no statistically significant difference between the Al-exposed and control workers. These studies are difficult to reconcile because of differences in worker age, Al exposure history, education, native intelligence and life style (including ethanol consumption). In addition, use

of Al-containing over-the-counter pharmaceuticals results in urinary Al levels that are equal to or greater than those associated with routine occupational Al exposures. Riihimäki and Aitio (2012) opined that in spite of the preliminary, variable and incomplete evidence for changes in cognition among welders exposed to poorly soluble Al particulate, those reports could not be discounted.

Neurotoxicity in laboratory animals—Table 1 summarizes recent observations concerning Al-induced neurotoxicity in rodents and rabbits; many of these studies examined Al exposures that are much higher than those experienced by humans. Data considered more relevant to published guidance and regulatory limits are described below.

Shati et al. (2011) studied Al-induced biochemical and molecular changes in the brain of adult Balb/c and C57BL/6 mice given AlCl_3 by repeated ip injections over 45 days. Li et al. (2012a) compared APP expression in the brain and selected internal organs of rats after ip injection of AlCl_3 at 1 mg Al/kg once every other day over 60 days. Abdel-Aal et al. (2011a) gave daily ip injections of AlCl_3 at 100 mg/kg-day for 60 days to male Wistar albino rats. Common limitations include only a single Al dose level, no details on clinical signs, food or drinking water consumption or the chemical purity of the test material and the pH of the administered AlCl_3 solution or the Al content in the laboratory stock diet and drinking water were not reported. No controls given equimolar doses of HCl were included in any of these repeated ip AlCl_3 injection studies. No neurobehavioral assessment (Shati et al. 2011) or only limited details of the conditions during the behavioral and neuromotor assays (e.g., blind examination) detract from these reports. Results from the Abdel-Aal et al. (2011a) study suggest that high-dose AlCl_3 injections over a prolonged period can reduce locomotor and cognitive functions in rats, but the reductions in cognitive function and physical activity occurred at doses that also reduced body weight gain suggesting that repeated AlCl_3 injections induced systemic toxicity.

Three recent studies examined the potential toxicity of ingested Al in novel protocols that gave mice AlCl_3 or Al lactate for at least 90 days (Akiyama et al. 2011, Ribes et al. 2010, 2011). These assays are unique in that transgenic mice with increased amyloid β -protein ($\text{A}\beta$) deposition as a result of human $\text{A}\beta$ precursor protein ($\text{A}\beta\text{PP}$) mutations (Tg2576) and (P301L) at the tau protein (Tg2576tau) were examined. The Tg2576 mouse carries the Lys670→Asn, Met671→Leu mutation and by six months of age they develop a 5-fold increase in $\text{A}\beta_{(1-40)}$ and a 14-fold increase in $\text{A}\beta_{(1-42/43)}$. The Ribes et al. (2010, 2011) protocols compared the responses seen in the Tg2576 mouse with those seen in wild-type mice. None of these studies examined more than one Al dose level.

Akiyama et al. (2011) followed the development of AD-like pathology in female $\text{A}\beta\text{PPsw}$ (Tg2576) transgenic mice and in $\text{A}\beta\text{PPsw}/\text{tau}$ (P301L, Tg2576/tau) doubly transgenic mice after long-term ingestion of Al. Akiyama et al. (2011) gave 5- to 8-month-old single transgenic Tg2576 mice or double $\text{A}\beta\text{PPsw}/\text{tau}$ (P301L) (Tg2576/tau) transgenic mice 400 mg Al/L in their drinking water as AlCl_3 *ad libitum* for 4–10 months. Assuming a body weight of 20 g and consumption of 5 ml drinking water/day (http://www.informatics.jax.org/mgi-home/other/mouse_facts1.shtml), the authors estimated the daily Al dose was 100 mg Al/kg bw. The first groups (six mice per group) of heterozygote $\text{A}\beta\text{PPsw}$ transgenic mice

were given deionized water or AlCl₃-treated drinking water for a total of 4 months (from ages 8–12 months) and subsequent groups were given identical treatments from age 8 months for ten months. The doubly transgenic (Tg2576/tau) mice were maintained on the AlCl₃-treated drinking water beginning at 5 months of age until 14 months. Histopathology was examined in serial sections from whole brains of two or three mice per group. Amyloid- β (A β) in all of the surviving mice and tau in the Tg2576/tau mice were determined using immunohistochemistry and quantitative image analyses. The A β was present as diffuse and consolidated deposits in the cerebral cortex and hippocampus. Variability between hemispheres and also within age groups was evident, but there was a consistent increase in A β deposition in the 18-month-old mice compared with the 12-month-old Tg2576 and 14-month-old Tg2576/tau mice. In the 18-month-old mice, A β deposition was widespread and the frontal and temporal cortices had the highest accumulations. The differences in A β deposition between the different treatment groups were not significant for the AlCl₃-treated group and the distilled water controls. Deposition of A β was not significantly different between treatment groups in the 14-month-old Tg2576/tau mice given AlCl₃ versus those given distilled water. Abnormally phosphorylated tau in the brains of the 14-month-old Tg2576/tau mice was assessed using AT8 immunostaining; quantitative comparisons between sections with the highest tau accumulation found no significant differences between groups. Concentrations of soluble A β increased with age, but no significant differences were observed between the different groups.

In sum, Akiyama et al. (2011) described brain pathology and A β deposition in transgenic mice and found an absence of excess tau in genetically susceptible mice given 100 mg Al/kg-day for nine months. Akiyama et al. (2011) concluded that Al ingestion failed to influence the amount of soluble A β or A β oligomer (A β *56) or accelerate or potentiate the pathogenesis of AD-type lesions in mouse brain. The authors also concluded that their results “did not show any significant effect of long-term intake of Al on the amount of A β accumulation in Tg2576 or of A β and tau accumulation in Tg2576/tau mice” and that “our results failed to demonstrate that excess Al in drinking water, a form which is considered to be more bioavailable than Al in food, increases AD pathology in transgenic mouse models.” While Akiyama et al. (2011) did not measure Al in the different brain areas, the authors cited the work of Gómez et al. (2008) who found feeding Al (as the lactate) at 1 mg/g in rodent chow for six months (equivalent to 1.3 mg Al/kg-day) to female Tg2576 mice increased Al concentrations in the hippocampus, cortex and cerebellum. It is noteworthy that Gómez et al. (2008) found no differences in the Al content of these brain regions between wild-type and Tg2576 mice.

In related protocols, Ribes et al. (2010) fed Al lactate in a stock rodent chow to male wild-type and Tg2576 transgenic mice for 210 days. Ribes et al. (2011) followed those studies by feeding dietary Al lactate to 15 male wild-type and 17 Tg2576 transgenic mice for 3 months. Ribes et al. (2011) measured Al in the cerebellum and frontal cortex and counted the numbers of amyloid plaques (double immunofluorescence staining for A β and glial fibrillary protein) in the hippocampus and in the parietal and temporal cortex. These results were then correlated with results of behavioral assessments using a functional observational battery (FOB) along with measures of habituation, training, and memory retention.

Ribes et al. (2010) evaluated learning, memory, and neurogenesis in 40 male wild-type and transgenic Tg2576 mice. Until 5 months of age, the animals had free access to laboratory chow containing 27 mg Al/kg and tap water containing 14 µg Al/L. Starting from 5 months of age, 10 wild-type and 10 Tg2576 transgenic mice were fed the stock diet supplemented with Al (1.1 mg Al lactate/g) for 210 days. Ten wild-type and ten transgenic mice (control) were fed the stock diet. Body weight, food intake, and water consumption were measured monthly during treatment, but the daily Al dose was not defined. After 7 months learning and memory were evaluated in a Morris Water Maze without habituation. Neurogenesis (proliferation, survival and differentiation of hippocampal cells) was assessed two days after behavioral testing. Primary bromo-2-deoxyuridine (BrdU) antibodies, NeuN and GFAP were used for immunohistochemistry. Optic microscopy was used to count BrdU, BrdU-NeuN, and BrdU-GFAP positive cells in the granular cell layer and hilus of the right and left hippocampus and dentate gyrus of coronal sections of six mice from each group. No significant effects of genotype or Al treatment were observed in relation to long-term retention (one week after the acquisition) and there were no differences between genotype/treatment groups in proliferation, survival, and differentiation of hippocampal cells. The authors concluded “we were unable to observe a clear effect from the Al factor” and that there was no effect of dietary Al or genotype on cell proliferation in the hippocampus. The authors measured body weight and food consumption once in every month, but the results were not given in the publication. Assuming average food consumption of 4.4 g/day by a 30-g adult male mouse (Bachmanov et al. 2002), the daily Al consumption may have been on the order of approximately 160 mg Al/kg-day. Verification of the dietary Al concentration was not mentioned and this is of concern due to an error in the amount of Al in the diet reported in an earlier publication by this same group (Gomez et al. 2008).

Ribes et al. (2011) fed 15 wild-type and 17 Tg2576 transgenic female mice (7–8 per group) dietary Al lactate (1 mg Al/g) *ad libitum* from six until nine months of age. Control mice received a stock chow (Hanlan, Barcelona). No data on body weight, or food and drinking water consumption were provided. The dietary concentrations correspond to 3.4 mg Al/kg bw/day in mice given the stock diet and 54 mg Al/kg-day in the treated mice (Gomez et al. 2008). After treatment a number of behavioral endpoints were evaluated in a FOB and the results were scored on a scale from 1 (normal) to 4 (severely abnormal). A novel object recognition test examined the numbers of rearings, distance traveled, and total time spent exploring. After behavioral testing, Al levels in cerebellum and frontal cortex were measured using a computer-controlled ICP-AES (detection limit = 1.0 µg/kg) and serum corticosterone was measured. Because Tg2576 mice develop amyloid plaques, β-amyloid plaques were determined in Tg2576 mice only: the total number of Aβ deposits was counted in the parietal and temporal cortex surrounding the hippocampus and in the hippocampus of both Al-treated and control Tg2576 mice. Two-way ANOVA revealed a significant Al effect (diminished) on climbing in both Al-treated wild-type and Tg2576 mice [$F(1,32) = 8.724$, $p = 0.006$] with lower activity in the Al-exposed Tg2576 group ($p < 0.05$, Mann-Whitney test). There was a significant Al effect [$F(1,32) = 10.702$, $p = 0.003$] on piloerection (increase) in both of the Al-exposed groups compared to the controls. No effect of genotype or Al × genotype interaction was found. There were no significant effects of Al ingestion on corticosterone levels or Al concentrations in frontal cortex and cerebellum of the wild-type

and Tg2576 mice. β -amyloid plaque depositions were observed in both the Al-fed and control Tg2576 animals with a higher number of plaques in the controls compared to the Al-treated Tg2576 mice, but there were no significant differences between these groups. Ribes et al. (2011) found that subchronic ingestion of Al lactate was associated with increased piloerection and diminished home cage activity in both Al-treated wild-type and Tg2576 mice. The Al-treated Tg2576 mice spent less time exploring new objects and this was taken as evidence for impaired long-term memory in the Tg2576 mice. Ribes et al. (2011) also concluded that increased β -amyloid plaques in Tg2576 transgenic mice had no correlation with deficits in recognition memory. Perhaps the most important conclusions were that “neither Al treatment nor genotype had any noticeable effect on Al concentrations in frontal cortex and cerebellum of mice” and that “Al did not alter the recognition memory and β -amyloid plaque loads in Tg2576 mice.”

The Akiyama et al. (2011) and Ribes (2010, 2011) data demonstrate that repeated high-dose Al ingestion increased brain Al concentrations, but increased brain Al failed to potentiate abnormal accumulation of A β , tau, or neuritic β -amyloid plaques in transgenic mouse models of AD. Since Al-induced pathology in rodent brain is different from that seen in AD (Wisniewski 1997, Klatzo et al. 1965), extrapolation of studies in transgenic rodents to assessment of human health risks posed by Al is limited.

Neurobehavioral studies in humans—Olabanji et al. (2011) measured Al in hair and whole blood from 43 healthy adults compared to 60 adults of whom 43 were diagnosed with schizophrenia, 8 who were bipolar, 7 who were diagnosed with non-specific mental illness, and 2 who suffered from post-partum depression. The authors suggested that the Al concentrations were higher in patients with behavioral disorders than in the referent group, but the authors admitted the higher values “may be due to considerable contamination during sample preparation”. The investigators were not blinded to the patient and referent samples and the admitted contamination is such that no useful information can be gained from the Olabanji et al. (2011) publication.

In a retrospective evaluation of 8 men and 22 women who had histologically confirmed focal Al accumulation on skeletal muscle biopsy and who were diagnosed with vaccine-induced macrophagic myofasciitis (MMF), Passeri et al. (2011) assessed visual memory, left ear extinction for interhemispheric connection using dichotic listening and signs of dysexecutive syndrome (characterized by generalized loss of autonomy, impaired planning ability, impaired abstract thinking, impaired social skills, repetitive actions, and poor impulse control). Participant emotional status was measured using the Montgomery/Asberg Depression Rating Scale and the Centre for Epidemiologic Studies Depression (CES-D) self-reporting system. Participants were evaluated using the Wechsler Adult Intelligence Scale, Digit Span test, the California Verbal Learning test, Grober & Buschke test, Benton Visual Retention test, Rey-Ostereith Complex Figure Recall, Verbal Fluency and Trail Making tests, Zazzo’s Cancellation Test for attention, and the Picture Naming DO 80 test.

Seventeen subjects were considered non-amnesic and ten were considered amnesic, but none were classified as demented. Depression tended to increase in 13 (72%) who had “severe” signs of “mild cognitive impairment” (MCI) compared to those classified as pre-

MCI (11%) or with clear MCI (17%). When these 30 patients were given MRI scans, five had cortical atrophy and three had callosal atrophy, but the imaging results found no correlation between brain anomalies and performance on any of these cognitive tests. Despite the authors' contention that "most people with MCI progress to dementia, mostly AD", no assessment of patient apoE ϵ 4 allele (Mui et al. 1996, Rao et al. 1996) or PICALM, CIU, CR1 and BIN1 (Harold et al. 2009, Lambert and Amouyel 2011) was undertaken. The Passeri et al. (2011) study is biased in subject selection, failure to include age-matched referents, and lack of investigator blinding to subject history.

Neurobehavioral studies in laboratory animals—Recent neurobehavioral studies in rodents with Al are presented in Table 2 and the more informative reports are discussed below. Common problems with these studies include: failure to justify the dose, frequency and duration of exposure and only a single concentration was examined (so there is no opportunity to determine dose-response); there were limited or no details on clinical signs, food and drinking water consumption, body weight, the chemical purity of the test material, verification of administered dose, and the pH of the injected, oral gavage, or drinking water solutions. Most of these reports had no information on the Al content in the laboratory stock diet or drinking water. No concurrent controls treated with equimolar doses of HCl were included in any of these studies (e.g., Ali et al. 2008). Providing extraordinarily high AlCl₃ concentrations results in acidic water of low palatability and this can lead to dehydration, reduced food consumption and reduced body weight gain. There was no report of evaluations of plasma urea or creatinine concentrations or other indicators of kidney function. Those parameters are important given the variable findings of renal toxicity reported in some intermediate and chronic duration Al exposure studies (ATSDR 2008). Most of the recent publications provide limited details on conduct of the behavioral and neuromotor assays and only a few include circulating or peripheral tissue Al concentrations.

Liu et al. (2010) evaluated memory, cerebral cortex, and hippocampus excitatory amino acids (glutamate and aspartate) and brain acetylcholinesterase (AChE) activity in male Kunming mice. Intraperitoneal AlCl₃ was given at 100 mg/kg once every other day for 60 days. Control mice received the same ip volume of water once every other day for 60 days. Learning and memory were assessed using a single trial passive avoidance task. Reduced performance on tests for memory, reduced glutamate, and aspartate levels and increased AChE activity in the Al-treated mice were reported. A related study by Kakkar and Kaur (2011) investigated subchronic oral gavage with 100 mg AlCl₃/kg-day AlCl₃ in relation to escape latency, hippocampus and cortex histology, brain LPO, SOC, GSH, catalase, and AChE activity in mice. Kumar et al. (2011) gave male rats AlCl₃ by oral gavage at 100 mg/kg-day for 42 weeks. It is not clear to what extent the reported changes in behavior, brain chemistry, edema, and neuron degeneration in the hippocampus and cortex may be due to the acidic properties of high-dose AlCl₃ and the influence of HCl on peritoneal tissues, drinking water consumption, hydration, and health of the animals.

Other recent studies suffer from similar limitations. Abu-Taweel et al. (2011b) gave adult male Swiss mice daily treatment "by oral route" with AlCl₃ at 0, 300, or 600 mg/kg-day in distilled water over 20 days. Dose-dependent reductions in social investigations, numbers of attacks, and numbers of fights were seen along with significant increases in latency to threat,

latency to attack, rears, and non-social investigations. The authors reported significant reductions in circulating T in both Al-treated groups. Significant declines in serotonin (5-HT) were seen at the high dose and declines in dopamine (DA) were reported at 300 and 600 mg/kg-day. Whole brain acetylcholine (ACh) was reduced at the low dose, but ACh was increased at the high dose. The authors concluded that daily AlCl₃ ingestion resulted in neurobehavioral impairment associated with reduced brain 5-HT and DA. There were no details on the purity or pH of the dosing solution; the numbers of mice per group was not identified and clinical observations, food and water consumption and body weight gain data were not provided. Neither pair-fed controls nor concurrent controls given equimolar doses of HCl were included in the study design.

Thirunavukkarasu et al. (2012) gave groups of eight rats 100 mg/kg-day of AlCl₃ in drinking water for 90 days and evaluated anxiety and memory. Aluminum concentrations in the cerebral cortex and hippocampus increased 13- and 6-fold, respectively, compared to the controls. Rats given AlCl₃ had an 8.5-fold increase in the number of escape trials and significant reductions in cortex and hippocampus AChE activity. Ingestion of AlCl₃ was associated with behavioural alterations, significant reductions in brain SOD, catalase, glutathione peroxidase (GPx) and, reduced GSH compared to the controls. "Shrunken" neuronal cells with vacuolated cytoplasm and massive cellular depletion along with severe necrosis were noted in the cerebral cortex and hippocampus. The changes in brain histology might reflect the increased Al levels in the cerebral cortex and hippocampus and behavioral changes; however, as no histologic evaluation of the gut and no data on food or water consumption were provided, it is difficult to determine whether the changes in behaviour and oxidative stress reflect direct consequences of Al or whether the changes were secondary to the acidic water.

Wang et al. (2010a) described the consequences of high-dose Al on memory in rats given 0, 2000, 4000, or 6000 mg/L AlCl₃ in distilled drinking water for 90 days. Body weights and drinking water consumption were monitored, but no results were provided. Assessments of memory and learning ability were measured using the step-down test, synaptic plasticity in the hippocampus was evaluated using long-term potentiation (LTP), expression of protein kinase C, assays of mitogen-activated protein kinase (MAPK), and measures of extracellular signal-regulated kinases (ERK1/2) and Ca⁺² calmodulin-dependent protein kinase II (CaMKII) expression. Absolute and relative brain weights and Al levels in whole brain and blood were measured. The average daily water intake declined as the AlCl₃ concentration increased; animals given 2000, 4000, or 6000 mg/L AlCl₃ consumed 25 ± 2, 20 ± 2, and 15 ± 2 ml per rat per day, respectively. By comparison, the control rats consumed 50 ± 2 ml of distilled water per day. These AlCl₃ concentrations in drinking water were associated with 4–16% reductions in body weight.

A significant concentration-dependent increase in the numbers of mistakes and reduced latency (indicators of memory) in the AlCl₃-treated rats were observed. Absolute (8–16%) and relative brain weights (6–11%) were reduced in the AlCl₃-treated groups. Wang et al. (2010a) concluded that ingestion of AlCl₃ reduced memory, impaired hippocampal synaptic plasticity, and decreased LTP induction-related kinases MAPK, ERK1/2, and CAMKII. As in studies by Erazi et al. (2011) and Thirunavukkarasu et al. (2012), the pH of the drinking

water was not reported and no concurrent controls given equimolar concentrations of HCl were included.

In a study similar to Wang et al. (2010a), Cui et al. (2012) investigated the influence of prolonged Al ingestion on learning and memory of rats by studying changes in the Ras/Raf/ERK signal transduction pathway. Young Wistar rats given 2000, 4000, or 6000 mg/L AlCl₃ in drinking water for 90 days had increased brain Al, reduced brain weight, and reduced LTP amplitude in the hippocampus. Ras protein and mRNA expression increased and Raf1, ERK2, and CREB declined. The authors concluded that subchronic Al exposure during early life may affect learning and memory as a result of Al-induced changes in the Ras/ERK signal pathway.

Xiao et al. (2011) gave AlCl₃ in distilled water to female Kunming mice at 0 or 20 mg/kg-day by gavage for 10 weeks. Learning and memory were measured using the Morris water maze. Whole brain Ach and choline acetyltransferase (ChAT) and AChE activities along with amyloid β (A β) and hyperphosphorylated tau (HFT) were determined at 8 and 10 weeks of exposure and after six weeks of recovery (i.e., 16 weeks from the beginning of the study). Histologic examination of senile plaque (SP)-like and neurofibrillary tangle (NFT)-like structures was conducted and A β was measured using mouse anti- A β ₁₋₄₂ antibody. After eight weeks there were no significant differences in escape latency, probing time in the target quadrant, or in brain Ach, ChAT and AChE activities. There were no detectable SP-like or NFT-like structures in the cortex or in the hippocampus. After 10 weeks there was a significant increase in escape latency among the AlCl₃-treated rats compared to the controls, but there were no significant differences in Ach, AChT, and AChE activities and no SP-like or NFT-like structures in the cortex or hippocampus. At 16 weeks (10 weeks of treatment + 6 weeks withdrawal) there were no significant differences in escape latency, probing time, brain Ach, AChT, and AChE activities or SP-like and NFT-like structures in the cortex or hippocampus. Similar to the Cui et al. (2012), Thirunavukkarasu et al. (2012), Wang et al. (2010a) reports, Xiao et al. (2011) provided no rationale for dose selection, examined only a single Al dose level and the pH of the AlCl₃ solution was not reported. Xiao et al. (2011) made no mention of Al concentrations in blood or brain or changes in body weight, food and drinking water consumption or clinical signs.

By and large the most recent laboratory reports (Tables 1 and 2) concerned with Al-induced neurotoxicity and neurobehavioral disorders have not identified exposures or outcomes that alter previous conclusions (ATSDR 2008, Krewski et al. 2007, Willhite et al. 2012). Some of the recently published studies support the plausibility that prolonged high-dose Al exposure can induce neurobehavioral disorders in rodents, but most of the recent studies that employed oral administration and high doses of Al (administered as AlCl₃) were such that increased mortality (Kakkar and Kaur 2011) and/or systemic toxicity (e.g., reduced body weight) (Cui et al. 2012, Wang et al. 2010a) complicate interpretation of the results. The majority of the recent reports in rats used different strains, doses, routes, durations and frequency of exposure, and make no mention of clinical signs, body weight change and drinking water or food consumption. Given the lack of consistency in experimental design and protocols, comparisons between results are problematic. Based on studies with Sprague-Dawley rats injected with AlCl₃ at 100 mg/kg-day for 16 weeks, Elsaid et al. (2011)

suggested that increased brain LPO and reduced brain AChE were “a major factor responsible for the memory deficit in AD”. Kaizer et al. (2008) found increased hypothalamus and striatum AChE and reduced cerebellar, hippocampus and cortex AChE after chronic Al exposures in mice, but reported reduced hypothalamus AChE activity in the Kaizer et al. (2005) publication. Reduced rat brain AChE activity was also reported by Bhadauria (2012), Chakrabarty et al. (2012), Shrivastava (2012), Stevanović et al. (2011), and Thirunavukkarasu et al. (2012); however, Ahmed et al. (2011), Bihaqi et al. (2009), Kakkar and Kaur (2011), Kumar et al. (2011), Liu et al. (2010), and Sharma et al. (2009) all reported increased brain AChE activity, but Xiao et al. (2011) found no significant effect of prolonged oral AlCl₃ on mouse brain AChE. Since there are no signs of cholinergic stimulation or inhibition seen after high acute doses of any Al form, the clinical significance of changes in AChE activity (if any) are not clear. Whether these differences are due to dose, duration or strain or species cannot be determined given the absence of brain Al concentration: time profiles. Similar discrepancies between the results of other rodent neurobehavioral assays after Al exposures were noted previously (Willhite et al. 2012).

Several studies were identified that examined exposure of laboratory animals to water-soluble Al materials with durations that spanned from 1 to nearly 6 months (Tables 1 and 2). Some of these studies used parenteral injections and others examined changes after Al (primarily AlCl₃) by repeated oral (gavage) administration or via drinking water. The objective of some of these studies was to investigate the neuroprotective effects of various drugs or plant extracts (Kumar et al. 2011, Thirunavukkarasu et al. 2011, 2012) on Al-induced toxicity or to investigate mechanisms of Al neurotoxicity (Cui et al. 2012, Wang et al. 2010a, Xiao et al. 2011) following prolonged Al administration. Only Akiyama et al. (2011) and Ribes et al. (2010, 2011) provided a rationale for duration of exposure and some (González-Muñoz et al. 2008a, 2008b) lacked concurrent vehicle controls. Many of these studies used a single level of Al (administered as the chloride or lactate) and examined sexually mature male or female rats (Erizi et al. 2011, Kumar et al. 2011, Thirunavukkarasu et al. 2012) or mice (Kakkar and Kaur 2011, Xiao et al. 2011). Cui et al. (2012) and Wang et al. (2010a) studied young rodents; Abu-Taweel et al. (2011a, 2011b), Abd El-Rahman et al. (2011), Kakkar and Kaur (2011), and Xiao et al. (2011) studied mature mice. The majority of these studies gave Al via gavage (Abu-Taweel et al. 2011, Ahmed et al. 2011, Belaid-Nouria et al. 2012, Bihaqi et al. 2009, Kakkar and Kaur 2011, Kumar et al. 2011, Thirunavukkarasu et al. 2012, Xiao et al. 2011) and others employed drinking water (Abd-Elghaffar et al. 2007, Cui et al. 2012, Wang et al. 2010a); only two of the studies examined more than a single dose level (Cui et al. 2012, Wang et al. 2010a). Six of the recent studies presented measurements of Al in the brain and blood and included brain histology along with results of neurobehavioral testing (Chakrabarty et al. 2012, Cui et al. 2012, Erizi et al. 2011, Kakkar and Kaur 2011, Kumar et al. 2011, Wang et al. 2010a).

Data showing increased brain LPO in rodents (Ahmed et al. 2011, Belaid-Nouria et al. 2012) and rabbits (Abd-Elghaffar et al. 2007) after repeated oral dose Al are abundant. In addition to alterations in the activity of brain antioxidant enzymes (Table 3), Wu et al. (2012a) listed consistent features of the Al neurotoxic mode of action: disturbances in Fe and other metal homeostasis, impaired mitochondrial function as a result of increased mitochondrial O₂^{•-} and •OH/H₂O₂ and alterations in NF-κB, p53, and JNK pathways that promote apoptosis.

The cerebral atrophy and neuronal necrosis in rabbits described by Abd-Elghaffar et al. (2007) were consistent with previous reports by Rabe et al. (1982) and Yokel (1989) who found Al-induced neurodegeneration and neurofibrillary changes in rabbits, but the Ahmed et al. (2011) report of neurofibrillary tangles in Sprague-Dawley rat brain after 4 months of daily AlCl₃ intubation and the Sun et al. (2009) report of increased cortex and hippocampus Aβ in Kunming mice after three months of daily AlCl₃ injections are novel and unlike the neurofibrillary damage described by Shrivastava (2012). Nevertheless, recent histopathological observations in the brain of laboratory animals after Al administration via oral or parenteral routes have not confirmed the neuritic plaques seen in human AD and the recent results are not sufficient to conclude that the damage seen in animals treated with high Al doses is equivalent to that seen in AD (Klatzo et al. 1965, Wisniewski and Wen 1992; reviewed in Kawahara and Kato-Negishi 2011).

None of the laboratory studies reviewed here met the current international test guidelines and most failed to specify the source and chemical purity of the test material. The experimental designs of the majority were limited to only one dose level and observations were performed at a single time point. Given the paucity of details and the absence of clinical chemistry parameters and urine analyses, it is difficult to determine the health of the animals and their renal function. In most of these recent publications blood and tissue Al levels were not measured; therefore, the absorbed and distributed doses cannot be identified and compared to those of other animal and human studies. Overall, none of the recent animal studies that examined Al oral administration provided clear indications of neurologic damage in the absence of systemic toxicity. While several studies on Al-induced neurotoxicity in laboratory animals have appeared, none of the recently published studies in animals are adequate upon which to base oral RfD or DNEI values for metallic Al, its oxides or the common Al salts.

Neurotoxicity in vitro—A number of in vitro studies focused on mechanisms of Al-induced neurotoxicity (Table 3). A brief overview of the laboratory data considered most relevant to Al hazard identification is provided below.

Niedowicz et al. (2011) described assembly of amyloid-β (Aβ) and the hyperphosphorylated pathologically folded microtubule tau polymers of the neurofibrillary tangles that together make up the neuritic plaques. In an effort to understand the self-aggregation of soluble amyloid β-peptide (Aβ) responsible for the protein mis-folding that leads to development of insoluble “senile” plaques, Atwood et al. (1998) incubated 10 μM synthetic human Aβ₁₋₄₀ with 0.6 or 30 μM Al³⁺ at pH 6.6, 6.8, or 7.4. No detectable Aβ₁₋₄₀ aggregation was observed over the pH range tested in the absence of Al³⁺ or other metal ions. Incubation of Aβ₁₋₄₀ with 0.6 μM Al³⁺ increased protein sedimentation as pH declined; incubation of synthetic human Aβ₁₋₄₀ with 30 μM Al³⁺ induced partial aggregation at pH 6.6, but there was no significant aggregation at pH 7.4. Atwood et al. (1998) interpreted their data as reflecting subtle changes in Aβ₁₋₄₀ conformation that account for metal ion-induced Aβ assembly mediated by [H⁺].

The Atwood et al. (1998) observations were consistent with previous reports (Barrow and Zagorski 1991, Burdick et al. 1992, Fraser et al. 1991, Kirshenbaum and Daggett 1995,

Wood et al. 1996, Zagorski and Barrow 1992) on Al concentration, pH and A β aggregation; as Al concentrations increased, there was an increase in Al⁺³-induced A β conformational change. Atwood et al. (1998) found that addition of Cu²⁺ and Zn²⁺ also induced A β ₁₋₄₀ aggregation at pH 6.8–7.4 and that the reaction was completely reversible with chelation or at higher pH. The Atwood et al. (1998) data could be taken as support for the suggestion that metabolic acidosis (Yates et al. 1990) associated with inflammation (Akiyama et al. 2000), impaired energy metabolism (Small et al. 2000) or increased oxidative stress coupled with the actions of ionized metals might contribute to the pathogenesis of AD and/or other neurologic disorders.

Many mechanistic studies (Table 3) are not directly relevant to Al hazard identification, but some offer (curious and/or conflicting) insights into A β and its interactions with Al. For example, Nday et al. (2010) cultured Sprague-Dawley rat hippocampal cells with 0, 10, 100, or 500 μ M Al⁺³ (as AlCl₃). Neuronal dendrite shrinkage and lethality increased with concentration and duration of exposure and neurons were far more susceptible than glial cells. In a companion effort, cultured mouse neuroblastoma N2a cells expressing the amyloid precursor protein APP695 were used to produce a supernatant that contained 8.2 pg A β ₁₋₄₀/ml. Addition of 750 μ l of that supernatant to 96 h cultures of rat neuronal and glial cells reduced their survival 26 and 14%, respectively. However, when 500 μ M Al⁺³ was incubated along with the same concentration of A β -bearing N2a supernatant, neuronal and glial cell survival was no different from that in cultures treated with the A β supernatant alone. When A β alone was added (4 days) to cultured neurons there was a significant reduction in polymerized tubulin, yet when 50 μ M Al⁺³ was added to neurons cultured under identical conditions there was no change in polymerized tubulin compared to cultures treated with Al⁺³ alone. The most important conclusion was that there was no significant interaction between A β ₁₋₄₀ and Al⁺³ in cultured rat neurons and glial cells.

The Nday et al. (2010) conclusion appears to conflict with that by Drago et al. (2007) who reported reduced survival of cultured rat endothelial cells after treatment with rat or human A β ₁₋₄₂ and that cytotoxicity was enhanced after exposure to human A β -Al. The Nday (2010a) conclusion is also at odds with that by Drago et al. (2008) who compared the viability and morphology of cultured human neuroblastoma cells treated with synthetic A β ₁₋₄₂ or A β -Al, A β -Cu, A β -Fe or A β -Zn conjugates (prepared via A β -binding with bare ions to yield monometalated molecules). Unlike Nday et al. (2010) who found native A β ₁₋₄₀ was cytotoxic for rat primary hippocampal neurons after 96 h incubation, Drago and associates (2008) found no significant toxicity of synthetic A β ₁₋₄₂ in transformed human neuroblastoma cells after 24 h in culture. Notably, of the A β ₁₋₄₂ metal conjugates only the A β -Al reduced cell survival. It is not clear whether the differences between the results from Nday et al. (2010) and Drago et al. (2008) are due to the specific nature of the N2a-produced A β ₁₋₄₀ compared to the synthetic A β ₁₋₄₂, to different culture conditions and durations of exposure, or to differential uptake of A β ₁₋₄₀ and A β ₁₋₄₂ by primary and transformed cells. While A β ₁₋₄₀ incubation with rat neurons and glial cells was prolonged (4 days) and fluorescent stains were used to measure polymerized tubulin, Nday et al. (2010) made no confirmation by ELISA or other means to determine the extent of mouse N2a-generated A β ₁₋₄₀ uptake into cultured rat hippocampal cells.

Bolognin et al. (2011) expanded on the Drago et al. (2007, 2008) efforts and found both A β -Al and A β -Fe induced annular protofibrils and fibrillar oligomers in cultured human neuroblastoma cells, yet only A β -Al triggered production of the amyloid precursor protein and tau 181 (Table 3). The latter observations were not consistent with the in vivo results presented by Ribes et al. (2011) and Akiyama et al. (2011) who found not only that prolonged ingestion of 54 or 100 mg Al/kg-day failed to increase the numbers of β -amyloid plaques or influence the amount of soluble A β or A β *56 oligomer, but also failed to influence the levels of abnormally phosphorylated tau in the brains of susceptible transgenic mice. In follow-up studies with cultured human neuroblastoma cells to ascertain A β , Bolognin et al. (2011) measured aggregated A β and A β -metal conjugates with conformation-specific antibodies to aggregated A β , but no direct immunoreactivity for monomeric A β was included in that protocol. Given the notable activity of small oligomeric A β species that readily diffuse through cell membranes, Bolognin et al. (2011) suggested that in contrast to the historical specific focus on A β it may be that prefibrillar and/or fibrillar A β oligomers are the primary targets of concern.

In another example, Gatta et al. (2011) examined the influence of A β ₁₋₄₂ or the A β ₁₋₄₂-Al complex on gene expression in cultured human SHSY5Y neuroblastoma cells and compared those results to gene expression profiles in cultures with A β ₁₋₄₂ or Al alone. At 4°C the A β self-aggregated into short irregular protofibrils, but the A β -Al complex was present as oligomers. Media was replaced every 2 days and the SH-SY5Y cells were incubated with 0.5 μ M A β ₁₋₄₂ or A β ₁₋₄₂-Al complex for 24 h. Other cultures were incubated under identical conditions with 5 μ M Al (10-fold higher than that used in the A β ₁₋₄₂-Al complex) as Al(C₃H₅O₃)₃ alone. Culture with the A β ₁₋₄₂-Al complex induced different gene expression patterns compared to the patterns induced after similar exposures to A β or Al alone. Of a total of 28,676 transcripts, exposure to the A β -Al complex promoted up-regulation of 1535 genes and down-regulation of 1815 genes. A gene subset correlated with clinical AD was identified from 584 AD-related genes of which 29 were up-regulated and 23 were down-regulated. Ingenuity pathway analyses revealed that these genes were involved in the modulation of Ca⁺² homeostasis as well as regulation of glutamatergic transmission and synaptic plasticity. Microarrays of 35,129 genes were conducted to investigate changes induced via exposure to the A β ₁₋₄₂-Al (A β -Al) complex on the expression profile. Down-regulated genes included those involved in cell-cell signaling, inflammation and free radical scavenging; up-regulated genes included those involved in amino acid and lipid metabolism and DNA replication. Based on these results, Gatta et al. (2011) concluded that the A β -Al complex might be involved in regulation of neuronal as well as synaptic function/dysfunction and that its presence might modulate AD-related pathways including glutamatergic transmission, Ca⁺² homeostasis, oxidative stress, inflammation and neuronal apoptosis. Limitations identified for the Gatta et al. (2011) study include the fact that cultured transformed neuroblastoma cells have limited relevance to normal neurons (Lidsky 2014). As with all of the in vitro assays (Table 3), Aremu et al. (2011), Castorina et al. (2010), Gatta et al. (2011), Nday et al. (2010), and Yang et al. (2011) provided no justification for the Al concentrations used in their assays. None of the authors compared their Al concentrations examined in vitro (Table 3) to the Al concentrations measured in human brain or other tissues (e.g., Akatsu et al. 2011, House et al. 2012, Rusina et al. 2011).

There is evidence to show that the tangles found in AD patients are associated with elevated brain Al (reviewed in Exley and House 2011, Walton 2010), but there is no consistency in the results of historical (Kasa et al. 1965) or recent studies of brain Al concentrations in patients with AD. Some studies involving bulk analyses of brain samples provide evidence of increased brain Al concentrations in AD patients compared to non-demented controls, while other studies do not. Similarly, there is no agreement between the results of different studies examining Al accumulation in senile plaques and neurofibrillary tangles. Different measurement techniques and their inherent limitations, variations in sampling strategies and sample handling and possible laboratory Al contamination may contribute the explanations for the conflicting data (reviewed in Krewski et al. 2007, Willhite et al. 2012). While Al can be present in senile plaques, this observation alone does not imply a direct role for Al in the pathogenesis of AD (Exley and House 2011, Walton et al. 2010). Wu et al. (2012a) summarized the current state of the science as follows:

“The controversy whether Al has a direct link to common human neurodegenerative diseases, such as AD, has been debated for decades. Conflicting data exist in the literature (Mizoroki et al. 2007, Savory and Ghribi 2007, Savory et al. 2006). Although it is relatively certain that Al displays multifaceted and complicated neurotoxicity at low dosages, some of which appears relevant to AD disease, there is still no evidence to link Al as a high risk factor for AD as happening in the general population.”

The data published to date do not support identification of Al accumulation in brain as the etiologic basis of AD (summarized in Wu et al. 2012a, Lidsky 2014). With respect to the Al hypothesis for AD (Graves et al. 1990, Kawahara and Kato-Negishi 2011, Krewski et al. 2007, Perl and Moalem 2006, Rusina et al. 2011, Tomljenovic 2011, Walton 2010, 2012a, 2012b), it remains unclear why Al welders and other Al workers (Akila et al. 1999, Giorgianni et al. 2012, Graves et al. 1998, Gun et al. 1997, Hanninen et al. 1994, Rossbach et al. 2006, Salib and Hillier 1996, Santibáñez et al. 2007) or people who experience very high prolonged Al exposures via PN, renal dialysis, and/or Al phosphate binders (Jenkins et al. 1989, Klein et al. 1984, Ott et al. 1982, Pei et al. 1992, 1995, Salusky et al. 1984, 1990, 1991, Smith et al. 1986) who accumulate substantial Al body burdens (serum Al 30–40 to 100 µg/L) and who show clinical signs of Al intoxication do not experience elevated AD risk.

Since AD shows heritability of up to 79% and the apolipoprotein A (apoE e4) gene increases AD risk, contemporary AD research focuses on the different functional loci involved in lipid processing (apoE, CIU, and ABCA₇), cell membrane integrity (PICALM, BIN₁, CD₃₃, and CD_{2AP}), and the immune system (CLU, CR₁, ABCA₇, CD₃₃, and EPHA₁) all of which play roles in Aβ clearance and confer increased AD susceptibility (Carrasquillo et al. 2011, Hollingworth et al. 2011). Other research that demonstrated “seeding” small soluble oligomers of human Aβ (complexed with other macromolecules) or aggregates of mutant P301S tau induced misfolding and filamentation of wild-type tau and AD pathology in naïve mice suggests infectious or prion-like actions in the pathogenesis of AD (reviewed in Guest et al. 2011).

Respiratory

Kongerud and Søyseth (2014) summarized factors related to development of “potroom asthma” among Al smelter workers. Donoghue et al. (2010) studied occupational asthma among employees in Al pre-bake smelters. Regular medical surveillance, including respiratory questionnaires and spirometry, was conducted at all smelters with intervals from 3 months to 2 years. No information was available on ages of the workers, gender or length of employment. Asthma cases were identified by surveillance and a few of the cases were diagnosed by family physicians. Pre-placement criteria and assessment of individual suitability for jobs with exposure to potroom dust, fumes, and gases were introduced before the study period; these criteria evolved over the course of the study and these criteria were not uniform at all smelters. Reported parameters included a history of asthma beyond childhood, reduced forced expiratory ratio and evidence of reversible airway obstruction. In some smelters, assessment of non-specific bronchial hyperresponsiveness using methacholine challenge was performed. Incidence rates for occupational asthma were calculated for each smelter and for all smelters combined and the data were presented for each year of the study. All cases of occupational asthma identified among smelter employees (regardless of job category) were divided by the total number of smelter employees (regardless of job category) and the incidence rates were expressed as the number of cases per 1,000 employees per year. Employees who worked “in close proximity to pot fume or bath material for several hours a week as part of their normal job” (e.g., potrooms, potroom services, rodding, potlining, cryolite recovery, scrubbing, and alumina) were defined as the highly “bath exposed” workers. Personal sampling of inhalable particulate, respirable particulate, particulate fluoride (F), gaseous hydrogen fluoride (HF), and total F were conducted for potroom employees. The study design was such that use of personal respiratory protection was not taken into account.

A total of 329 cases of occupational asthma were identified and the highest rate in 1992 (9.46/1,000 per year) declined to 0.36/1,000 per year in 2006. Of the 329 cases, 180 (55%) occurred in potroom employees and 243 of those occurred among employees assigned to the “bath exposed” areas. A number of control measures were implemented and as a result, the concentrations of inhalable particulate, respirable particulate, particulate F, gaseous HF, and total F in the workers’ breathing zone declined over the study period. Significant correlations were observed between reductions in asthma and reductions in total respirable particulate, total F, particulate F, and gaseous HF.

In contrast, Martin and Larivière (2014) described a study of 5000 employees of Canadian Al smelters in which the incidence of post-hire asthma was no different between fume-exposed workers and non-exposed workers. Another study that collated symptoms among 490 male employees (36.75 ± 6.9 years) of three Al industries (mean duration 12.3 years) found that 77% complained of back, shoulder and other pain, but there was no indication of respiratory or any other health issues (Aghilinejad et al. 2012).

Mechanistic data

Aluminum added as AlCl_3 at 1, 5, 10, 50, or 100 μM to cultured human transformed HaCat epidermal keratinocytes or primary human dermal fibroblasts for two or three days,

respectively, failed to induce significant proliferation. Based on these in vitro observations, Jenkins et al. (2011) suggested that the (conflicting) reports of pulmonary fibrosis in workers exposed to fine dusts of alumina, Al pyro powders or bauxite (reviewed in ATSDR 2008) were not due to Al-induced proliferation of fibroblasts.

Hematology and cardiovascular

Elevated Al reduces the erythrocyte lifespan and interferes with hemoglobin synthesis; these factors contribute to the microcytic hypochromic anemia that develops after prolonged Al exposure in patients with compromised kidney function (Lin et al. 1996, Rosenlof et al. 1990, Touam et al. 1983). This Fe—resistant anemia is due to reduced erythrocyte membrane integrity, inhibition of δ -aminolevulinic dehydratase, reduced Fe uptake by Al-transferrin, down-regulation of transferrin receptor expression and impaired intracellular delivery of Fe from transferrin (McGregor et al. 1990, Niemoeller et al. 2006, Rosenlof et al. 1990).

Elshamaa et al. (2010) compared serum Al in 43 children on chronic renal dialysis (where dialysate Al was less than 10 $\mu\text{g/L}$) to serum Al in 43 healthy children. The dialysis patients used Ca acetate or carbonate to control circulating phosphate, and none of these children received Al-containing phosphate binders. Serum Al was significantly higher (18.4 ± 4.3 $\mu\text{g/L}$) in renal patients than in healthy referents (6.5 ± 1.6 $\mu\text{g/L}$). The source of the elevated serum Al in these cases appeared to be erythropoietin (EPO).

In a cross-sectional study of whole blood Al determined in men and women with a history of cardiovascular incidents or diabetes or who had taken diuretics, aspirin, antihyperlipidemics, or “any regular drug”, Lind et al. (2011) found a significant non-linear (inverted U-shape) relation between Al and the prevalence of ultrasound-confirmed atherosclerotic plaques in the carotid artery. This relation remained after adjusting for gender, waist circumference, body mass index, fasting blood glucose, systolic and diastolic blood pressure, HDL and LDL cholesterol, serum triglycerides, smoking, antihypertensives or statins, diabetes mellitus and coronary heart disease. Lind et al. (2011) offered the suggestion that development of carotid plaques might be associated with Al-catalyzed oxidation of low-density lipoproteins.

After male Wistar rats (200–230 g) were given repeated ip injections of AlCl_3 at 15 mg/kg-day for ten days, Cheng et al. (2012) found significant reductions in erythrocyte counts, hemoglobin concentrations, mean corpuscular volume, mean corpuscular hemoglobin and hematocrit. These animals also developed increased brain LPO and reduced GST and SOD; however, no mechanistic data were presented to explain the anemia. The Cheng et al. (2012) study is compromised by study of only one exposure level and failure to provide justification for the relatively high AlCl_3 dose. Neither the pH of the test solution, mention of concurrent controls given equimolar injections of HCL, nor necropsy results of the peritoneal cavity were reported. Reductions in erythrocyte counts were also seen after rats consumed 430 mg/L AlCl_3 in their drinking water for 90–150 days (Zhang et al. 2011a). Prolonged exposure to this high concentration also reduced body weight gain and the limitations to the Zhang et al. (2011a) report are similar to those for Cheng et al. (2012).

There are at least two recent publications concerning the influence of elevated Al on vascular cells. After 0.001–100 µg/ml Al₂O₃ (39.7 nm) particles were cultured with human cardiac microvascular endothelial cells for 24 h, there was no evidence for cytotoxicity, ROS generation, increased cell permeability or inflammatory markers (Sun et al. 2011b). Compared to the potent cytolethality of Cu, Mg, and Zn oxide nanoforms in vitro, Sun et al. (2011a) attributed the reduced toxicity of this nano Al oxide to its larger specific surface area. Mikkelsen et al. (2012) compared the toxicity of particulate platelet or 30–75 nm kaolinite (Al₂SiO₅) interior wall paint dust in cultured human umbilical vein endothelial cells to the toxicity of crystalline Al₂O₃ (20–40 to 1930 nm). Cytotoxicity was significant only after exposure to the highest concentration (100 µg/ml) of kaolinite. The Mikkelsen results confirm that toxicity depends on the particular Al physical and chemical form.

Of the recent mechanistic reports that by Vota et al. (2012) is one of the more informative. Since high Al concentrations interfere with heme synthesis and disrupt the EPO receptor (Vittori et al. 2005), fresh human erythrocytes were cultured in pH 7.3 medium at 4° C for 21 days (during which time media was refreshed every two days) in the presence of 100 µM AlCl₃ • 6H₂O (equivalent to 11 µM Al or 298 µg Al/L). By way of comparison, plasma and serum Al concentrations in healthy humans range from less than 1.6 to 6 µg/L (median = 3.2 µg/L or 0.12 µM) and very high Al concentrations (to 255 µg/L or 94 µM) occur in seriously ill renal patients (Krewski et al. 2007). These culture conditions increased the numbers of acanthocytes and stomatocytes, but failed to induce hemolysis. These conditions also increased the concentrations of O₂ •⁻ and OH• three-fold, increased intracellular Ca and reduced significantly the intracellular levels of GSH. These changes and the eryptosis were abolished in parallel assays that included 5 mM of the antioxidant thiol N-acetylcysteine. The Vota et al. (2012) results implicate the pro-oxidant properties of Al⁺³ in its adverse effects on erythrocytes.

Musculoskeletal

Humans—Gherardi and Authier (2012) presented evidence for Al oxyhydroxide [AlO(OH)]-induced MMF after its use as an adjuvant in French hepatitis and tetanus vaccines. The time that elapsed from vaccination until patient presentations ranged from 0.5 to 84 months with most MMF diagnoses made long after the initial onset of symptoms. One remarkable feature was that although ultrastructural examination of muscle at the injection site confirmed macrophages with agglomerations of submicron/micron Al inclusions, almost never was muscle pain or tenderness associated with the injection site, but these symptoms occurred either in the legs or were non-specific and diffuse. Gherardi and Authier (2012) suggested that uptake by antigen-presenting cells of nano-size (~13 nm) AlO(OH) particles as submicron aggregates facilitated Al translocation to organs distant from the muscle via the lymphatics. However, the current literature search found no independent definitive characterization of the proposed MMF or ASIA (autoimmune syndrome induced by adjuvants) (Shoenfeld and Agmon-Levin 2011) condition.

Laboratory animals—del Pilar Martínez et al. (2011) compared Al(OH)₃-induced reductions in bone strength in young Sprague-Dawley rats to that caused by reduced atmospheric pressure (hypobaric hypoxia). Two of four groups were given 20% glycerol as a

control and two groups were given three ip injections of 27 mg Al/kg as Al(OH)₃ per week for three months. One Al-treated and one vehicle control group were maintained at sealevel barometric pressure; one Al-treated and one vehicle control group were exposed to simulated hypoxia (506 mbar equivalent to 5484 m altitude) 18 h/day for 30 days. Bone Al increased 14–15x among the Al(OH)₃-treated groups compared to the vehicle controls. Repeated Al(OH)₃ injections also reduced the mean hematocrit and increased the percent reticulocytes in both the ambient and hypobaric groups. Hypoxia increased erythropoiesis, hematocrit, and reticulocyte counts. Body weights and femur length and width were reduced with prolonged hypobaric exposures, and the reductions in bone strength (ultimate, elastic load, and elastic energy absorption) after hypoxia were more pronounced than after repeated Al injections. The effect of combined Al and simulated high altitude on bone was no greater than hypobaric conditions alone.

Li et al. (2010) studied Al ingestion in relation to Al levels in bone and cartilage in rats. Healthy rats were given drinking water (free access) containing 400 mg/L AlCl₃ and control rats were given distilled water during 150 days. Ten rats from each group were sacrificed on Days 30, 60, 90, 120, and 150 at which times Al in serum, bone and cartilage was measured. The body weights of the treated rats were significantly less than the controls beginning at Day 60 and the serum, cartilage, and femur Al concentrations were significantly higher in the Al-treated rats. The Li et al. (2010) study examined the influence of Al on bone metabolism during the primary phases of skeletal growth, but failures to justify the single high AlCl₃ concentration, report Al levels in the diet, report the pH of the drinking water, record drinking water consumption and the absence of precautions to avoid sample contamination by environmental Al detract from the study. The relatively high serum Al levels in the control group suggest that external Al contamination may have occurred or that background serum Al levels were elevated due to the diet or other factors.

Li et al. (2011a) examined the influence of drinking water (pH 5.6) containing 100 mg/L AlCl₃•6H₂O (99% purity) on bone Al, Ca, and P content during growth of young rats. A concurrent control group was given distilled drinking water (pH 7.0) for the same 150 days under the same conditions. All rats had free access to water and standard pellet diet (no details regarding the Al content of the diet or the control drinking water were reported). The body weights of the Al-treated rats were significantly lower than the controls from Day 60 until Day 150. The serum pH of the Al-treated rats was reduced ($p < 0.05$) on Day 150. The mean Al content in femurs was significantly higher than the controls beginning at Day 30. Bone Ca and P concentrations were reduced significantly in the Al-treated group compared to the controls at Day 150. Li et al. (2011a) concluded that long-term ingestion of high Al concentrations in drinking water led to Al accumulation in bone, inhibition of bone formation, and bone loss in rats.

Li et al. (2011b) then conducted a follow-up investigation on the influence of 150-day consumption of 430 mg/L AlCl₃ in drinking water on Ca, P, and Mg during rat bone formation. Ten rats from each group were killed every 30 days and the Al content in right femurs was measured. The body weights in the Al-treated group were significantly less than the controls from Day 60. The mean Al content in bone increased significantly compared to the control on Days 30–150 and the Ca, Mg, and P levels were significantly lower in the Al-

treated group compared to the controls on Days 120–150. The results were similar to those reported by Li et al. (2011a) where a 100 mg/L AlCl_3 concentration in drinking water was also associated with reduced bone Ca, Mg, and P. Li et al. (2011b) suggested that prolonged consumption of AlCl_3 in drinking water increased Al levels in rat bone and inhibited bone mineralization through disruption of trace element metabolic pathways. The major limitations to the Li et al. (2011b) study are similar to those described for the Li et al. (2011a) study.

Hirayama et al. (2011) studied the influence of age on the endogenous or “background” concentrations of Al in rat femur. Groups of five female Wistar rats were reared from 4 weeks to 113 weeks on a laboratory stock diet and tap water. Elemental Al concentrations in the stock diet and in tap water were 60 mg/kg and 0.038 mg/L, respectively. Five rats were sacrificed at 5, 9, 13, 17, 21, 25, 33, 42, 50, 59, 68, 77, 85, 95, 105, and 113 weeks of age (4 rats at 113 weeks). The mean Al concentration in bone at 17 weeks was 0.31 $\mu\text{g/g}$ and for all ages the mean was 0.53 $\mu\text{g/g}$. Uptake rates of Al into bone varied among individual rats and the values were broadly distributed.

Unlike healthy humans where bone Al increases with age (Hellstrom et al. 2005, Priest 2004), accumulation of Al in rat bone is limited. The Hirayama et al. (2011) data are consistent with those of Slanina et al. (1984) who found little change in the Al content of adult rat bone even after daily oral dosing with 100 mg $\text{Al}(\text{OH})_3$ for nine weeks. Very young rats accumulate Al in bone, but older rats tend to accumulate Al in their kidneys (Greger and Radzanowski 1995). This response depends on exposure in that rats can accumulate sufficient Al in bone to elicit osteomalacia after repeated injections of very high Al doses (Goodman et al. 1984, Robertson et al. 1983).

In vitro—When transparent Al ceramic (Al_2O_3 and MgAl_2O_4) discs (99.7–99.8% pure) were incubated for five days with human fetal osteoblasts, cultures with MgAl_2O_4 discs had higher mitotic rates than cells cultured on Al_2O_3 discs. Other than these differences in proliferation there was no evidence of cytotoxicity associated with these Al ceramics (Bodhak et al. 2011).

Digestive tract

Lindquist et al. (2011) compared the effects of reduced fat milk (pH 6.6), tap water (pH 7.0), carbonated mineral water (pH 7.0), gum Arabic and 1.1 g of a commercial $\text{Al}(\text{OH})_3$ gastric antacid tablet on neutralization of 10 ml of dilute HCl (pH 1 or 2) in the mouths of 11 volunteers (33 ± 9.3 years). Volunteers used a series of two min oral rinses after each one min HCl rinse (to mimic the pH of acid reflux) and the acid: base balance in the mouth was followed for 30 min. There was no mention of irritation or other effects of any of the solutions, but overall the results with $\text{Al}(\text{OH})_3$ were consistent with those of Meurman et al. (1988) who found chewing an $\text{Al}(\text{OH})_3$ tablet was an effective means to combat dental softening and erosion due to chronic acid regurgitation.

Maghraoui and coworkers (2012) examined Al deposition in the gastric mucosa of rats. At two h after a single gastric intubation of $\text{Al}(\text{NO}_3)_3$ at 70 mg/kg, Al was retained in the

cytoplasm and lysosomes of the mucosal parietal cells similar to that seen in lysosomes of human gastric mucosal cells after ingestion of $\text{Al}(\text{OH})_3$ (Florent et al. 1991). There was no suggestion of histologic or ultrastructural damage to the liver or gastric mucosa after ingestion of either $\text{Al}(\text{NO}_3)_3$ or $\text{Al}(\text{OH})_3$.

Renal

Patients with compromised kidney function are at increased risk for systemic Al toxicity (Hou et al. 2010, Jenkins et al. 1989, Yokel 2012, 2013). Azik and associates (2011) compared circulating Al, P, Ca, and PTH concentrations in six girls and four boys diagnosed with urinary tract disease (reflux nephropathy, glomerulosclerosis, glomerulonephritis, and neurogenic bladder) to those parameters in 12 healthy girls and 8 boys. Of the 10 children who were in kidney disease stages 2–4, 3 were on peritoneal dialysis (mean = 44 months) and one was on HD (1 month). Mean circulating Al (27.2 $\mu\text{g}/\text{L}$) was significantly greater in those with renal disease than in the healthy referents (2.5 $\mu\text{g}/\text{L}$). Since PTH increases Al uptake by stimulating synthesis of 1, 25-DHC in the kidney, Azik et al. (2011) gave these children a four-week course of 1, 25-DHC at 15–45 ng/kg-day. Circulating Al declined promptly after dosing with 1, 25-DHC.

Mahieu et al. (2003) examined renal function in relation to histology and oxidative stress in rats given ip injections of Al lactate thrice/week at 5.7 mg/kg-day over 90 days. These injections failed to influence glomerular filtration or renal clearance. Repeated ip injections reduced GSH and GST and increased LPO in proximal tubule cells. These cells developed toxicity consistent with oxidative damage induced by Al^{+3} as seen in other studies (Bhaduria 2012, Kaneko et al. 2004, Viezeliene et al. 2011, 2012).

Hepatic

Signs of systemic Al intoxication are manifest in skeletal and neurological damage and microcytic anemia, but there are few data to suggest liver disease (e.g., fatty degeneration, apoptosis, necrosis) in humans as a result of either acute or chronic high-dose Al exposure (ATSDR 2008, Krewski et al. 2007, Willhite et al. 2012). Nevertheless, studies of the liver in Al-treated animals and of hepatocytes in vitro have provided valuable insights into ROS and apoptosis (reviewed in Percy et al. 2011, Mailloux et al. 2011).

Humans

Gatti et al. (2011) measured Al concentrations in maternal blood and in fetal liver and kidney (characterized as micro- and nano-scale particles) in eight aborted fetuses (21–23 weeks gestation) afflicted with spina bifida. Those concentrations were compared to Al from eight referent fetuses without defects of the neural tube. Aluminum concentrations in all maternal blood samples were less than the analytical limit of detection (data not shown). Aluminum concentrations were elevated significantly in the malformed fetuses. Routine pathology found no anomalies in the liver or kidney of any of the abortuses.

Laboratory animals

Alemmari et al. (2011) studied intravenous AlCl_3 at 1.5 mg/kg-day in newborn piglets (1978 ± 257 g) as a model of neonatal human PN. The dose given to piglets was substantially greater than the mean Al (15.2 ± 8.0 $\mu\text{g}/\text{kg}\cdot\text{day}$) received by 10 human neonates from PN solutions (Bohrer et al. 2010, Poole et al. 2008). This 1.5 mg/kg-day dose was 750x the maximum Al recommended for adults (2 mg/kg-day) by the ASCN/ASPEN (1991) and it was up to 300x higher than the 4–5 μg Al/kg-day dose recognized by US FDA (2013) above which Al accumulates and produces systemic toxicity (Fewtrell et al. 2009, Smith et al. 2007). Groups of four piglets each received AlCl_3 for one, two, three or four days or an equivalent volume of saline via an indwelling venous catheter. Although Alemmari et al. (2011) acknowledged the magnitude of their Al exposure compared to humans, the authors based their study design on Klein et al. (1987) who found elevated serum bile acids and increased hepatic lysosomes in piglets subjected to identical doses. Serial timed sacrifice was made and blood, urine, bile, and liver samples were collected in Al-free containers. Serum, urinary, and hepatic Al concentrations increased as duration of exposure increased. There was a direct correlation between total bile acids and urinary Al levels with hepatic Al concentrations. Transmission electron microscopy confirmed dilated bile caniculi, inflammatory infiltrate and increased numbers of Al-containing hepatic lysosomes.

In discussing these data Alemmari et al. (2012) stated that small-volume parenterals are the main Al source providing typical infant doses of 10–60 μg Al/kg-day. The authors noted that more than 80% of the Al in infant PN comes from Ca gluconate and that if an Al-free Ca gluconate was to be used daily infant Al exposures could be reduced 85%. Those estimates were confirmed in Yucatan miniature piglets given an Al-free 98% pure Ca gluconate PN solution that delivered 6 μg Al/kg-day compared to a standard PN that delivered 38 μg Al/kg-day (Alemmari et al. 2012). Neonatal injury induced by Al in PN solutions is a multifaceted medical issue (Wier and Kuhn 2012) involving Al-contaminated nutrients (soluble vitamins, lipid emulsions, trace elements, and amino acids) (Popinska et al. 2010), bags, burettes and syringes (de Oliveira et al. 2010), prematurity, duration of exposure, lack of enteral feeding and the need to sterilize PN solutions.

Other reports of Al-associated hepatotoxicity in animals are confounded by selection of the particular Al salt, route of administration and magnitude of the dose. After a single ip injection of 32.5 mg/kg $\text{Al}(\text{NO}_3)_3$, increased serum ALT and AST, reduced hepatic GSH and catalase activities and increased LPO were evident in the liver, kidneys, and brains of adult rats (Bhaduria 2012). In another example, gross necropsy of male gerbils after five day per week ip injections of 10.4 $\mu\text{mol}/\text{kg}$ (1.33 g/kg-day) of AlCl_3 found accumulations of “white deposits” on the surface of the liver, kidneys, mesentery and throughout the peritoneum (Garrosa et al. 2011). These accumulations were accompanied by peritoneal irritation, diffuse granulomas, focal hepatocellular degeneration, and periportal inflammation. Garrosa et al. (2011) compared their results to those of Fiejka et al. (1996) who found no signs of peritonitis after repeated 233–265 mg/kg-day ip injections of $\text{Al}(\text{OH})_3$ in Pzh:SFIS strain mice. Aluminum chloride is a potent irritant (Krewski et al. 2007) and the development of chronic peritonitis after repeated injections of neat AlCl_3 can be attributed to its hydrolysis product HCl (ATSDR 2008). Garrosa et al. (2011) qualified their experiment in that “the

particular properties of AlCl₃ solution, such as its lower pH, might account for the appearance of peritonitis, adhesions and portal inflammation, rather than the intrinsic toxic effect of Al³⁺.

Zhu et al. (2013) gave AlCl₃ in drinking water to rats at concentrations sufficient to deliver 0, 64.18, 128.36, or 256.72 mg/kg-day for 120 days. These exposures resulted in a dose-dependent increase in liver Al, reduced body weights, reduced liver: body weight ratios, decreased hepatic microsomal protein and reduced hepatic cytochrome P450 enzymes. As neither drinking water nor food consumption were measured and given that no concurrent controls given equimolar doses of HCl were included, it is difficult to determine whether the changes were due to the actions of ingested Al or were consequences of chronic dehydration/inanition associated with avoidance of acidic drinking water.

A number of laboratories identified Al-induced oxidative stress as a major or contributing factor to damage in the liver and other organs (reviewed in Krewski et al. 2007). In a series of studies by Viezeliene et al. (2011, 2012) concerning potential amelioration of Al—induced liver damage by selenite, BALB/C mice were given ip injections of 25 mg/kg AlCl₃ and 1.25 mg/kg Na₂SeO₃; selenite injection was made 20 min prior to administration of AlCl₃. At 16-h post-injection there was an increase in hepatic protein synthesis and serum ALT, but Na₂SeO₃ injection alone had no influence on ALT. When Na₂SeO₃ was given prior to AlCl₃ serum ALT was no different from that after AlCl₃ alone. Hepatic GSH was reduced significantly after AlCl₃, but when selenite was given prior to AlCl₃ the levels of oxidized glutathione (GSSG) and GSH in the liver were no different from the controls. Thus, parenteral Al reduced both hepatic GSH and the GSH/GSSG ratio. The authors interpreted these changes as indicative of Al-induced oxidative stress in mouse hepatocytes secondary to Al disruption of hepatocyte membranes and/or interference with PO₄ and ATP generation. Limitations to the Viezeliene et al. (2011, 2012) reports include the absence of dose-response descriptions and measures of Al and Se in blood or liver.

These observations of Al-induced oxidative stress were consistent with those made in liver (El-Demerdash 2004, González et al. 2007, Yousef 2004), testes (Guo et al. 2009), kidney (Kaneko et al. 2004), and brain (Chakrabarty et al. 2012, Gómez et al. 2005, Kaiser et al. 2005, Kumar et al. 2009a, 2009b, Savory et al. 1999). Mechanistic studies with ip AlCl₃ have also been conducted in adult male CF-1 mice by El-Sayed et al. (2011) and in BALB/c and C57BL/6 mice by Shati et al. (2011). Among mice given a single 25 mg/kg injection, there was a significant increase in serum ALT and TNF- α at 24 h; hepatic MDA and reduced catalase, GST, GPx and NADPH-quinone oxidoreductase were increased compared to saline controls. However, there was no change in overall hepatic glutathione levels. Pretreatment of identical mice with taurine at 100 mg/kg-day for five days abolished the reductions in hepatic catalase, GST and GPx and the authors speculated taurine acted by scavenging free radicals to prevent lipid peroxidation. The observations by Shati et al. (2010) are consistent with El-Sayed et al. (2011) in that repeated ip injection of AlCl₃ in saline (pH 6.8) at 40 mg/kg-day for 45 days increased serum ALT, AST, and bilirubin in both mouse strains. The liver damage was consistent with increased hepatic LPO and increased circulating triglycerides and total cholesterol.

In keeping with the Al metabolic disruptions articulated by Mailloux et al. (2011), Bhasin et al. (2012) examined the influence of supplemental Zn (given as ZnSO₄) on AlCl₃—induced hepatotoxicity in rats. Controls were given tap water *ad libitum* for 2 months; a second group was given AlCl₃ by oral gavage at 100 mg/kg-day; a third group was given drinking water sufficient to provide 1–2 mg Zn/kg-day and a fourth group was given Zn along with AlCl₃. Histologic study of the AlCl₃—treated rats found increased vacuolization of hepatocytes. Gavage with AlCl₃ increased cytosolic ALT and AST and reduced hepatic catalase and GST. Supplemental Zn restored catalase and GST activity to control levels. Catalase contains four porphyrin heme (Fe⁺³) groups and Bhasin et al. (2012) suggested (consistent with Mailloux et al. 2011) that the reduced catalase may be due to Al substitution for Fe or that Zn induction of metallothioneine acted as a free radical scavenger. However, no kinetic or other mechanistic studies on Al inhibition of catalase or GST were included, and no data on hepatic Al or Zn concentrations were provided.

Development and reproduction

Humans—The hazards associated with excessive Al in neonates and young children are well known (Bozynski et al. 1989, Chedid et al. 1991, Crisponi et al. 2011, Freundlich et al. 1985, 1986, 1990, IPCS 1997, Klein 1995, Klein et al. 1982, Klein and Coburn 1994). Historical Al concentrations in commercial PN solutions ranged from less than 50 to as high as 300 µg/L, but those levels declined over time (Arnold et al. 2003) primarily as a result of substitution of crystalline amino acids for casein hydrolysate. Calcium gluconate continues to be a source of Al contamination in PN solutions (Koo et al. 1986, Hernández-Sández et al. 2013), but elevated Al is also due to contaminated inorganic PO₄ and cysteine HCl (Hernández-Sández et al. 2013) and it leaches from glass containers during storage and autoclaving (Poole et al. 2011). Beaney and Smeaton (2010) reported 4925–6160 µg Al/L in commercial 10% Ca gluconate packaged in glass ampules for compounding PN injections compared to 30–33 µg Al/L when packaged in plastic.

Patients who receive repeated intravenous doses sufficient to supply higher than 4–5 µg Al/kg-day can accumulate sufficient body Al burdens so as to elicit encephalopathy, impaired neurologic development, and osteomalacia (Bates et al. 1985, Bishop et al. 1997, Klein 1995, Klein et al. 1991). Popinska et al. (2010) examined 24 patients on chronic PN (2–14.7 years) and found their Al intake was 5.8–29.6 µg/kg-day. United States regulations [21 CFR 201.323] intended to control Al concentrations in large volume parenterals (25 µg/L) were issued years ago (US FDA 1998, 2003), but there is currently no limit on the Al content of pharmacy bulk packages or small volume parenterals (US FDA 2013). Excessive iatrogenic Al exposure among neonates continues (Bishop et al. 1997, Bohrer et al. 2010, Fewtrell et al. 2009, 2011, Poole et al. 2008, 2011). Poole and associates (2008) examined records for 13,384 in-patient days for premature neonates, children with reduced renal function and children on prolonged PN. Using the Al content printed on the manufacturer's labels for PN constituents, Poole et al. (2008) calculated daily exposures for those with body weights less than 3 kg (who represented nearly 50% of all patients) at 30–60 µg Al/kg-day or 6–12x the recommended maximum 5 µg Al/kg-day. Compliance with the recommended maximum Al dose using standard PN solutions could be realized only in older children with body weights more than 50 kg. Poole et al. (2010) then compared empirical Al

concentrations in 40 different PN solutions and 16 different components used to formulate those products to the US FDA 25 µg/L limit on Al for large-volume parenterals. Using patient body weights to calculate daily Al exposure, the highest dose (23 µg Al/kg-day) was received by the smallest infants (< 1 kg). After comparing the Al content in PN solutions, the daily Al dose was 3–5x the US FDA (2013) maximum. Investigation of constituents used to formulate the PN solution found that Ca gluconate and the K and Na phosphates accounted for the majority of the Al present in hospital pharmacy-formulated PN solutions.

In a similar effort, Bohrer et al. (2010) studied 10 preterm hospitalized infants who received total PN over 5–10 days. The mean total Al dose given by infusion was 186 ± 106 µg (15 ± 8 µg/kg-day; range: 5–27 µg/kg-day). Only two of ten patients received Al at less than 5 µg/kg-day. Although the study was restricted to a small number of premature babies (32–36 weeks gestation), the daily Al exposure was such that a majority received thrice the maximum tolerable dose.

Fewtrell et al. (2009) followed the long-term consequences of Al exposure on bone in young people. Among 59 adolescents, 26 had received neonatal PN that provided 45 µg Al/kg-day and 33 were given 4.0–4.5 µg Al/kg-day. The origin of the elevated Al in these solutions was traced to Al leachate from glass bottles used to store Ca gluconate. Children afflicted with neurologic conditions or who had a prior Bailey score less than 85 were excluded from the study. Participants were matched for birth weights, gestation, and duration of intravenous nutrition. Dual-energy radiograph absorptiometry was used to measure bone mineral content (BMC), bone area (BA), and bone mineral density at the lumbar spine (LS), hips, and WB. Total neonatal Al exposure, as a continuous and categorical variable (< 55 µg/kg vs. > 55 µg/kg), was examined in relation with adolescent bone mass after adjusting for potential confounders including duration of PN and severity of neonatal illness.

Mean Al intake was significantly higher for those given the standard PN solution as compared with those given PN with low Al. The bone density measurements tended to be higher in the low Al group, but significant differences were observed only for BMC and BA at the LS (44.9 vs. 39.8 g and 40.5 vs. 37.8 cm², respectively). The increase in LS BMC may be attributable to increased bone size in the low Al group, as no difference between the groups in LS BMC was seen after adjusting for height, weight, and LS BA.

After adjusting for relevant neonatal variables in a nonrandomized analysis, total Al exposure as a continuous variable was not a significant predictor of adjusted BMC at any site. When Al exposure was categorized using the median (55 µg/kg) as a cut-off, children with high exposure had significantly lower (7.6%) hip BMC. Children who experienced higher Al exposure as neonates had significantly reduced lower hip BMC than children whose neonatal Al exposures were some ten-fold lower.

Fewtrell et al. (2011) expanded the presentation and explained the results from Bishop et al. (1997) wherein 227 premature (gestational age < 34 weeks) infants who received either standard PN (25 µg Al/dl) or reduced Al (2.2 µg/dl) PN (equivalent to daily Al of 19 ± 8 or 3 ± 1 µg/kg-day) beginning at postnatal day 2 or 3 that continued for a median 10 days. There were marked individual variations in the daily Al dose. For 157 of these infants (with no

signs of neuromotor delay at 18 months), their Al doses were associated with a one point per day decline on the Bayley Mental Development Index. Those declines were considered materially significant and children exposed to elevated Al in PN solutions were at increased risk for cognitive problems and educational difficulties. Of the 59 adolescents followed at 15 years of age, no consistent differences in academic achievement, memory, intelligence and ability to solve complex problems (e.g., planning and organizational behavior) could be detected. Fewtrell et al. (2011) noted the main limitation to their conclusion was the small number of children available for assessment.

Zeager and associates (2012) surveyed 23 clinical laboratories in the United States that measure Al in serum and urine and found these facilities use different criteria. The reference (“background”) concentrations used to compare different patients depended on whether the laboratory used atomic absorption or ICP-MS. When Zeager et al. (2012) attempted to align biological monitoring data with Al-induced pathology, they concluded “there is currently a lack of data to support a correlation between Al exposure doses, Al levels measured in biological samples and adverse clinical outcomes”. Krewski et al. (2007) described time lines for Al measures in plasma, serum and urine from non-exposed healthy individuals and in people who consume Al antacids, in people given PN and in occupational cohorts. Plasma collected from volunteers with no known Al exposure generally contains 2.7 µg/L (with an upper normal limit of ~6 µg/L), serum generally contains up to approximately 3 µg/L and urine generally contains approximately 1–9 µg/L. The Zeager et al. (2012) conclusion is not consistent with others who have used blood and urinary Al to monitor HD patients (Pei et al. 1992, 1995), Al welders and other industrial workers (DFG 2007, Riihimaki et al. 2008, Riihimaki and Aitio 2012).

Two studies (Yu and Zhang 2011, Huang et al. 2011) were identified that examined associations between environmental Al exposures and the risk of neural tube defects (NTDs). Yu and Zhang (2011) collected samples of soil, water, and food from an area with elevated congenital defects (study area) and from an area with lower rates. Regression analyses revealed a significant correlation between lower Al levels in surface and groundwater and elevated rates of certain birth defects. Huang et al. (2011) examined associations between Al in soil and NTD risk in an area that had the highest prevalence of NTDs in China. Aluminum concentrations were measured in soil from 112 villages and those values were matched with village records of birth defects. The association between NTDs and soil Al levels was evaluated using the maximum likelihood method. Huang et al. (2011) concluded that higher Al concentrations in soil were associated with increased NTD risk. However, no actual Al exposure data were presented and no efforts were made to quantify maternal folate status (Bower et al. 1993, Czeizel and Dudas 1992) or related genetic factors (e.g., defects in the gene for 5, 10-methylenetetrahydrofolate reductase, folate receptor- α) (Finnell et al. 1998, Ou et al. 1996, van der Put et al. 1995, Whitehead et al. 1995). Nevertheless, based on the results of controlled intervention studies (Czeizel and Dudas 1992, Wald 1993), Oakley (1993, 2002) concluded that up to 60% of all NTDs in China could be reduced with supplemental dietary folate. Given these deficiencies, the results of the Huang et al. (2011) study are not considered reliable.

Bell et al. (2010) conducted a county-wide ecological study wherein ambient air particulate matter (PM_{2.5}) exposures were calculated for mothers of 76,788 Connecticut and Massachusetts infants on a per week basis. The weekly exposures were extrapolated to total particulate exposure by trimester. The mothers were primarily Caucasian, married and had a mean age of 29.3 years; tobacco was used by not more than 13% and ethanol was used by not more than 1.8% of the mothers. Relative PM_{2.5} as Al was associated primarily with roadway dust, but the dust also contained Si, Ca, Fe, Mn, and Ti whereas regional ambient air PM_{2.5} also contained Na, S, V, Ni and chloride (due apparently to road salt). Linear regression was used to relate birth weight to PM_{2.5} total mass, sources and constituents and the results were presented as change in birth weight (grams) and increased risk of small-at-term birth per quartile range (IQR) by source, PM 2.5 and constituent. The mean ambient air Al concentration ($0.042 \pm 0.02 \mu\text{g}/\text{m}^3$) corresponded to an IQR of $0.03 (\mu\text{g}/\text{m}^3)$ and this was associated with an 11% increased risk (3–20%; 95% CI) for low birth weight. Strengths of the Bell et al. (2010) study stem from the large numbers of births and adjusting for gestational length, infant gender, prenatal care, maternal age, ethnicity, education, and tobacco and ethanol consumption during pregnancy. However, the protocol did not account for other constituents in ambient air (e.g., CO, NO, NO₂, NO_x, elemental carbon, and PM_{2.5} from motor vehicle exhaust) or for maternal conditions (e.g., low pre-pregnancy weight, anemia, antibiotics, cardiovascular disease, multiple offspring, and low socioeconomic status) that are associated with low birth weight (Wilhelm et al. 2012, Yu et al. 2013). Moreover, the chemical form of Al in the airborne dust was not identified and no personal sampling was conducted. Given the mixed exposures it is not possible to conclude that one or another individual constituent in roadway dust was responsible for the results.

Giaccio et al. (2011) measured semen volume, pH, sperm concentrations, sperm motility, total sperm counts, and sperm Al for 600 infertile men. No mention was made concerning tobacco and ethanol use among the subjects. There was no correlation between soil Al and reduced fertility among these men.

Laboratory animals—The reproductive and developmental toxicity of Al was examined by Hirata-Koizumi et al. (2011a) in a two-generation study with Al₂(SO₄)₃ (98.5%) administered to CrI:CD(SD) rats. A preliminary range-finding study was conducted with drinking water containing 0, 1000, 3000, 10,000, and 30,000 mg Al₂(SO₄)₃/L. Males were dosed for 7 weeks, beginning 14 days before mating, and females were dosed for 6–8 weeks beginning 14 days before mating and until PND 4. Administration of Al₂(SO₄)₃ reduced water consumption, reduced body weight gain and reduced food consumption at concentrations 3000 mg/L or higher. Among litters from dams given 10,000 mg/L Al₂(SO₄)₃ or higher there was a significant reduction in pup body weights on PND 4. The rats given 30,000 mg/L were euthanized within 2 weeks of initial exposure due to dehydration and marked reductions in body weight. Macroscopic examination found thickening of the limiting ridge in the stomach and atrophy of the thymus and spleen in rats given 10,000 mg/L. The relative liver, thymus, and spleen weights were reduced in females given 3000 or 10,000 mg/L.

Based on the preliminary results, the concentrations of Al₂(SO₄)₃ selected for the main study were 0, 120, 600, and 3000 mg/L (equivalent to total Al daily doses from food and

water of 1.62–2.35, 2.96–4.72, 8.06–14.0 and 31.2–55.6 mg Al/kg-day). The pH of the drinking water was 3.57–4.20. Twenty-four animals per sex and group (F0 generation) were given $\text{Al}_2(\text{SO}_4)_3$ in deionized drinking water beginning at 5 weeks of age for 10 weeks until mating, during mating, throughout gestation and lactation. The control animals received only deionized water under the same conditions. Drinking water provided to the F1 offspring contained the identical $\text{Al}_2(\text{SO}_4)_3$ concentrations as those of their parents. Endpoints included clinical signs, drinking water and food consumption, and body weights. Parameters recorded at parturition included the number of live and dead offspring, sex ratio and the numbers and types of gross malformations. The F1 and F2 pups were observed daily for clinical signs of toxicity, and the body weights of live pups were recorded. Developmental parameters included sex ratios, neonatal body weights, pinna unfolding, anogenital distance (AGD), incisor eruption, eye opening, surface righting reflex, negative geotaxis and mid-air righting reflex. In the F1 pups selected as parents, the males were observed for timing of preputial separation and the females were observed for timing of vaginal opening. Spontaneous locomotor activity was assessed at four weeks of age and at six weeks of age a water-filled multiple T-maze test was administered.

Reproductive success was evaluated based on copulation index (%), percentage of motile and progressively motile sperm, sperm swimming speed and pattern, sperm counts per gram epididymal tissue, the percentage of morphologically abnormal sperm, precoital interval, fertility index, gestation index, gestation length, delivery index, estrous cycle numbers of litters and numbers of pups. There were no clinical signs, but drinking water consumption was reduced significantly in all treated groups. Body weights and food consumption of the F0 males and females given 3000 mg/L were reduced significantly during the first few weeks of the study. No treatment-related changes were observed in the numbers of litters, numbers of pups delivered, sex ratios or viability on PND 0, 4, and 21. Gross examination found no differences in the incidence of malformations in either the F1 or F2 generations.

There were no significant treatment-related effects on age at completion of pinna unfolding, age at incisor eruption, eye opening, or AGD in the F1 and F2 male pups and in the F1 female pups. In the female F2 pups, the completion time of pinna unfolding on PND 2 was delayed in those given 600 mg/L. There were no treatment-related differences in the time to F1 preputial separation and there were no significant differences in righting reflex (PND 5), negative geotaxis reflex (PND 8), or mid-air righting reflex (PND 18). In the F1 females vaginal opening was delayed in those given 3000 mg/L (31.4 ± 1.7 days vs. 29.5 ± 2.1 days in the concurrent controls). At the time of vaginal opening, the body weight “was slightly heavier than the control” (119.0 ± 13.3 g vs. 109.6 ± 11.6 g) in the 3000 mg/L group. No significant differences were observed in male and female F1 rats regarding spontaneous locomotor activity or in their performance on the water-filled T-maze test.

Ingestion of $\text{Al}_2(\text{SO}_4)_3$ failed to influence the oestrus cycle in either the F0 or F1 generation. Following the F0/F1 or F1/F2 matings there were no significant differences in copulation, fertility index, gestation index, precoital interval, gestation length, numbers of implantations, pups delivered or delivery index (i.e., number of pups/number of implantations). There were no significant differences regarding sperm parameters with the exception of a reduction in the absolute number of sperm in the F0 males given 3000 mg/L, but this change was not

significant when expressed as per gram of tissue. Necropsy of the F0 and F1 parents found no treatment-related lesions or alterations in the reproductive organs. The results provide no evidence for adverse effects of daily $\text{Al}_2(\text{SO}_4)_3$ ingestion on ovarian or testicular function in CrI:CD(SD) rats.

Despite the lower relative liver and spleen weights in the F1 males, examination of the F1 and F2 weanlings showed no treatment-related histopathology in the liver or spleen. The primary changes observed in rats consuming 3000 mg/L $\text{Al}_2(\text{SO}_4)_3$ were the reductions in pup body weight on PND21 (F1 males and females and F2 females) and a slight delay in vaginal opening (F1 females). However, interpretation of developmental landmarks is difficult due to treatment-related reductions in drinking water and food consumption. Hirata-Koizumi et al. (2011a) found it was not possible to separate the effects of the reduced drinking water consumption and dehydration from the possible influence of Al on offspring body weight. Hirata-Koizumi et al. (2011a) assigned a conservative LOAEL for parental systemic toxicity and reproductive/developmental toxicity of 3000 mg/L (31.2 mg Al/kg bw/day or 188 mg $\text{Al}_2(\text{SO}_4)_3$ /kg bw/day) and identified a NOAEL of 600 mg/L (8.06 mg Al/kg bw/day or 41.0 mg $\text{Al}_2(\text{SO}_4)_3$ /kg bw/day). Grip strength was not measured, precluding comparisons with previous studies that found significant alterations in forelimb and hindlimb grip strength in rodents born to Al-treated dams (reviewed in ATSDR 2008).

The reproductive and developmental toxicity of ingested Al was also examined by Hirata-Koizumi et al. (2011b) in a two-generation reproductive toxicity study of Al ammonium sulfate [$\text{NH}_4\text{Al}(\text{SO}_4)_2$, 99.5%] administered to CrI:CD(SD) rats in drinking water. The study design complied with OECD TG 416. A preliminary range finding study was conducted with deionized drinking water containing $\text{NH}_4\text{Al}(\text{SO}_4)_2$ (AAS) at 0, 300, 1000, 3000, or 10,000 mg/L. Administration of AAS reduced water consumption in all groups and at concentrations 3000 mg/L or higher water avoidance was associated with reduced body weights. Gross necropsy found thickening of the gastric limiting ridge at 10,000 mg/L, but there were no changes in any reproductive or developmental parameter. Based on the results of the preliminary study, the AAS concentrations for the definitive study were 0, 50, 500, and 5000 mg/L (equivalent to total Al daily doses from food and water of 1.56–2.39, 1.98–3.10, 5.35–9.36, and 36.3–61.1 mg Al/kg-day). The pH of the drinking water was not specified. The study design and parameters measured were the same as those described for Hirata-Koizumi et al. (2011a).

No treatment-related deaths or clinical signs of toxicity were observed. Water consumption among treated rats was reduced in males and females of both generations in a concentration-dependent manner. In the F1 males and females given 5000 mg/L, body weights were reduced during the first 1–2 weeks of treatment. Food consumption was reduced among the F0 females of the 500 and 5000 mg/L groups during the first week of treatment and during the second and third weeks of lactation in both F0 and F1 dams given 5000 mg/L.

There were no treatment-related differences in the numbers of implantations, delivery index, incidence of malformations, sex ratio, or viability index. No gross abnormalities were found and there were no differences in birth weights. Reduced body weights were noted among the F1 offspring at 5000 mg/L, but no such change was seen at the lower concentrations. There

were no treatment-related effects on pinna unfolding, incisor eruption, eye opening, or AGD. There were no differences in age at preputial separation, but a significant delay in vaginal opening was evident in the F1 females given 5000 mg/L (32.3 ± 1.8 days vs. 30.2 ± 2.1 days in controls). There were no changes in estrous cyclicity or weight or histology of the weanling and adult reproductive organs among rats given 5000 mg/L. There were no significant differences in surface righting response times or negative geotaxis reflex. There were no consistent differences in behavioral parameters by gender, generation, or dose. No treatment-related changes were detected on the water-filled T-maze or in spontaneous locomotor activity.

No treatment-related gross lesions were found. Changes in body weights and in absolute and/or relative seminal vesicle, epididymis, testis, ovary, uterus, kidney, adrenal, liver, thymus, brain and pituitary weights were observed at 500 and 5000 mg/L, but there were no dose-response relations. Hirata-Koizumi et al. (2011b) considered these findings secondary to the reduced body weights and attributed the reductions in growth and development of the offspring to “the astringent taste of AAS which would decrease the palatability of drinking water in the AAS-treated groups”. There were no treatment-related histologic changes in the male or female reproductive organs.

Hirata-Koizumi et al. (2011b) identified a LOAEL of 5000 mg/L for AAS-induced parental toxicity and developmental toxicity based on the reduced body weight gains and delayed sexual development in the F1 females. The LOAEL corresponds to 305 mg $\text{NH}_4\text{Al}(\text{SO}_4)_2/\text{kg-day}$ or 36.3 mg Al/kg-day. The NOAEL corresponds to 33.5 mg $\text{NH}_4\text{Al}(\text{SO}_4)_2/\text{kg-day}$ or 5.35 mg Al/kg bw per day. However, due to the clear treatment-related reductions in drinking water consumption taken together with the decreased food consumption by the F0 and F1 dams during the later stages of lactation, it is difficult to determine whether reduced growth was a direct effect of Al or whether reduced growth was due to dehydration, inanition, and/or decreased nursing by dehydrated dams. The strengths and limitations of the Hirata-Koizumi et al. (2011b) study are similar to those noted for Hirata-Koizumi et al. (2011a). Grip strength was not measured in this study, which limits comparison of the results with other studies that reported changes in neuromuscular parameters (ATSDR 2008).

Poirier et al. (2011) conducted a combined developmental toxicity/chronic toxicity study with Al citrate in deionized drinking water (pH 6–7) administered to Sprague-Dawley rats using a design based on OECD TG 426. Doses were selected based on the results of a 90-day pilot drinking water study and the highest concentration was based on the maximum solubility of Al citrate in water. The study design included groups given deionized water, Na citrate in deionized water or Al citrate (equivalent to 30, 100, or 300 mg Al/kg-day). Fresh solutions were prepared each week and the Al concentrations in water were verified by independent ICP-MS. The study covered continuous exposure from 6 days post-conception until one year after birth. Behavioral endpoints (motor activity, T-maze, auditory startle, a FOB targeting autonomic, and sensimotor function and physical activity, neuromuscular and physiological function and cognition as measured on the Morris swim maze), brain weights, clinical chemistry, hematology, neuropathology, and Al concentrations in blood, liver, femur, brain cortex, cerebellum, brainstem, and cervical and thoracic spinal cord were measured.

Whole blood Al concentrations in the water controls, the Na citrate controls and the low-dose Al citrate males and females were similar. By Day 23 of Al citrate exposure the highest Al concentration was present in whole blood (800 µg/ml) and Al concentrations declined as blood > brainstem > femur ~ thoracic and cervical spinal cord > cerebellum > liver > cerebral cortex. The high-dose Al citrate rats developed a low-grade microcytic anemia (reduced hematocrit, mean cell hemoglobin, and mean cell volume) and elevated serum alkaline phosphatase. The most notable observation was hydronephrosis. Several animals developed distended abdomens, only to become hypothermic and die (due to apparent hyperkalemia). Morbidity was elevated among the high-dose Al citrate males and the survivors were euthanized on study day 98.

Body weights of Na citrate-treated male and female offspring were depressed compared to the low- and mid-dose Al citrate groups; pup development (measured as time to vaginal opening and preputial separation) was delayed in the Na citrate-treated group compared to those given deionized drinking water, but the developmental delay was longer in those given the highest Al citrate concentration. Treatment of identical rats with Na citrate alone reduced pre-weaning body weights in both sexes and there were consistent reductions in post-weaning body weights among the female pups. Poirier et al. (2011) considered the delayed sexual development treatment-related, but whether the effect was secondary to growth retardation as evidenced by reduced body weight is not clear. Drinking water consumption was greater among those given Na citrate alone, but this could be due to the elevated Na content of the drinking water as contrast to the citrate concentration since circulating Na was elevated.

The highest dose (300 mg/kg-day) exceeded the maximum tolerated dose in that at PND 84 pup mean body weights were 30% less than control. At 100 mg/kg-day, Poirier et al. (2011) found no adverse effects of ingested Al citrate on memory or learning, but stated that neuromuscular functions (hind limb grip strength and foot splay) were impaired in the mid- and high-dose Al citrate groups. There was no significant difference in any FOB parameter for neonatal males or females. Poirier et al. (2011) assigned a LOAEL of 100 mg Al/kg-day and a NOAEL of 30 mg Al/kg-day based on deficits in grip strength and foot splay in the mid-dose group. Poirier et al. (2011) qualified their conclusion in that “the high dose of Al citrate is therefore considered to have had an adverse effect on body weights of male pups” and that “Al may affect neuromuscular performance in a dose-dependent manner, either primarily or secondarily to its effects on body weight in the mid- to high-dose groups.” While the authors considered delayed development related to ingested Al, this delay also occurred in the reference citrate group without Al exposure and this speaks to a relation between high citrate consumption and delayed development. Aluminum concentrations among the high-dose rats were increased in the cerebral cortex, cerebellum, brainstem, and thoracic spinal cord, but whether the changes in hind limb grip strength and foot splay were the result of Al accumulation in those tissues or were secondary to reductions in body weight is not clear. The high citrate concentration in the Al-treated groups and the similar delays in sexual maturity in the Na citrate-treated rats “due to alterations in water and/or food consumption” cloud the contribution of Al to the changes reported.

Prenatal and perinatal toxicity studies—Erazi et al. (2011) evaluated the effects of AlCl_3 administration in drinking water at 0 or 0.3% (3000 mg/L) among four groups of five male and female Wistar rats in two separate protocols. In the first study, rats were given AlCl_3 beginning at 3 months of age and this continued for 4 months. In the second study, maternal rats were given AlCl_3 from mating through gestation, parturition and lactation. Newborns were not treated directly. After weaning the offspring were given AlCl_3 in their drinking water until 3 months of age. The authors measured tyrosine hydroxylase (TH) immunoreactive neurons using a TH-specific antibody at four months of age. Prenatal, lactational, and perinatal exposure of rats to AlCl_3 reduced the numbers of TH reactive neurons within the substantia nigra, reduced immunostaining in the substantia nigra and reduced locomotor activity in the offspring. Erazi et al. (2011) suggested that Al-associated changes in neurologic parameters were more pronounced in rats exposed to AlCl_3 from conception to maturity compared to rats given AlCl_3 as adults.

The Erazi et al. (2011) report cannot be relied upon due to limitations in experimental design and conduct: the authors failed to account for the physical condition of their rats as neither body weights nor food or drinking water consumption were recorded and there were no measures of the pH of the AlCl_3 solution. High AlCl_3 concentrations result in acidic drinking water of low palatability, leading to dehydration, inanition, reduced body weight gain, and poor nursing. Since only a single concentration was examined it is not possible to determine dose-response. The study design included neither pair-fed controls given equivalent volumes of drinking water nor controls given equimolar HCl in their drinking water. The very small numbers of rats per group (20 litters/dose group are normally required) compromise the study. No effort was made to quantify either circulating or tissue Al. Failure to document maternal and offspring body weights and to measure drinking water and food consumption leaves open the possibility that changes in TH immunoreactive neurons were due to impaired health of these animals as contrast to an Al-specific effect. The reported reduced spontaneous locomotor activity among rats given AlCl_3 in their drinking water is not consistent with Hirata-Koizumi et al. (2011a) who found no such changes in male and female CrI:CD(SD) rats given drinking water with 3000 mg/L $\text{Al}_2(\text{SO}_4)_3$ (up to 338 mg/kg-day) from conception until four weeks of age.

Abu-Taweel et al. (2011a) investigated neurobehavioral changes after AlCl_3 was given in drinking water to pregnant Swiss-Webster mice. Mated females were provided tap water or 300 or 600 mg/L AlCl_3 in tap water *ad libitum* from gestation day 1 through PND 15. Significant concentration-dependent reductions in postnatal body weight gain, locomotor activity, learning ability, and cognitive performance were reported. Delays in eye opening, hair growth and sensory motor reflex were also reported. Significant concentration-related reductions in dopamine and serotonin were observed in homogenized forebrain (including hippocampus and cerebral cortex) from PND 7 until PND 36. The authors suggested that prenatal and lactational exposure to high Al levels can cause developmental toxicity in mice. The pH of the AlCl_3 -treated drinking water was not specified and drinking water consumption was not measured; the authors acknowledged: "It is likely that the present high concentrations of Al used in the drinking water might have affected total fluid intake due to its astringent properties, but no efforts were made to assess any such differences in total fluid

intake specifically.” Abu-Taweel et al. (2011a) assumed based on rat (Yumoto et al. 2001, 2003) and rabbit (Yokel and McNamara 1985) data that Al administered to the mother was passed to the pups via milk, but there were no significant changes in the reflexes of Al-treated pups compared to the controls at the end of lactation. The authors suggested body weight, learning and memory declined in the post-weaning period, but given the astringent properties of high-concentration AlCl_3 in drinking water it is possible avoidance of the water and dehydration may have contributed to the reported changes.

Moselhy et al. (2011) investigated changes in rat testes after 34 mg/kg AlCl_3 was given (apparently by daily gavage) to 45 sexually mature Wistar rats for 60 days. Five rats from each group were sacrificed on Days 30, 45, and 60 of treatment. No significant changes were observed in testis, epididymis, prostate gland, and seminal vesicle weights compared with the controls. Significant reductions in serum testosterone were seen in the treated rats at 30, 45, and 60 days of exposure. Testicular MDA levels were increased 163% after 60 days and sperm motility was reduced significantly at 30, 45, and 60 days. The percentages of live spermatozoa were reduced and the numbers of total sperm abnormalities increased 304, 211, and 283% compared to the controls at 30, 45, and 60 days.

Histological examination of the AlCl_3 -treated rats revealed degeneration of spermatogenic cells with exfoliation into the lumen “arrows” at 30 days. At 45 days those changes progressed to thinning and disorganization of the seminiferous germinal epithelium. By 60 days degeneration and necrosis of spermatogenic cells were abundant. No differences were seen in the epididymis between the treated and control groups at 30 days post-exposure, but Moselhy et al. (2011) noted desquamation and vacuolation of some epithelial cells along with diminished amounts of intraluminal sperm at 45 days. By 60 days the damage progressed to the point of complete lack or only very few sperm in the epididymal lumen. No significant histological changes were seen in the prostate at 30 days post-exposure, but by 45 days the size of the prostatic acini without intra-luminal secretions was reduced. By 60 days the epithelium became thin with multiple calcified intraluminal deposits. Limitations of the Moselhy et al. (2011) study include failure to justify the dose, study of only a single dose level and absence of information on clinical signs, body weights or food and drinking water consumption. There was no mention of the pH of the AlCl_3 solution. Thirunavukkarasu et al. (2010) described damage in the seminiferous tubules and vascular degeneration in the spermatogenic epithelium and Sertoli cells of rats given AlCl_3 at 100 mg AlCl_3 /kg-day by gavage for 90 days. The strain, age, and numbers of rats were not provided. The strength of the study rests with the subchronic duration of exposure, but there was no effort made to study the reproductive performance of these rats and the single dose level precludes dose-response. Limited details on body weight and food and water consumption as indicative of general health of these rats limit interpretation of the Thirunavukkarasu et al. (2010) report. Given the absence of testicular toxicity seen in the guideline-compliant Hirata-Koizumi et al. (2011a, 2011b) repeated oral (2–8x higher Al) dose studies with $\text{Al}_2(\text{SO}_4)_3$ and AAS in rats, confidence in the Moselhy et al. (2011) and Thirunavukkarasu et al. (2010) conclusions is reduced.

Wang et al. (2012a) gave 40 female Wistar (5 weeks old) rats free access to drinking water with AlCl_3 to provide 0, 64.18, 128.36, or 256.72 mg AlCl_3 /kg-day for 120 days. These

doses were extrapolated based on generic mean water consumption for a 100 g rat whereas rats that survived to 120 days weighed 250–300g. Serum and ovarian Al concentrations, estrogen (E2), progesterone (P), testosterone (T), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) were measured at termination. There were significant concentration-related reductions in body weight among the treated groups beginning on Day 30 and these decrements became more pronounced by Day 120. The authors reported E(2), P, FSH, and LH were reduced, that serum and ovarian Al concentrations were increased in all Al-treated groups and that ovarian Al concentrations were greater than those in serum. Testosterone concentrations were significantly higher in the low- and medium-dose groups, but not in the high-dose group compared with controls. Wang et al. (2012a) gave no information on pH of the AlCl₃ drinking water and food and water consumption was not measured. No studies of fertility or reproductive performance of the AlCl₃-treated rats were included. Wang et al. (2012a) also reported changes in reproductive hormones of AlCl₃-treated female rats, but those conclusions failed to account for avoidance of acidic drinking water leading to possible dehydration and inanition as contributors to the reductions in body weight gain and hormonal disruptions.

This same laboratory gave 40 young male Wistar rats AlCl₃ at 0, 64, 128, or 257 mg/kg-day in drinking water *ad libitum* for 120 days. Circulating levels of T and LH in the mid- and high-dose groups were significantly lower than in controls, but no significant changes in FSH were detected. Androgen receptor (AR) protein expression and the levels of AR mRNA expression in mid- and high-dose groups were reduced. A positive dose–response relation was evident between AlCl₃ exposure and AR protein expression. Sun et al. (2011b) considered their serum T results consistent with those of Reza and Palan (2006) and Guo et al. (2001, 2005) who treated male rats and male mice, respectively, with daily ip AlCl₃ injections at up to 175 mg/kg-day for 20 or 12–16 days. Sun et al. (2011b) gave no measures of drinking water consumption so it is difficult to determine how the Al doses were determined. No pair-fed controls, concurrent control HCl group, drinking water pH or body weight data were included. Sun et al. (2011b) did not evaluate reproductive performance or success of AlCl₃-treated rats. The limitations to the Sun et al. (2011b) report are similar to those in the Wang et al. (2012a) report. In the absence of Al blood and tissue data, it is difficult to relate results with repeated high-dose AlCl₃ injections in rodents compared to the far lower environmental Al exposures experienced by humans.

Overall, the non-guideline studies provide limited details on test material, study design, and exposure conditions (e.g., the actual doses cannot be established). Common features include failure to account for or control the astringent properties of the acidic Al salts in relation to drinking water consumption and failure to account for dehydration and reduced body weights in relation to the parameters examined. Other than the iatrogenic skeletal toxicity induced by excessive Al in neonates (Bohrer et al. 2010) and impaired neurological development in premature infants given standard PN solutions with elevated Al (Bishop et al. 1997), a direct causative role of Al in production of adverse effects on reproduction and development has not been demonstrated. It is noteworthy the (variable) reductions in grip strength seen in offspring of Al maltolate-treated mice (Golub et al. 2000) were consistent with the reductions in grip strength seen in the offspring of Al citrate-treated rats (Poirier et al. 2011).

Endocrine

Following up on a 1989 report concerning 21 Al workers with reduced circulating thyrotropin (TSH) and prolactin at 12–18 months after initial employment (that subsequently resolved; Alessio et al. 1989), Orihuela (2011) gave 7 mg Al/kg-day as Al lactate in saline by ip injection to adult male Wistar rats for 6 weeks. Serum concentrations of TSH, triiodothyronine (T3), thyroxine (T4), and Al were measured along with thyroid Al and ^{125}I uptake. Among the Al-injected rats mean serum Al increased 4500x compared to the saline-injected controls and there was a significant increase in mean thyroid Al and thyroid gland LPO. There was no influence of repeated daily Al lactate injections on circulating TSH or T4. Thyroid ^{125}I uptake was diminished in treated rats at 25 h after Al injection compared to that in controls, but by 50–100 h ^{125}I uptake was no different between the two groups. No justification of dose, route or duration of exposure was offered and only a single dose level was examined, precluding dose-response or identification of a NOAEL. Regardless, the authors stated: “We can conclude that in adult rats the Al would not act as a thyroid disruptor.”

Contini et al. (2011) compared the effects of repeated (3/week for 12 weeks) ip doses of Al lactate (5.75 mg Al/kg at each injection) in 8-week-old intact and ovariectomized Wistar rats. There were no differences in food or drinking water consumption, serum E_2 or estrous cycles for the intact rats and none of the animals showed clinical signs of Al intoxication (other than body weight reductions in ovariectomized rats who remained in permanent diestrus). Among the Al-injected rats, serum, renal, and hepatic Al increased 150-, 19- and 30-fold, respectively. There was no influence of repeated Al injections on serum Na or K concentrations despite the fact that both intact and ovariectomized Al-treated rats had significantly higher serum aldosterone levels than rats that remained untreated. There were no differences in serum osmolality, urinary K excretion, or glomerular filtration rates between the groups. Consistent with reports by Bhadauria (2012), El-Demerdash (2004), González et al. (2007), Kaneko et al. (2004), Mahieu et al. (2003), Prabhakar et al. (2011) and Yousef (2004), Contini et al. (2011) found that hepatic LPO increased and catalase activity declined in the livers and kidneys of Al-injected rats compared to the untreated controls.

Citing the report by Alessio et al. (1989) and describing reductions in prolactin after high Al exposures in lambs, rats and mice, Calejo et al. (2010) cultured AlCl_3 at 300 nM–3 mM with primary lactotrophic cells isolated from the anterior pituitary of male Wistar rats for 1–4 days. The highest concentration tested represented the limit of AlCl_3 solubility in culture media. After incubation with up to 3 μM AlCl_3 , there was no influence on cell viability. Identical culture with 300 μM or 3 mM caused cell death within 30 min. Calejo et al. (2010) noted their data were consistent with the apoptotic cell death in cultured human lymphocytes treated with 25 mg/L AlCl_3 (Banasik et al. 2005) and deformation of human erythrocytes treated with 10–100 μM AlCl_3 (Niemoeller et al. 2006), but none of these studies accounted for the influence of elevated HCl on cultured cells.

Calejo et al. (2011) followed up their earlier work by observing 14–46% reductions in prolactin secreted from cultured Wistar rat pituitary lactotroph cells exposed for 24 h to a

sub-lethal 30 μM AlCl_3 concentration. This reduction was associated with reduced exocytosis as a result of reduced membrane capacitance, perhaps related to reductions in the diameter of the fusion pore size. Calejo et al. (2011) suggested the spectrum of clinical signs seen in chronic Al intoxication include prolactin depletion, but other than the one report of a transient change in prolactin among Al workers (Alessio et al. 1989), no confirmation of that possible connection could be located. As with their previous study, Calejo et al. (2011) failed to report media pH or include concurrent HCl controls.

Skin

Controversy continues over whether Al in cosmetics and personal care products presents health risks (AFSSAPS 2011). While case reports cannot be utilized to assess quantitative health risk, those observations when aggregated can provide insights for more formal investigation. No guideline-compliant studies in animals were located that reported dermal reactions after acute or short-term repeated topical exposure to Al compounds. Clinical trials, recent case reports and in vitro assays support Al dermal irritation after application of Al-containing deodorants. This local irritation is usually mild, sensitization is rare and only a small fraction of the Al applied to intact healthy skin is available for uptake.

Swaile et al. (2012) described use of a 6.5% AlCl_3 solution in anhydrous ethanol to treat profuse underarm perspiration. This solution acts by diffusion into the eccrine sweat gland where reactions with OH^- , lactic acid, and protein generate $\text{Al}(\text{OH})_3$ that blocks sweat movement to the skin surface. At the same time, HCl liberated from AlCl_3 can cause local irritation, pain, and erythema. When 35 healthy males were treated with AlCl_3 or a commercial underarm deodorant with Al zirconium trichlorohydrate glycine using a randomized block (paired comparison) design, about 10% developed irritation by Day 7 and Day 10, 20% had objective skin irritation.

Consistent with observations that Al^{+3} binds structurally diverse anions, including histidine and hydroxyl-containing amino acids (Rezabal et al. 2007), polypeptides (Hollender et al. 2006, Zuo et al. 2005) and protein (Bhasin et al. 2012, Tomljenovic 2011), Swaile et al. (2012) noted that men with unshaven axillae experienced less local irritation than those with shaved skin because Al^{+3} bound to underarm hair. Streker et al. (2010) found that among 20 patients (26.9 ± 4.3 years) with excessive idiopathic axillary hyperhidrosis who used a commercial under-arm deodorant each day for 42 days, six experienced local skin irritation. Based on the incidence and nature of the response, the authors concluded that daily application of an AlCl_3 antiperspirant was “an effective, safe and inexpensive treatment” for idiopathic hyperhidrosis.

Garg et al. (2010) described the case of a 28-year-old woman who presented at the hospital with eczema in both axillae. The patient complained that her condition occurred after the use of deodorants that contained ACH. Patch testing was performed to the British Contact Dermatitis Society baseline series, in addition to a fragrance series and AlCl_3 . The results were scored according to International Contact Dermatitis Research Group criteria. This patient responded with a 3 + reaction to 2% AlCl_3 (in petrolatum), but there was no skin

reaction after contact with an 8-mm Aluminum Finn Chamber[®]. After she avoided all Al-containing deodorants, her eczema cleared completely.

Watson et al. (2012) evaluated whether the use of Al-based antiperspirants while receiving external beam radiotherapy for Stage 0, I, or II breast cancer could exacerbate local irritation to damaged axilla skin. A total 198 participants were randomized to either the antiperspirant or a standard care-wash only control group. The skin reactions in both groups were measured weekly and at two weeks after cessation of treatment using the National Cancer Institute Common Toxicity Criteria Adverse Events (version 3) criteria. No significant differences were observed between the antiperspirant group and the control group.

Wooley-Lloyd and Valins (2009) (as described in Yanagishita et al. 2011) investigated topical exposure to Al chloride hexahydrate in a salicylic acid gel for treatment of hyperhidrosis. Local irritation with transient itching was evident after repeated gel application, but it should be noted that topical antiperspirants contain not only Al salts, but other active non-ionic and ionic agents (Quatralé 1985). As such, the Yanagishita et al. (2012) observations did not quantify the irritant potential of Al constituents present in commercial underarm deodorants.

Immunology and vaccine adjuvants

Aluminum adjuvants (often the oxyhydroxide and/or phosphate) are included in vaccines to enhance and extend the immune response (Exley et al. 2010, Kool et al. 2011). After Al adjuvant injection, Al-containing particles are taken up via phagocytosis by an antigen-presenting cell. These actions increase the immune response by delivery of antigen to T-cells in the lymph nodes (Rimaniol et al. 2004, Sokolovska et al. 2007). Immunopotentiality was originally attributed to the formation of a depot of antigen at the inoculation site (Glenny et al. 1926) suggesting it provided prolonged exposure of the antigen to the immune system resulting in higher antibody titers than antigen alone; adsorption of the antigen with the Al adjuvant has been regarded as essential to this mechanism (Gupta 1998). However, a direct correlation between the persistence of antigen at the inoculation site and the resulting antibody response has never been demonstrated (Hutchison et al. 2012).

Noe et al. (2010) studied the relation between depot formation and immunopotentiality by comparing the retention of antigen at the inoculation site with antibody production in rats. A labeled alpha casein (IDCAS) antigen was adsorbed onto either Al(OH)₃ or AlPO₄ adjuvant, or onto a non-adsorbed IDCAS with phosphate-treated AlPO₄ (PTAP). The response after inoculation of those preparations was compared with that after injection of an adjuvant-free IDCAS solution. The final Al concentration in all of these formulations was 1.7 mg/ml. When incubated with human plasma in vitro, approximately 90% of the IDCAS eluted from AlPO₄ within 24 h while only 25% of the IDCAS eluted from Al(OH)₃ at 72 h. Those results suggested that antigen adsorption was higher with Al(OH)₃ than with AlPO₄. Antigen retention at the inoculation site was Al(OH)₃ > AlPO₄ > non-adsorbed with PTAP. Adsorption with PTAP was equivalent to that seen with the adjuvant-free IDCAS solution. However, the AlPO₄-adsorbed IDCAS produced a significantly higher antibody titer in rats than did the Al(OH)₃-adsorbed IDCAS. Antibody titers declined as: non-adsorbed PTAP =

AlPO₄ adsorbed > Al(OH)₃ adsorbed solution. These data were consistent with Hansen et al. (2007, 2009) and Egan et al. (2009) who found that tight antigen binding to an Al-adjuvant inhibited antibody production by interfering with antigen processing in dendritic cells (DCs), resulting in reduced T-cell activation. Tight antigen binding may also reduce B-cell activation by reducing the amount of antigen available for B-cell recognition in the draining lymph node (Hansen et al. 2007). Noe et al. (2010) confirmed the concept that Al adjuvants are necessary for immunopotentiality, but that a “depot mechanism” was not supported by their results.

Following a similar line of inquiry De Veer et al. (2010) measured uptake of particulate antigen from an intradermal injection in sheep by lymphocytes in the presence or absence of 50 mg Al adjuvant (Rehydrigel). De Veer et al. (2010) concluded that the Al adjuvanticity failed to correlate with slow antigen release, but that it correlated with retention of antigen at the injection site and Al increased uptake of particulate antigen by mature migratory DCs. Wagner et al. (2012) compared the immunogenicity of anthrax vaccine in CD-1 mice immunized once by ip injection of fresh Al hydrogel formulations to the same formulations stored at 25° or 37° C for 3 weeks. Mice immunized with freshly prepared Al formulations developed significantly higher antibody titers compared to mice immunized with stored formulations. This difference might reflect the relative stability of Al adsorption over time or the influence of storage conditions on the vaccine itself.

Mechanisms of Al adjuvant actions—Although Al compounds have been used as human vaccine adjuvants for many decades, their mechanism of action is not completely understood. The influence of physico-chemical parameters on both the antigens and Al adjuvants and the associated immune response have only recently been investigated (Clapp et al. 2011). Early studies by Goto et al. (1997) and Naim et al. (1997) concluded that adjuvanticity of Al correlated with inflammation produced at the inoculation site. These inflammation-related pathways include: recruitment of phagocytic cells (including DCs) to the inoculation site (Guyton and Hall 2000), increased antigen uptake by DCs (Morefield et al. 2005), activation and maturation of DCs and macrophages (Kool et al. 2008a, Sokolovska et al. 2007), and release of DC cytokines (Kool et al. 2008a). Recent in vitro studies demonstrated direct activation by Al of the NLRP3 (also known as Nalp3 or cryopyrin) inflammasome complex leading to the processing of several pro-inflammatory cytokines including IL-1 β (Eisenbarth et al. 2008, Li et al. 2008). Some authors have pointed to indirect inflammasome activation via Al-induced release of uric acid crystals (Kool et al. 2008b, Lambrecht et al. 2009, Marrack et al. 2009) and their role in activation of DCs and macrophages (Eisenbarth et al. 2008). At the same time, others found no involvement of the NLRP3 pathway in macrophage (Kuroda et al. 2011), DC or lymphocyte activation by Al salts or adjuvants (Franchi and Núñez 2008, Li et al. 2008, McKee et al. 2009). These differences could be related to different Al adjuvants, test systems or the different conditions and protocols used in these studies.

Adverse outcomes with Al adjuvants—Recent randomised controlled trials, semi-randomised controlled clinical trials, and comparative cohort studies that investigated the safety and immunogenicity of Al-containing vaccines are summarized in Table 4. Most of

the recent studies did not include groups given only the Al adjuvant, but where concurrent Al referent groups were included those studies are described below.

Descamps et al. (2009) studied the safety of the human papilloma virus (HPV)-16/18 AS04-adjuvanted cervical cancer vaccine (Cervarix™) in a cohort of almost 30,000 girls and women aged 10–14, 15–25 and above 25 years who received the same three-dose regimen at 0, 1, and 6 months. The AS04 adjuvant is comprised of Al(OH)₃ (500 µg per dose) and 3-O-desacyl-4'-monophosphoryl lipid A (MPI) (50 µg per dose). Reference groups were given equivalent injections of Al(OH)₃ alone. Compliance was 93.4% for the HPV-16/18 group and 96.4% for the Al(OH)₃ group. No immediate hypersensitivity reactions occurred and injection site pain (consistent with results from Chotpitayasunondh et al. (2008); Ehrlich et al. (2008); Romanowski et al. (2011) and Zhu et al. (2009) with other vaccines) was the most common acute complaint. Erythema and swelling at the injection site developed in those aged 15–25 and above 25 years during the 7 days after each vaccination and these were 2.4–3.2 times, respectively, higher in the groups given the HPV-16/18 vaccine compared to those given Al(OH)₃ alone. Complaints of fatigue, headache, and myalgia were common among those given the vaccine. There were no differences between the HPV-16/18 vaccine group and the Al(OH)₃ group with regard to fatigue, fever, gastrointestinal distress, headache, rash, arthralgia, myalgia, and urticaria. The overall rate of serious adverse effects (SAEs) after injection of Al(OH)₃ was almost 10 times higher in women 15–25 years of age than among those above 25 years (8.4% compared with 0.9%, respectively). A higher percentage of SAEs—including spontaneous abortion—was observed among the 15- to 25-year olds in the Al(OH)₃ group compared to HPV-16/18 vaccine group. Descamps et al. (2009) observed that the spontaneous abortion rate for these women was within the range reported for the United States and explained that the increase could be due to differences in the longer follow-up for those in given Al(OH)₃ (5.5 years) compared to 1.5 years for those given the HPV-16/18 vaccine. A higher percentage of new cases of chronic asthma, urticaria and hypersensitivity among the 15- to 25-year olds in those given only Al(OH)₃ was recorded compared to those given the HPV-16/18 vaccine (1.1% compared with 0.3%, respectively). There were no differences in the frequency of new cases of autoimmune disease at any age. The Descamps et al. (2009) analysis examined large sample sizes (29,953 subjects, 45,988 vaccine doses), gave separate presentations of outcomes for the vaccine and Al(OH)₃ groups by age and it included follow-up observations at 0–7 months, 7–12 months and more than 12 months.

Netterlid et al. (2013) conducted a randomized, controlled, single-blind study of Al contact allergy. This was a multicentre evaluation of children and adults that involved patch-testing with allergen extracts containing Al(OH)₃ and AlCl₃•6H₂O in white petrolatum at 2.0, 10.0, and 20.0% w/w. Seventy-eight children and 127 adults completed the study and positive results were found in eight (5/78 children and 3/127 adults). There were no positive reactions to the empty Finn Chamber, but seven tested positive to 10% AlCl₃•6H₂O and five tested positive to 2% AlCl₃•6H₂O. Four members of the control group also tested positive to Al. Six of eight participants with contact allergy to Al reported previous atopic dermatitis and four of those six were in the exposed group. In sum, the Netterlid et al. (2013) study demonstrated a 3.9% proportion of Al contact allergy in atopic individuals with allergic

disease. Among those who developed Al-induced allergic reactions, children and adults with atopic dermatitis were more highly represented.

A syndrome known as MMF has been associated with prolonged Al retention (e.g., years) at the site of vaccinations that contained Al(OH)₃ (Exley et al. 2009, Gherardi and Authier 2012). Aluminum-containing macrophages gather in the myofascii at the injection site and these accumulations have been confirmed in deltoid muscle biopsy (Siegrist 2005). A small proportion of vaccinated people present with delayed onset diffuse myalgia, chronic fatigue, and cognitive dysfunction. None of the clinical manifestations commonly associated with MMF (fever, myalgias, arthralgia, asthenia, and muscle weakness) are specific (Israeli et al. 2011, Gherardi and Authier 2012). A number of attempts have been made to link local vaccine reactions to those complaints; however, no firm etiological association with vaccination has been established (Lindblad 2004, Batista-Duharte et al. 2011) and these conditions as related to Al adjuvants remain uncertain (Shoenfeld and Agmon-Levin 2011).

A number of studies examined the potential of Al adjuvant-containing vaccines to elicit inflammation, attention deficit hyperactivity disorders, delays in speech or language development (Tomljenovic and Shaw 2011a, 2011b, 2012), neurodevelopmental delay (Dorea 2011, 2012a, 2012b) and impaired cognition (Couette et al. 2009). These concerns were highlighted by Dorea and Marques (2010) who reported that infants receiving immunizations were given 225–1750 µg Al per injection. On the other hand, Nøkleby (2007) and Mitkus et al. (2011) concluded that the risk of adverse effects including neurotoxicity posed by Al adjuvants received during childhood vaccinations was “low” and Ehrlich et al. (2008) observed only increased complaints of headache. In their study of 9600 people enrolled in 13 clinical trials of vaccines against influenza H5N1 virus, Manzoli et al. (2009) found no serious adverse events associated with Al adjuvants. Theeten et al. (2005) found that systemic adverse events were rare and a significant difference among Al study groups was found only for fatigue. The Global Advisory Committee on Vaccine Safety concluded there was no discernible relation between vaccinations and adverse outcomes (GACVS 2012, Kelso et al. 2012). Limitations to the published results include “incorrect assumptions about known associations of Al with neurological disease, uncertainty of the accuracy of the autism spectrum disorder prevalence rates in different countries, and accuracy of vaccination schedules and resulting calculations of Al doses in different countries” (GACVS 2012).

Twenty recent clinical studies of different Al-containing vaccines were available for review. Some of these studies reported a diminished or limited immunogenic role for Al(OH)₃ adjuvant in certain vaccines (Brady et al. 2009, Keitel et al. 2009, Manzoli et al. 2011, Liang et al. 2010, Yin et al. 2011, Zhu et al. 2009). Depending on the vaccine and dose, Bresson et al. (2006) and Ehrlich et al. (2008) found that influenza vaccines with alum adjuvant were no more effective toward inducing an immune response than influenza vaccines without adjuvant. Zhu et al. (2009) found that influenza H1N1 vaccine without Al adjuvant was associated with fewer local reactions and greater immune response than vaccine with adjuvant. Theeten et al. (2005) suggested limited or possible stimulatory roles for Al(OH)₃ in adsorbed DTaP vaccines, but there was no clear or consistent relation between immunogenicity and the Al quantity in the vaccine or total Al dose. The contributions of Al

adjuvants to immune response after vaccination appear to vary with antigen as well as with patient age (Zhu et al. 2009).

Contact reactions (delayed-type hypersensitivity with painful erythematous and pruritic eruptions, edema, and blistering) to Al at injection sites do occur (Table 5), but they are rare (Bergfors et al. 2005, Ehrlich et al. 2008, Leventhal et al. 2012, Zhu et al. 2009). These reactions can develop weeks, months, or even years after injection of an Al-containing vaccine (Leventhal et al. 2012). Histological examinations of biopsies from the injection sites revealed granulomatous and foreign body reactions (Garcia-Patos et al. 1995) and people with hypersensitivity to Al-containing vaccines generally demonstrate positive patch testing to Al (Bergfors and Trollfors 2012, Beveridge et al. 2011, Lehman et al. 2008, Netterlid et al. 2013).

There is little consistency among the 20 studies regarding their designs, event definitions, event types, and the age categories examined. The diversity of protocols, vaccines, methods, and data presentation in these publications makes it difficult to determine the relative safety of different Al adjuvants present in the different vaccines. Given the absence of standardized quantitative measures designed to calculate the therapeutic ratio, the comparative safety and/or efficacy of Al adjuvants in these vaccines, especially in children and pregnant women (Wijnans et al. 2011), remains unknown. Moreover, no formal effort was identified to establish causality between the systemic reactions following immunization with an Al adjuvant. A number of recent case reports describe delayed hypersensitivity after vaccination with Al adjuvants (Table 5) and while those results are suggestive, case reports cannot be considered definitive evidence for or the circumstances under which Al adjuvant injections may elicit undesirable effects in humans. In a 2012 study, Yokel found that of the Al present in pediatric vaccines (125–330 µg/dose) the amount absorbed each day from the depot was approximately 0.07 µg/kg (assuming 30 injections over the first 6 years of life and a mean body weight of 20 kg). The lack of suitable experimental models and standardized predictive methods, mixed exposures (Dorea 2010, 2012a, 2012b, Marques et al. 2010), issues in quantifying immunotoxicity and problems with detecting rare events make determination of causal relations between vaccines, their Al content and adverse outcomes difficult (Batista-Duarte et al. 2011).

Laboratory animals—Recent reports on immune system parameters in rats exposed orally to Al are summarized in Table 6. Details of the multi-generation bioassays by Hirata-Koizumi et al. (2011a, 2011b) with $\text{Al}_2(\text{SO}_4)_3$ and $\text{NH}_4\text{Al}(\text{SO}_4)_2$ in rats are described at the preceding discussion of developmental toxicity. Findings there include reduced absolute and relative thymus and spleen weights after ingestion of 3000 ppm $\text{Al}_2(\text{SO}_4)_3$ in drinking water, but necropsy found no dose-related histologic lesions in those organs. Interpretation of the reduced spleen and thymus weights is problematic due to the reductions in drinking water and food consumption. The Hirata-Koizumi et al. (2011b) study with $\text{NH}_4\text{Al}(\text{SO}_4)_2$ also found reduced absolute and relative thymus and spleen weights. As these changes may be related to maternal dehydration and inanition the utility of these observations for health risk assessment is limited.

There is some evidence that repeated exposure to high doses of different Al forms may stimulate (Lauricella et al. 2001, Yoshida et al. 1989) or suppress the immune response in rodents (Golub et al. 1993, Khalaf et al. 2008, Yoshida et al. 1989). Tsunoda and Sharma (1999) found no change in mRNA expression for cytokines TNF α , IL-1 β , and INF γ in peripheral cells of the immune system (TNF α and IL-1 β in splenic macrophages and INF γ in splenic lymphocytes) of mice given Al₂(SO₄)₃ in their drinking water at 0, 5, 25 or 125 mg/L (equivalent to 0, 0.95, 4.3, and 21 mg Al/kg-day) for one month. An effect of Al on the rodent immune response appears to vary with age, dose, onset, and duration of exposure (Glynn et al. 1999, Becaria et al. 2006), study design and/or physiological state (Khalaf et al. 2008, Yoshida et al. 1989). There is some evidence to suggest that changes in the immune system after high-dose Al exposure during development may be more pronounced in the offspring than in the dams (Khalaf et al. 2008). Zhu et al. (2012b) found decreased relative spleen weights in rats following ingestion of AlCl₃ at up to 256 mg/kg-day during 120 days and suggested that Al immunotoxicity could be due to disruption of Fe, Cu, and Zn in the spleen and interference with cytokines that regulate immune activation and homeostasis. Golub et al. (1993) suggested that Al-induced immunosuppression might result from a specific extrinsic effect, from a specific intrinsic deficit or from nonspecific disruption of physiological, hormonal or metabolic processes. At the present time, the underlying mechanisms associated with an immunological role for Al in rodents cannot be defined.

Genotoxicity

Krewski et al. (2007) concluded that Al compounds produced mostly negative results in standard short-term prokaryotic and eukaryotic test systems. Some of the early studies with soluble Al conducted in mice and rats produced mixed results. Recent data point to cell culture conditions and administration of excessively high (near-lethal) doses that contribute to the mixed results seen in the earlier reports.

Laboratory animals—Turkez et al. (2010) studied the clastogenic activity of Al in hepatocytes of adult male Sprague–Dawley rats (8-weeks old, 5 animals per group) after gavage with 34 mg/kg bw AlCl₃ along with 50 mg/kg bw propolis for 30 days. Turkez et al. (2010) found that repeated gavage with AlCl₃ induced a significant increase in the numbers of micronucleated hepatocytes (MNHEPs). Simultaneous administration of propolis attenuated the increased numbers MNHEPs induced by oral AlCl₃. Repeated high oral doses of AlCl₃ also caused a significant increase in alkaline phosphatase, transaminases (AST and ALT) and LDH and induced histopathological changes in the liver. The authors suggested the observed clastogenicity after oral AlCl₃ may have been mediated, at least in part, by free radicals (Abubakar et al. 2003). Similar MNHEP results were obtained after four repeated daily ip injections of 5 mg/kg of AlCl₃ in rats (Turkez et al. 2013). There was no justification for the doses examined, there was no study of dose-response and the genetic damage occurred after exposures that induced cytotoxicity. As written, it is not possible to exclude the possibility that the genetic damage was associated with oxidative stress in the liver as contrast to direct actions of trivalent Al.

Geyikoğlu et al. (2013) conducted a liver MN assay in adult male Sprague-Dawley rats given daily ip injections of AlCl₃ at 5 mg/kg-day for 10 weeks. A control group of six rats

received daily ip injections of saline. The MN assay was performed in accord with methods described by Turkez et al. (2010). Daily injections of AlCl_3 over 10 weeks resulted in a 4-fold increase in the numbers of MNHEPs. Histopathology suggested that the clastogenicity might be a consequence of cytotoxicity. These findings mirrored those by Manna and Das (1972) who found increased CAs in mouse bone marrow following repeated ip injections of AlCl_3 . The Geyikoglu et al. (2013) report failed to identify the pH of the injected AlCl_3 solution, there were no concurrent controls given equimolar injections of HCl and there were no measures of circulating or tissue Al concentrations.

Cytotoxicity and genotoxicity in vitro—Table 3 summarizes recent observations on Al toxicity in cultured cells. Data considered more relevant to weight of evidence comparisons are described below.

Turkez and Geyikoğlu (2011) conducted CA and SCE assays with $\text{Al}_2(\text{SO}_4)_3$ in cultured human lymphocytes. Blood was collected from three healthy non-smoking donors with no history of exposure to genotoxic agents. The $\text{Al}_2(\text{SO}_4)_3$ concentrations tested were 0, 10, and 20 $\mu\text{g}/\text{ml}$ (equivalent as 0, 1.57 and 3.15 $\mu\text{g Al}/\text{ml}$). Addition of 10 $\mu\text{g}/\text{ml}$ $\text{Al}_2(\text{SO}_4)_3$ failed to influence the frequency of SCEs or CAs; identical study with 20 $\mu\text{g}/\text{ml}$ increased the frequency of SCEs per cell and CAs compared with controls, but the change was not biologically significant (< 2-fold change in SCEs/cell as shown in publication Figure 1). There was no effect of $\text{Al}_2(\text{SO}_4)_3$ at 10 $\mu\text{g}/\text{ml}$ on oxidative stress markers in erythrocytes, but treatment with 20 $\mu\text{g}/\text{ml}$ reduced erythrocyte GSH and caused significant decrements in the activities of antioxidant enzymes (G-6-PDH, SOD and catalase). The authors suggested that the increased SCEs and CAs seen at 20 $\mu\text{g}/\text{ml}$ were the result of reduced antioxidant enzyme activity. The Turkez and Geyikoglu (2011) protocol examined only one time point and no reference mutagen (positive control) was included. Only thirty well-spread metaphases were scored per sample for the CA assay whereas OECD Test Guideline #473 requires at least 200 well-spread metaphases. The number of second cycle metaphases examined for SCEs was not reported. The highest Al concentration (3,157 $\mu\text{g}/\text{L}$) was ~300x the Al concentrations (1.9–10.3 $\mu\text{g}/\text{L}$) present in normal human plasma and serum (Krewski et al. 2007). No control cultures treated with equimolar concentrations of H_2SO_4 were included, there was no mention of media pH and there was no mention of light microscopic evaluations of these cells. Structural CAs can occur as a result of cytotoxicity (Galloway et al. 2000) and in the presence of > 50% cytotoxicity, CA increases are most all artifactual and can represent false positives (Battersby 2007, Kirkland et al. 2007, Galloway 2000). Cytotoxicity, solubility of the compound in the test system, changes in pH and changes in osmolality must always be considered in selection of the highest test substance concentration in these assays (OECD Test Guideline 473). Overall, the results of the Turkez and Geyikoglu (2011) study are equivocal.

Sappino et al. (2012) investigated 0, 10, 100 or 300 μM AlCl_3 or ACH (purity 99%) in cultured MCF-10A cells and in cultured human primary mammary epithelial cells. Sappino et al. (2012) suggested that “at the expected pH of the cell culture medium (pH ~7.2), AlCl_3 and ACH yield the same dissociation product, aluminum hydroxide”. There were no visual precipitates in these cultures and addition of AlCl_3 had a minor effect on pH. Incubation of MCF-10A cells with 100 μM AlCl_3 for six weeks induced loss of contact inhibition and

increased anchorage-independent growth. Culture of MCF-10A cells with 100 or 300 μM AlCl_3 reduced the numbers of cells, but there were no signs of apoptosis. Culture with 10, 100 or 300 μM AlCl_3 increased the percentage of senescence-associated β -galactosidase-positive cells in proliferating MCF-10A cells after 7 days. At the same time, exposure to 100 or 300 μM AlCl_3 increased the expression of p16/INK4a, a cyclin-dependent kinase inhibitor and tumour suppressor that enforces growth arrest (Baker et al. 2011). The addition of 10, 100 and 300 μM AlCl_3 increased DNA DSBs in a dose- and time-dependent manner in proliferating MCF-10A cells, but it had little or no effect on proliferating HaCaT keratinocytes. There was no influence of AlCl_3 on X-ray induced DSB repair in MCF-10A cells, but there was upregulation of the p53/p21 pathway. Companion studies found no effects of AlCl_3 on anchorage-independent growth in HaCaT keratinocytes or C26Ci human colonic fibroblasts cultured for 17 weeks in the presence of 300 μM AlCl_3 . Based on their results with MCF-10A cells, Sappino et al. (2012) suggested that AlCl_3 (at up to 300 μM or 60 μM as Al) induced proliferation, increased DSBs and accelerated senescence. According to the authors, the results indicated that induction of DSBs by AlCl_3 treatment occurred slowly, suggesting that this effect was indirect and possibly cell specific.

A number of observations can be made with regard to the Sappino et al. (2012) report. There was no justification offered for the Al concentrations examined and no empirical data were provided to support the suggested correlations between ACH and AlCl_3 exposures. The Al concentrations examined by Sappino et al. (2012) were 800–4200x the median 0.07–0.38 μM ($< 10 \mu\text{g/L}$) present in serum and plasma of healthy people (reviewed in Krewski et al. 2007). No positive control group was included, no equimolar HCl controls were included and it was not clear if the expected pH (7.3) was measured in fresh or long-term culture media. Since cytotoxicity increases after in vitro exposure to HCl and other acids (Morita et al. 1992) and weakly acidic conditions (pH 6.6–6.8) are mutagenic and clastogenic for cultured cells, it is possible that the Sappino et al. (2012) findings (even at non-cytotoxic concentrations) reflect oxidative stress (e.g., increased free radicals and ROS associated with LPO) associated with HCl. While Sappino et al. (2012) pointed to positive results from other Al studies, exposure to acidic media in those older reports cannot be excluded (reviewed in Krewski et al. 2007). There is evidence to support the fact that acidic conditions in cultured human (Morita et al. 1992, Güngör et al. 2010) and rodent (Cifone et al. 1987, Morita et al. 1989, 1992) cells can increase the numbers of CAs (e.g., chromatid breaks and gaps). At neutral pH AlCl_3 transforms to Al trihydroxide and Al oxidehydroxide and these hydroxides precipitate (Mayeux et al. 2012). While Sappino et al. (2012) stated that they did not observe visually-evident precipitates (detection method not reported), microscopic Al precipitates may have existed in these cultures (particularly at the highest concentration). Therefore, in the absence of data on cytotoxicity, it is possible that these cells were exposed to HCl and Al(OH)_3 particulate and that the findings are associated with acidic media and particulates as contrast to a direct genotoxic effect of Al^{+3} .

Lima et al. (2011) summarized older reports on the genotoxic activity of Al-containing atmospheric dust, Al(NO)_3 , AlCl_3 and irradiated Al ions. Other reports examined treatment of cells from Parkinson's patients with 1 mM Al and study of waste materials from an Al products factory. These reports included results with cultured V79–4 Chinese hamster cells, cultured Balb c3T3 cells, *Vicia faba* and *Allium cepa* cells. The results with the waste

materials are confounded by a positive response in *S. typhimurium* tester strains associated with aromatic amine contaminants. Based on polyploidy and clastogenesis in cultured human lymphocytes with 5–25 μM AlCl_3 (Lima et al. 2007), Lima et al. (2011) considered AlCl_3 genotoxic. Lima et al. (2011) also noted cytotoxicity at those same concentrations and that gaps were included in the statistical comparisons of breaks and reduplications. Therefore, the Lima et al. (2007) conclusions regarding structural and numerical chromosome aberrations induced by AlCl_3 may be called into question. Certainly all of the concentrations examined by Lima et al. (2007) are 42–360 \times higher than the mean or median Al concentrations in serum and plasma from healthy infants and adults (1.9–10.3 $\mu\text{g/L}$ or 0.07–0.38 μM) and in patients on PN (15.9 $\mu\text{g/L}$ or 0.59 μM). The Al concentrations employed by Lima et al. (2007) are consistent with serum Al concentrations (to 808 $\mu\text{g/L}$ or 29.7 μM) in HD patients who died as a result of Al intoxication (reviewed in Krewski et al. 2007). The conclusions reached by Lima et al. (2011) contrast with those drawn by others based on results of standard short-term in vivo and in vitro assays with water-soluble Al salts (IPCS 1997, Krewski et al. 2007, Willhite et al. 2012).

After correlating Al concentrations with reductions in % adenine + thymine interphase (quiescent) heterochromatin in relation to 50–500 nM $\text{Al}_2(\text{SO}_4)_3$ inhibition of RNA polymerase II-mediated transcription in human neuronal glial cells, Lukiw (2010) formulated his ‘Al compaction’ hypothesis. This theory is based on Al^{+3} affinity for binding A-T nucleotides and suppression of regulatory promoter gene expression compared to Al^{+3} affinity for G-C rich templates. This theory recalls Al binding to nucleotide phosphates previously held responsible for in vitro binding of $\text{Al}(\text{OH})_2^+$ to DNA and that was thought to reduce unwinding at pH 6–7.5 and contribute to DNA crosslinking (Karlik et al. 1980). Lukiw (2010) presented neither in vivo nor other direct in vitro evidence to support the DNA binding theory in relation to Al-induced cytotoxic or genotoxic activity.

Carcinogenicity

It has been recognized for at least 30 years that exposures during Al production present an increased risk of lung and bladder cancer (IARC 1987). This increased risk has been attributed to the presence of known carcinogens including polynuclear aromatic hydrocarbons in those operations (ATSDR 2008). Gibbs and Labrèche (2014) confirmed those observations and noted that the airborne concentrations of benzo[a]pyrene are used as an index of exposure to carcinogenic (benzene-soluble) coal tar pitch volatiles. Krewski et al. (2007) concluded that experimental studies in animals failed to demonstrate carcinogenicity attributed solely to Al exposure. No reports of recent carcinogenicity bioassays or initiation/promotion protocols with any Al form were located in the open literature. Recent epidemiologic data and case reports are compared below with those summarized by Krewski et al. (2007).

Friesen et al. (2009) investigated associations between alumina and bauxite dust exposures with circulatory and respiratory disease mortality and cancer in employees of four bauxite mines and three alumina refineries. These individuals were employed on or after January 1, 1983. For people employed prior to the initial 1995–1996 survey, work history and smoking status were obtained from company records. Outcomes were determined by linkage with the

national mortality database and the national and state cancer incidence registries. Cumulative exposure to inhalable bauxite and alumina were estimated using a task-exposure matrix for those employed during 1995/1996. A less detailed job-exposure matrix was required for subjects who left employment before 1996. Before 1998, total dust was measured using a NIOSH cassette that was subsequently found to underestimate the inhalable fraction. Measurements taken after 1998 used an Institute of Medicine recommended device to quantify inhalable dust. The study cohort had a mean age of 32 ± 10.5 years at entry, a mean duration of 14.1 years and a mean person-year (PY) contribution of 16.2 ± 4.8 years (equal to 93,420 PYs of follow-up). A greater percentage of the bauxite-exposed workers were either current (29% vs 24%) or former (29% vs 25%) smokers compared to the unexposed referent group. The alumina-exposed workers and the unexposed workers did not differ with respect to smoking. The median, mean and maximum cumulative measures of bauxite dust among the bauxite-exposed workers were 5.7, 13.4, and 187 mg/m³-yr, respectively. The median, mean and maximum cumulative measures of alumina dust among the alumina-exposed workers were 2.8, 14.5, and 210 mg/m³-yr, respectively. Exposure categories were defined based on the tertiles in the few cases. The relative risk of death from non-malignant respiratory disease showed a significant trend (7 deaths; $p < 0.01$) with cumulative bauxite exposure after adjustments for age, calendar year and smoking. These deaths were due to chronic obstructive pulmonary disease, asbestosis, unspecified bronchopneumonia and interstitial pulmonary fibrosis. Cumulative alumina exposures showed a marginally significant trend with increased mortality from cerebrovascular disease (10 deaths; $p = 0.04$). No notable associations or trends were observed for cancer. These analyses were based on only a few cases that accrued during the relatively short follow-up and adjustment for smoking was done using only a crude categorical variable. The absence of significant associations between occupational Al exposures and cancer risk by Friesen et al. (2009) are consistent with the conclusions reached by Fritschi et al. (2008), IARC (1987) and ATSDR (2008).

Pan et al. (2011) investigated residential proximity to Canadian Al smelters and risk of female breast cancer in a population-based case-control study using data collected by the National Enhanced Cancer Surveillance System. This study was based on individual data collected from 21,020 Canadians diagnosed with one of 19 types of cancers and it included 5039 population controls (aged 20–76 years). The study examined 2343 incident cases of breast cancer (863 premenopausal and 1480 postmenopausal) compared to 2467 controls. Breast cancer cases were identified by the population-based provincial cancer registries and all cases were verified by pathology reports. Breast cancer was defined as C50 according to the International Classification of Diseases for Oncology and questionnaires were sent to 3013 cases and 2982 cases were contacted. Completed questionnaires were received from 2362 cases, representing 78.4% of cases. Questionnaires were also mailed to 3847 women without diagnosis of cancer and these women were selected as potential controls using a random sample stratified by age group. In total, 2492 women without diagnosis of cancer completed and returned the questionnaire (representing 64.8% of the ascertained controls). These self-administered questionnaires collected information on education, average family income over the last five years, marital status, ethnic group, height, weight, physical activity, alcohol consumption, diet and vitamin and mineral supplements for the past 20 years. These

questionnaires also gathered smoking history, menstrual and reproductive history (including menopausal status), a lifetime residential and employment history, the distance between a residence and an industrial source and the number of years of proximity. Assessments also included dietary frequency, patterns and portion sizes for each of 69 foods consumed during the two years before interview. Distance to an industrial source was estimated using the locations and years of production for Al smelters and nine other major industries: copper smelters and refineries, lead smelters, nickel smelters and refineries, zinc smelters and refineries, petroleum refineries, paper mills, pulp mills, steel mills, and thermal power plants. Distance was categorized as less than 0.8 km (0.5 mile), 0.8–3.2 km (0.5–2 miles), and more than 3.2 km (> 2 miles). The change-in-point estimate approach was used to assess potential confounding factors: age, educational level, family income, alcohol consumption, smoking, body mass index, total calorie intake, recreational physical activity level, menopausal status, and number of live births. The final multivariate models were adjusted for age (years, continuous), province of residence, education (years, continuous), number of live births (none, 1, 2, 3, and 4), age at menarche (years, continuous), alcohol consumption (servings per week, continuous), pack-years of smoking (continuous), total caloric intake (kilocalories per week, continuous), and employment in the specific industry under consideration (yes or no). For postmenopausal women, the models were also adjusted for body mass index and recreational physical activity. In order to evaluate the trends for all models of categorized data, the different categories were treated as a single ordinal variable. The risk of breast cancer associated with residential proximity to Al industrial facilities was estimated based on odds ratios and corresponding 95% confidence intervals using unconditional logistic regression.

Data from 2343 breast cancer cases (863 premenopausal cases and 1480 postmenopausal cases) and 2467 controls (835 premenopausal controls, 1604 postmenopausal controls, and the menopausal status unknown for 28 controls) were used. The premenopausal cancer patients were older, had slightly higher family income, started menstruation at an earlier age and had longer menstruation compared with their controls. The postmenopausal women were slightly younger, had higher education, consumed more alcohol and tobacco, had higher body mass index, started menstruation at an earlier age and had fewer live births and more years of menstruation compared with their controls. The results indicated no increased risk of breast cancer among premenopausal or postmenopausal women living within 0.8–3.2 km of an Al smelter. After adjustment for age, province of residence, education, smoking pack-years, alcohol consumption, number of live births, age at menarche, total energy intake, and employment in the industry under consideration, the odds ratios were not statistically significant for premenopausal breast cancer among women living 0.8–3.2 km from Al smelters compared to the controls (8 breast cancer patients and 13 controls; OR = 0.52 [0.21–1.31]) or for those living less than 0.8 km from smelters (two breast cancer patients and one control; OR = 2.08 [0.18–23.72]). After adjustment for age, province of residence, education, smoking pack years, alcohol consumption, numbers of live births, age at menarche, total energy intake and employment in the industry under consideration, the odds ratios for postmenopausal breast cancer patients were not statistically significant for women living 0.8–3.2 km from Al smelters compared to the controls (19 breast cancer patients and 14 control; OR = 1.06 [0.50–2.23]) or for those living less than 0.8 km from

smelters (six breast cancer patients and six controls; OR = 0.97 [0.27–3.41]). For both pre- and postmenopausal breast cancer patients, the odds ratios for those living greater than 3.2 km from an Al smelter were all unity.

Among the strengths of the Pan et al. (2011) population-based study are the relatively large sample sizes and the length of time that participants had lived near Al smelters. A number of potential confounders were controlled, including employment in the specific industry under consideration. The Pan et al. (2011) inquiry has a number of limitations including no information on the ages of the women when they resided near a plant; information was not available for all patients on family history of breast cancer, benign breast disease, *BRCA1/2* status or use of oral contraceptives or estrogen replacements. No exposure measures for Al or any other airborne material were provided.

Donoghue and Coffey (2014) described community health risk assessments for five Australian Al smelters with NO₂, SO₂, PM₁₀, arsenic, and cadmium emissions that found arsenic accounted for 75% of the total incremental cancer risk (1.2×10^{-6}) 3 km downwind of these facilities. The 0.3–1.1 acute hazard index for those residents was due to airborne PM₁₀, formaldehyde, NO₂, SO₂, CO, and mercury, but the elevated risk was not related to Al.

Darbre (2001, 2006) declared that Al underarm antiperspirants and cosmetics cause human breast cancer, a conclusion based in part on a data from a Comet assay with cultured canine cells (Yiu 2004). However, Yiu (2004) evaluated complex mixtures (e.g., Secret Platinum[®] for women, Old Spice[®] for men and Crystal Natural[®]) and the Darbre conclusion (2001 (2006) ignored the absence of AlCl₃ and Al₂(SO₄)₃ mutagenic activity in standard assays (reviewed in IPCS 1997, Krewski et al. 2007, Willhite et al. 2012). Notable among the oft-cited reports concerning Al – induced clastogenesis are those by Banasik et al. (2005) and Lima et al. (2007) who cultured human peripheral lymphocytes for 72 h with AlCl₃. The Lankoff et al. (2006) study with cultured human lymphocytes examined AlCl₃ • 6H₂O at 4.15–103.75 μM (equivalent to 0.8–21 μM Al⁺³) where the higher concentrations induced apoptotic death. The DNA damage occurred after exposure to 40 μM AlCl₃ (equivalent as 8 μM Al⁺³), a concentration that was at least 67x normal median human blood Al concentrations (3.2 μg/L or 0.12 μM) (Krewski et al. 2007). These in vitro results are difficult to interpret due to the high AlCl₃ concentrations and whether the apoptosis and increased MN at cytotoxic concentrations were due to Al⁺³ or to HCl. Nevertheless, reversible Al(OH)²⁺ binding with DNA bases can occur in vitro, and Al-DNA binding can be attenuated by chelators; these changes are related to Al⁺³ binding with nucleotide phosphates and these reactions can precipitate DNA crosslinks in vitro (reviewed in Willhite et al. 2012).

Exley et al. (2007b) measured Al in mastectomy tissues from 17 patients treated for breast cancer. Defatted dry weight Al concentrations were between 4–437 nmol/g. Exley et al. (2007b) suggested ‘within-individual trends’ were seen for Al in mammary adipose tissue, but neither those distributions nor the total Al concentration in mammary fat were significant. No comparisons were made between the Al concentrations in these patients and Al concentrations in mammary adipose tissue from healthy matched donors. Exley et al.

(2007a) concluded: “we have no direct evidence that the aluminum measured in these breast biopsies originated from antiperspirant”.

Mannello et al. (2011) compared Al concentrations in nipple aspirate from 16 healthy women ($131 \pm 9.6 \mu\text{g/L}$) to those in 19 women diagnosed with breast cancer ($268 \pm 28.1 \mu\text{g/L}$). Based on the highly significant ($p < 0.0001$) difference, Mannello et al. (2011) suggested that either human breast tissue accumulates Al or that the elevated Al concentrations were related to use of Al-containing underarm antiperspirants. Following up on that suggestion, Darbre et al. (2011) cultured human mammary adenocarcinoma MCF-7 cells with 0 or 0.0001 M (100 μM) ACH (equivalent to 31 μM Al) for 21 weeks. There was no influence of ACH on cell proliferation, but 50 genes (including mRNAs for five Ca-binding proteins) were up-regulated and 57 were down-regulated. No protein synthesis data were included, no effort was made to establish concentration-response relationships and the single concentration examined was $> 250\times$ the median Al (0.12 μM) present in plasma from healthy humans (reviewed in Krewski et al. 2007).

There are at least two large epidemiology studies that examined antiperspirant/deodorant use and risk of female breast cancer, one of which was a population-based case-control study that found no relation whatsoever (Mirick et al. 2002). The second suggested an earlier age for diagnosis of the disease with increasing antiperspirant use (McGrath 2003). McGrath (2009) suggested a novel, indirect potential [but not empirically-verified] observation between topical Al-containing antiperspirant use and human breast and prostate cancer and put forward the idea that $\text{Al}(\text{OH})_3$ obstruction of sweat glands in an as-yet unidentified manner increased systemic uptake of “sex hormones and pheromones (androgens) from apocrine sweat glands”.

Fakri et al. (2006) compared antiperspirant use by 54 women who presented with breast cancer to that of 50 healthy women of similar age; 82% of the healthy women reported antiperspirant use compared to 51.8% of those with the disease. Fakri et al. (2006) concluded that underarm antiperspirant use had no association with risk of female breast cancer, but that family history and oral contraceptive use were related to excess risk. However, neither Fakri et al. (2006), Darbre (2001, 2006, 2011) nor McGrath (2003, 2009) accounted for *BRCA1/2* mutations, the dose and duration of oral contraceptives or addressed other well-known risk factors for human breast cancer (Lee et al. 2008).

Namer et al. (2008) identified 59 studies published to 2007 in an effort to determine a) whether existing biological data support an association between the use of underarm deodorants/antiperspirants and female breast cancer, b) whether use of those products increased breast cancer risk and c) whether data exist to support a causal relation between use of underarm deodorants/antiperspirants and increased risk for breast cancer. Of the 59 candidate studies, 19 were judged appropriate to evaluate the hypothesis. Namer et al. (2008) concluded that there was “no scientific evidence to support the hypothesis” that use of Al-containing antiperspirants increased the incidence of human mammary upper outer quadrant gland cancer.

Alumina-on-alumina total hip arthroplasty has been popular for at least three decades (Hannouche et al. 2011) during which time at least three case reports of soft tissue sarcoma have appeared (Ingram 1988). Yoon et al. (2011) described the case of an 80-year-old woman who received a titanium hip prosthesis with an alumina-on-alumina bearing. At five years after surgery, she developed a palpable cystic mass around her greater trochanter. Upon resection the mass was identified as a malignant fibrous histiocytoma and metastatic nodules were present in her lungs and axillary lymph nodes; her death was attributed to multiple lung metastases. Yoon et al. (2011) noted the similarities in their case to that detailed by Ryu et al. (1987) who noted the contribution of wear debris to sarcomatous degeneration.

Nanomaterials

Synthetic alumina, mixed Al silicate ($\text{SiO}_2/\text{Al}_2\text{O}_3$) and Al oxide nano materials have a host of industrial (Kaste and Rice 2004, Najafpour et al. 2012, Patra et al. 2012, Yu et al. 2011), agricultural (Costa et al. 2011, Stadler et al. 2010), consumer product (Maquire-Boyle et al. 2012, Sadiq et al. 2009) and medical (Monteiro-Riviere et al. 2010, Li et al. 2011c, Zhao and Castranova 2011) applications. Aluminum-reinforced carbon nanotubes and composites with Al oxide coatings are increasingly common (Gupta et al. 2011, Keshri et al. 2010, Seo et al. 2012).

Nanosized Al oxide particles are also generated during Al welding and corundum grinding (Curwin and Bertke 2011, Dasch and D'Arcy 2008, Gomes et al. 2012a, 2012b, Pfefferkorn et al. 2010). The Al nanoparticles generated during Al fettling, cutting and molding are comprised of metallic Al and Al oxides and as are those those generated during Al thermal spray (Bémer et al. 2010). The primary Al nanoparticles present in Al welding fume (10–75 nm) agglomerate in air by adhesion into larger particles and the primary Al nanoparticles in corundum (crystalline Al_2O_3) dust (10–35 nm) also aggregate (Schneider et al. 2013).

Controversy exists over the (potential) toxicity of engineered nanotubes, nanocapsules, nanospheres, nano quantum dots and nanoshells (Card et al. 2011, Nel et al. 2006, Oberdörster et al. 2005, Powers et al. 2013, Yokel and MacPhail 2011). Some (Chen et al. 2008, Oesterling et al. 2008, Zhang et al. 2011b) have suggested nanoscale alumina is a more potent pro-oxidant than bulk or common micron-sized Al oxides whereas others (Radium et al. 2011, Sun et al. 2011b) concluded that Al_2O_3 nanomaterials pose little hazard. Oesterling et al. (2008) observed that primary nano alumina agglomerated at physiological pH in serum-containing culture media giving rise to particles ranging from nano to micron size. The primary particles agglomerate in culture media due to hydrophobic and Van der Waals forces and binding with protein and polysaccharides (Powers et al. 2006).

Data that might be taken to support the view that Al nanoparticles may be of greater concern than similar micron-sized particles include those from Lordan et al. (2011) who cultured human HepG2 cells with different montmorillonite particles (one tactoid at 30–100 μm and one agglomerated at 3–35 μm). After 24 h in culture these Al particles clumped into larger bundles to the point that the cultures were obscured and the cells could not be seen under a light microscope. At these concentrations there was an increase in intracellular reactive

oxygen and viability was reduced 23–27%, but there was no increase in caspase-3/7 activity. These particles were relatively non-toxic in that at 500–1000 µg/ml there was no or only a slight elevation in LDH release. Lordan et al. (2011) considered that the death of these cells was not due to apoptosis; death was attributed to necrosis, but no histologic or other data were presented to support that conclusion. Long-term dietary studies with refined montmorillonite and related Al silicate particles in humans (Afriyie-Gyawu et al. 2008) and rodents (Afriyie-Gyawu et al. 2005, Phillips 1999, Phillips et al. 2008, Wiles et al. 2004) found no evidence for particle accumulation or toxicity, but fatty hepatic degeneration occurred in mice after chronic feeding as a result of particle binding with choline in the intestine (Wilson 1953, 1954).

Prabhakar et al. (2011) compared the acute oral toxicity of bulk Al₂O₃ (99%) with that of 30 nm or 40 nm Al₂O₃ in rats given 0, 500, 1000 or 2000 mg/kg. No adverse signs were evident and food consumption and organ weights were no different from those of the controls. Among rats given 30 or 40 nm Al₂O₃ there was a significant increase in hepatic LPO; catalase activity increased, reduced GSH declined and SOD activity decreased. These changes resolved by day 14 save in those given the highest dose. Intubation of 30 or 40 nm Al₂O₃ caused greater GSH reductions than did an equivalent dose of bulk Al₂O₃. Dilated central veins and distended portal tracts developed in rats given 2000 mg/kg of the nano Al₂O₃ whereas rats given an identical dose of bulk Al₂O₃ showed no anomalies. The extent of LPO was greater in rats given nano Al than in those given bulk Al, but there was no significant difference in hepatic LPO between rats given the 30 or 40 nm Al₂O₃. Prabhakar et al. (2011) attributed the higher oxidant response in the liver after nano Al compared to bulk Al to a higher delivered dose but no empirical data were presented to support that conclusion.

Substantial differences exist regarding Al nanoparticle cytotoxicity in vitro. Many of these differences likely relate to the physical form(s) of these materials in culture media (Powers et al. 2006). There is no question that sufficiently high (µM–mM) concentrations of synthetic Al nanoparticles can kill cultured fibroblast, keratinocyte, melanoma, and mammary carcinoma cells (Maduray et al. 2012, Rocha et al. 2012). Rocha et al. (2012) attributed Al nanoparticle-induced cytotoxicity to generation of O₂ •⁻, OH• and related free radicals. After cultured rat alveolar macrophages were exposed to nanoscale metallic Al at 100–250 µg/ml for 24 h significant reductions in viability were observed. When macrophages were treated with Al₂O₃ nanoparticles under the same conditions, phagocytosis was impaired but only ‘marginal’ reductions in viability were seen (Wagner et al. 2007). In contrast, there was no evidence of cytotoxicity after 24 h culture of human epidermal keratinocytes with 50–80 nm Al nanoparticles at 0.0004–4.0 mg/L (Monteiro-Riviere et al. 2010) and there was no significant toxicity in human lung fibroblasts (Zhang et al. 2011c), human lung epithelial 1929 and A549 carcinoma cells (Kim et al. 2010), human foreskin BJ and mouse fibroblasts (Radziun et al. 2011) or primary human brain microvascular endothelial (hCMEC/D3) cells (Chen et al. 2008). Extraordinarily high concentrations in vitro (> 100 µg/ml) can reduce viability, increase cell shrinkage and promote apoptosis, but whether those changes are specific to Al⁺³ released from the particles or whether these represent non-specific particulate damage is not clear. Differences in nano Al cytotoxicity in vitro depend on

particle behavior just as was the case in vivo after inhalation of 10 or 40 nm γ -AlOOH (Pauluhn 2009a).

Neutral Al nanoparticles can bind purines and pyrimidines in vitro (Jin et al. 2012). High concentrations (5–10 mg/L) of Al₂O₃ nanoparticles increase ROS, increase TNF- α , increase IL-6 and induce cyclooxygenase-2 in cultured murine macrophages (Nishanth et al. 2011). Aluminum nanoparticles increased micronuclei in cultured Chinese hamster ovary cells, but failed to increase the frequency of SCEs (Di Virgilio et al. 2010). These particles (20–30 nm) were neither clastogenic for cultured human fibroblasts (Tsaousi et al. 2010) nor mutagenic in *S. typhimurium* strains TA 100, TA 1535, TA 98, TA97a or TA 102 either in the presence or absence of fortified rat liver S9 (Balasubramanyam et al. 2010, Pan et al. 2010).

Dong et al. (2011) compared the toxicity of four nano γ -aluminas to that of Al₂O₃ powder in cultured C17.2 neural stem cells (NSC). The study included cell morphology, viability, membrane integrity, necrosis, apoptosis and particle uptake. All of these primary nano γ -alumina particles were crystals; sample numbers 1, 2 and 4 were rods and sample 3 particles were of irregular shapes. The chemical purity was 99.9% and the mean primary particle size was 6.3–18.9 nm. The agglomerated particle sizes in the media varied from 420–650 nm. Particle solubility in the media ranged from less than the limit of detection for sample number 1 to 180 ng Al/ml for sample number 2. Irregular micron size crystalline Al₂O₃ particulates (402 nm) were used as a reference and these had the highest solubility (920 ng Al/ml) of all of the forms.

Dong et al. (2011) cultured the NSC in 10% fetal bovine serum and 5% horse serum under humidified 5% CO₂ and 95% air at 37°C for 24 h with 0 or 10–500 μ g/ml test material. All of the nano Al particles aggregated to the point that they had similar sizes in the media (450–650 nm). Concentration-dependent toxicity was observed after treatment with nano sample 4 at 72 h. The duration of exposure (up to three days) failed to influence cell viability and there were no adverse effects of media pre-treated with alumina (to evaluate the influence of nutrient depletion) on viability. A concentration-related release of LDH was observed in all Al nano-treated cultures, but the differences between the four types of Al nano-forms were small. After 24 h many particles accumulated in the NSC cytoplasm, but there were no particles in the nucleus. There were no ultrastructural anomalies at 24 or 72 h culture with any of the Al nanoforms. A concentration-dependent increase in ROS was seen at 24 h following treatment with 100 μ g/ml N1–N4 and the increased ROS was consistent with concentration-dependent reductions in viability. There was no evidence of apoptosis following exposure to nanoAl (N1–N4) or Al₂O₃ at 24 h. Dong et al. (2011) concluded that alumina particles were readily internalized by cultured cells but that the cytotoxicity of nano γ -alumina in cultured NSC cells was low. The Dong et al. (2011) study is important because it compared the toxicity of various agglomerated Al nanoparticles to that of conventional Al₂O₃ and found that none of the Al nanoforms were significantly more toxic than the bulk Al₂O₃. However, the brief durations of exposure and the in vitro nature of the study make extrapolations to in situ conditions tenuous.

Definitive studies on the pulmonary toxicity of Al oxide nanoparticles are those by Pauluhn (2009a, 2009b, 2009c, 2011) and Adamcakova-Dodd et al. (2012). These studies point to general principles of the behavior of inhaled ultrafine Al particles. One goal of the Pauluhn (2009a) investigation was to “test whether the pulmonary effects (toxicity and fate) following exposure to aluminum oxyhydroxides of differing primary and agglomerated particle size are more dependent on the primary than agglomerated particle size”. Pauluhn (2009b, 2009c) then followed the initial observations with more detailed analyses of cumulative lung particle burden in relation to inhaled concentrations, particle volume, macrophage activity and pulmonary inflammation. The Pauluhn (2009a, 2009b, 2009c, 2011) series explains Al nanoparticle characteristics [primary particle size, chemical composition, shape, diameter and surface properties (e.g., smooth, thin) that determine relative flexibility/rigidity] in relation to agglomeration, deposition and retention in the respiratory tract. Among the generalizations that come from this and related work on the inhalation toxicology of poorly soluble ultrafine particulates include the observation that acute pulmonary inflammation after high dose exposure appears more closely related to particle surface area and reactivity, but the sustained inflammation seen after prolonged pulmonary retention depends more on particle volume than on particle surface area.

Pauluhn (2009a) exposed groups of 54 adult male Wistar Bor:WISW (SPF-Cpb) rats by nose-only inhalation 6 h/day, 5 days/week for 4 weeks to 0, 0.4, 3 and 28 mg/m³ of 10 or 40 nm calcined Al oxyhydroxide (γ -AlO(OH) or boehmite) crystals. The particle mass median aerodynamic diameter (MMAD) of one boehmite was 1.7 μ m (10 nm Dispersal[®] of 39.4% Al) and that of the other was 0.6 μ m (40 nm Pural[®] of 43.9% Al). Despite the differences in primary particle size, the geometric diameters of the agglomerated particles in the inspired air were identical (2.7 and 2.6 μ m, respectively). The post-exposure observation period was three months. An interim sacrifice was made on day 10 during exposure and post-exposure sacrifices were carried out one day after the end of exposure then at 12 days, 33 days and 91 days after termination of exposure. Twelve animals were exposed per concentration and time-point; six were subjected to bronchoalveolar lavage and histopathology and six were used in determination of Al tissue concentrations. Pulmonary inflammation was assessed by measuring total protein and total cell counts, numbers of neutrophilic granulocytes (PMNs) and LDH, γ -glutamyltransferase (γ -GT) and β -N-acetylglucosaminidase (β -NAG) activities in bronchoalveolar lavage fluid (BALF) and histopathological examination included all five lung lobes, bronchi, lung-associated lymph nodes, olfactory bulb, ethmoid turbinates and the olfactory nerve. Aluminum concentrations were measured in urine, brain, the right lung lobe, BAL cells, hilar lymph nodes, kidney and liver.

There were no deaths, clinical signs or treatment-related changes in body weight. As the concentration and duration of exposure increased, Al concentrations in the lung increased. The increase in lung Al was greater in rats that inhaled the 40 nm particulate than in rats that inhaled the 10 nm particulate. Rats that inhaled the 40 nm particulate consistently received higher daily Al doses (1.85, 15.7 and 130 μ g/day) than rats that inhaled identical concentrations of the 10 nm particulate (1.06, 8.7 and 77.2 μ g/day). Pulmonary Al elimination $t_{1/2}$ values were similar for both particulates at the lower concentrations, but pulmonary elimination by rats inhaling 28 mg/m³ found the smaller 10 nm particulate had an Al elimination half-time that was more than twice that of the larger 40 nm particulate.

There was no measurable increase in Al in lung-associated lymph nodes after rats inhaled 0.4 or 3 mg/m³ of either preparation and there were no time or concentration-dependent increases in brain, liver or kidney Al. There were no changes in urinary Al associated with either duration or magnitude of exposure.

There were no significant differences in BALF cytology or biochemical parameters at 0.4 or 3 mg/m³ of either preparation, but after rats inhaled 28 mg/m³ was there an inflammatory response in the lung. Histology after four weeks of exposure to the highest concentration found particles within the alveoli and particle accumulation in enlarged, foamy alveolar macrophages. Slight to minimal focal septal thickening, increased numbers of epithelial cells and increased inflammatory infiltrate were evident. Increased LDH activity followed a similar profile for both the 10 and 40 nm boehmites and increased levels of β -NAG, total protein and γ -GT followed increased total cell and PMN counts. Focal septal collagen increased only after rats inhaled 28 mg/m³ of either preparation. Even though measurable Al was present in lungs from rats inhaling 0.4 or 3 mg/m³, there were no adverse effects in the lung despite the sensitive endpoints employed to evaluate toxicity. Histopathological study of the bulbus olfactorius and ethmoid nasal passages found neither signs of local tissue alterations nor evidence for γ -AlO(OH) particle translocation. The results demonstrated that the size of the agglomerated γ -AlO(OH) particles was more closely related to total lung particle burden than was the size of the primary particle.

Lung Al concentrations increased after male C57Bl/6 mice inhaled (WB exposure) 3.3 mg/m³ of a dry aerosol of 2–4×2800 nm Al₂O₃ nanowhiskers, 4 h/day, 5 days/week for two or four weeks (Adamcakova-Dodd et al. 2012). Measures of particle size distribution found the primary particles formed 150 nm agglomerations with protruding nanowhiskers. Although pulmonary macrophage increased with duration of exposure, there were no signs of pulmonary damage or inflammation (based on LDH, IL-6, IFN- γ , MIP-1 α , TNF- α and MIP-2 in BALF) among treated mice compared to their controls. Methacholine challenge found no evidence for airway hyperreactivity and histology found no sign of airway remodeling, inflammation, lymphoid aggregates or fibrosis. The results from Adamcakova-Dodd et al. (2012) are consistent with the results from Pauluhn (2009a), but the former is limited by examination of only a single concentration.

Pauluhn (2009b) extended his work to quantify exposure using the kinetics of inhaled 10 and 40 nm γ -AlO(OH) particulates. The pulmonary elimination $t_{1/2}$ values for γ -AlO(OH) increased as the particle concentrations in the inspired air increased. The $t_{1/2}$ was longer for the 10 nm (177 days) than for the 40 nm (94 days) particles and the elimination rates correlated with lung burden. The cumulative lung particle burden was proportional to the PM concentrations in the inspired air; rats that inhaled the highest γ -AlO(OH) PM concentrations accumulated the highest particle concentrations in their lungs. Rats that inhaled the 40 nm PM had higher pulmonary loads than those that inhaled an identical concentration of the 10 nm particles. Pulmonary inflammation (measured as relative PMN counts) was most closely correlated ($r = 0.93$ – 0.97) with mass-based measures of dose than with particle surface area. Pulmonary inflammation was not evident when lung particle loads did not impede normal macrophage clearance. These data point to the conclusion that the toxicity of γ -AlO(OH) in rat lung was not due to leaching or dissolution of Al⁺³ from these

non-redox active agglomerates, but it was reflected in the capacity of pulmonary macrophages to clear these poorly-soluble particles.

The work by Pauluhn (2009c) builds on concepts of pulmonary particle overload and toxicity in the lung (Oberdörster 1995, Oberdörster et al. 2005). Pulmonary overload has been defined as a two- to four-fold reduction in alveolar clearance beginning when pulmonary macrophages accumulate a particle mass $60 \mu\text{m}^3$ and become immobilized. This value is equivalent to a lung particle burden of $\sim 1 \text{ mg/g}$ (ILSI 2000). In the case of 10 and 40 nm γ -AlO(OH) particles, the size of their closely-packed, poorly soluble agglomerates leads to high composite volumes of phagocytized particles. A smaller total nanoparticle mass than that seen with larger microsized particles can exceed the volumetric overload limits of pulmonary macrophages. It is only after sufficient agglomerates are retained in immobilized macrophages that pulmonary inflammation was evident in rats that inhaled 10 or 40 nm γ -AlO(OH). The work by Pauluhn (2009a, 2009b, 2009c) supports the concept that prolonged pulmonary retention and sustained inflammation depend upon particle volume as contrast to particle surface area.

Pauluhn (2011) extrapolated the γ -AlO(OH) data together with the results of other studies on ultrafine PM to calculate a generic OEL based on volume-based mass concentrations. This OEL ($0.54 \mu\text{l PM}_{\text{resp}}/\text{m}^3$) is designed to preclude lung particle overload and prevent intraluminal pulmonary inflammation after exposure to poorly soluble nano- to submicron-size PM. Assumptions implicit to those calculations were that the inhaled Al PM presents no risk for neoplastic lung disease and that systemic uptake of the Al PM is insignificant. In the case of inhaled γ -AlO(OH) there was no evidence for extra pulmonary translocation (Pauluhn 2009a). Pauluhn (2011) advanced the concept of non-reactive lung particle overload as the determining factor in health risks posed by airborne Al nanoparticles. The potential for pulmonary inflammation and damage associated with exposure to airborne nanoscale aluminas is related primarily to the size and composite volume of the agglomerated material as contrast to the size of the primary crystals.

Standards and guidelines

Current standards and guidelines include German and United States regulations on Al in foods, the EFSA Tolerable Weekly Intake (TWI), the Minimal Risk level (ATSDR 2008), the WHO drinking water limit, the French deliberations on Al in cosmetics (AFSSAPS 2011) and Occupational Exposure limits (OELs) (Table 7). At the present time, there is no European Union OEL for metallic Al or its compounds (Health Council of the Netherlands 2010).

Food standards

The US FDA considers common Al compounds used as multiple purpose, sequestrant, anticaking, leavening and emulsifying agents in foods ‘generally recognized as safe’ (GRAS) (Yokel 2012). Stahl et al. (2011) summarized German regulations on the maximum permissible levels of Al in food. Australia and New Zealand (FSANZ 2011) as well as Brazil (Aparecida 2009) have adopted standards for the maximum Al content in foods.

The United States has been content to require warning labels on PN materials that contain > 25 µg Al/L (US FDA 1998, 2003). The United Kingdom Medicines and Healthcare Regulatory Agency (2010a, 2010b) issued contraindications for Ca gluconate packaged in small-volume glass containers (10 ml) used to compound PN solutions. The intent of the UK action is to reduce the adverse effects of parenteral Al on bone mineralization and neurological development in premature infants.

TWI

The European Commission has been considering directives to ensure that the EFSA recommended TWI (equivalent to 280 µg/kg-day) (Benford et al. 2012) for dietary Al is not exceeded (EFSA 2011). In contrast to the EFSA (2011, 2013) assumption that gastrointestinal uptake of all ingested Al materials is equivalent to that measured for Al citrate, Berthon (2002) compared the different dietary constituents that either promote (e.g., ascorbate, citrate, glutamate, malate, oxalate, tartrate) or retard (e.g., phosphate, soluble silicates) Al uptake. Under current EFSA (2011, 2013) and Benford et al. (2012) guidance, Al exposures associated with consumption of trace levels of bentonite/montmorillonite ($[(\text{Na,Ca})_{0.33}(\text{Al, Mg})_2(\text{Si}_4\text{O}_{10})(\text{OH})_2 \cdot n\text{H}_2\text{O}]$) in wine that are not systemically available (Wiles et al. 2004) are cumulative with total Al exposures from more water-soluble and bioavailable forms like $\text{Al}_2(\text{SO}_4)_3$ (van der Voet and de Wolff 1986–87).

MRL

ATSDR (2008) calculated an intermediate (15–364 day) minimal risk level (MRL) for ingested Al of 1.0 mg/kg-day. The ATSDR (2008) identified a NOAEL of 26 mg/kg-day and applied a total uncertainty factor of 100 and used a modifying factor of 0.3 (to account for differences in gastrointestinal uptake of Al lactate compared to the Al forms in drinking water and food) to calculate the intermediate MRL. The ATSDR (2008) also calculated a chronic (365 day) MRL for ingested Al of 1.0 mg/kg-day.

Drinking water

In 1984 the WHO recommended a maximum drinking water concentration of 0.2 mg Al/L to control discoloration. This recommendation was based on consumer complaints of ‘foul’ or discolored water at Al concentrations > 0.1 mg/L (WHO 2004, 2010).

Cosmetics

The US FDA limits the concentrations of Al in cosmetics as the polymerized $\text{Al}_y(\text{OH})_{3y-2}\text{Cl}_2 \cdot \text{H}_2\text{O}$ to 25% w/v and $\text{Al}_2\text{Cl}_7\text{H}_7\text{O}_7\text{Zr}_2$ to 20% w/v (US DHHS 1982, 2003). The US FDA commented that underarm deodorants with higher Al concentrations (e.g., up to 35%) can be skin irritants; increasing the concentrations of Al antiperspirant ingredients in these products “increases the acidity of the material and irritation of the skin”. The final decision included epidemiologic data from Graves et al. (1990) and concluded: “The agency does not find the current evidence sufficient to conclude that aluminum from antiperspirant use results in Alzheimer’s disease.”

On January 4, 2013 the European Commission limited the concentration of $\text{Al}_x\text{Zr}(\text{OH})_y\text{Cl}_2$ and AlZrClOH glycine complexes in cosmetics to not more than 20% and prohibited their use in aerosol spray dispensers (EC 2013).

Vaccines

Of the vaccines currently registered in the United States (Leventhal et al. 2012), 12 contain $\text{Al}(\text{OH})_3$ and 23 contain other Al compounds (Kelso et al. 2012). Standard adjuvants in diphtheria, tetanus, and pertussis (DTP) and other vaccines include alum ($\text{AlK}(\text{SO}_4)_2$, $\text{Al}_2(\text{SO}_4)_3$, Adju-Phos ($\text{Al}(\text{PO}_4)_3$) Imject Alum ($\text{Al}(\text{OH})_3 + \text{MgOH}$) and alhydrogel ($\text{Al}(\text{OH})_3$) (Kelso et al. 2012, Marrack et al. 2009). The United States FDA limits the elemental Al content of a single vaccine injection to 0.85 mg (Eickhoff and Mayers 2002), a value equivalent to 2.45 mg $\text{Al}(\text{OH})_3$ per dose.

OELs

Different OELs for Al have been adopted in different countries (ILO 2011, IFA 2011a, 2011b); some countries rely on OELs developed in the United States whereas others rely on those adopted by the Deutsche Forschungsgemeinschaft (DFG), Safe Work Australia, the United Kingdom Health & Safety Executive, the Health Council of the Netherlands or by the Nordic Expert Group (Arbete Och Hälsa) (Table 7). Some OELs are legally enforceable limits (e.g., OSHA Permissible Exposure Limits (PELs), 1993, Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (IFA), 2011b). The enforceable limits may be identical to or may be substantially different from non-binding 'guidance' values for the same material (Deveau et al. 2014).

Riihimäki and Aitio (2012) reviewed occupational exposure to Al welding fume in relation to Al concentrations in urine and blood and concluded that urinary Al was a more sensitive indicator of Al uptake and body burden than serum Al. Yokel (2012) calculated daily Al uptake from the lung after exposure to workplace air containing 25–2500 $\mu\text{g}/\text{m}^3$ and found that pulmonary uptake (0.6–8 $\mu\text{g}/\text{kg}\text{-day}$) was substantially greater than that received after swallowing airborne Al particles (0.008–1.0 $\mu\text{g}/\text{kg}\text{-day}$). The Finnish Institute of Occupational Health adopted a limit of 6 $\mu\text{mol}/\text{L}$ for Al in pre-shift urine after two days without Al welding. The current German Biological Workplace Chemical Tolerance Value (BAT) is 2.2 $\mu\text{mol Al}/\text{g creatinine}$ (pre-or postshift) corresponding to the MAK maximum Al concentration in workplace air of 1.5 mg/m^3 (respirable fraction). The Polish MAC for airborne Al_2O_3 dust (1.05 mg/m^3) corresponds to 2.1 $\mu\text{mol Al}/\text{L}$ urine. Riihimäki and Aitio (2012) proposed a urinary Al 'action limit' of 3 $\mu\text{mol}/\text{g}$ (corrected to a relative urine density of 1.021 or 2.3 $\mu\text{mol Al}/\text{g creatinine}$) based on reports of impaired cognition in Al welders with many years of exposure to the fume. This proposed limit assumes workers do not consume Al-containing antacids or buffered aspirin and that diet and beverages do not contribute to elevated urinary Al.

The Health Council of the Netherlands (2010) considered the available data insufficient to derive health-based OELs for metallic Al or Al compounds other than ACH. The Health Council assigned an OEL to ACH of 0.05 mg/m^3 based on the development of multifocal granulomatous pneumonia and microgranulomas in the peribronchial lymph nodes of rats

and guinea pigs inhaling ACH (Steinhagen et al. 1978). The Health Council of the Netherlands (2010) emphasized that except for ACH, existing data are not adequate to recommend OELs for bulk Al metal or other Al compounds. The Nordic Expert Group (2011) concurred with the Health Council of the Netherlands (2010) in that the repeat exposure 'minimal' inhalation LOAEL (0.061 mg Al/m^3) was an appropriate point of departure for derivation of an OEL for ACH.

Synthesis and conclusions

The results of the present review demonstrate that health risks posed by exposure to inorganic Al depend on its physical and chemical forms and that the response varies with route of administration, magnitude, duration and frequency of exposure. These results support previous conclusions that there is little evidence that exposure to metallic Al, the Al oxides or its salts increases risk for AD, genetic damage or cancer (Krewski et al. 2007). The present review also found that the notion that Al dose can be accounted for, measured by, and the data interpreted as 'total Al' (e.g., Sorenson et al. 1974), as contrast to chemical-specific analyses (BASF 2011, Rödelsperger et al. 1987), can lead to possibly inappropriate conclusions regarding Al health risks.

The present review found that the majority of the rodent studies (Tables 2 and 3) are of limited relevance for Al human health risk assessment. The designs of exploratory studies (e.g., Abdel-Aal et al. 2011a, 2011b, Abu-Taweel et al. 2011a, 2011b, Akiyama et al. 2012, Cheng et al. 2012, Cui et al. 2012, Elsaid et al. 2011, Garrosa et al. 2011, Kumar et al. 2011, Moselhy et al. 2011, Sun et al. 2011b, Thirunavukkarasu et al. 2010, 2011, 2012, Viezeliene et al. 2011, 2012, Wang et al. 2010a, Xiao et al. 2011) and of even those that meet current regulatory guidelines (e.g., Hirata-Koizumi et al. 2011a, 2011b) failed to include concurrent controls treated in an identical manner with equimolar doses of the hydrolysis products (e.g., HCl, H_2SO_4). It is clear these hydrolysis products confound the interpretation of in vivo (e.g., Hirata-Koizumi et al. 2011a) and in vitro (Castorina et al. 2010, Cifone et al. 1987, Güngör et al. 2010, Kamalov et al. 2011, Morita et al. 1989, 1992) data, particularly where media Al concentrations $10 \mu\text{M}$ are equivalent to lethal or near-lethal serum Al concentrations in humans (Krewski et al. 2007). Only a handful of the relatively large numbers of published studies were designed for regulatory purposes. While ip injections and gastric intubations represent convenient routes of administration in the laboratory, inhalation and dietary studies are more appropriate for assessing human health risk.

The current pathways, sources and magnitude of current human Al exposures are broadly consistent with those measured four decades ago (reviewed in Krewski et al. 2007). Dietary Al intake depends on the age of the individual, soil characteristics (including pH) and local dietary customs. These differences are reflected in Al doses that range from $1.61 \mu\text{g/kg-week}$ for Russian infants to 8.47 mg/kg-week for Russian adults, values that were consistent with or higher than those for adolescent boys living in the Czech Republic (1.14 mg/kg-week) or for those living in Washington, D.C., San Francisco and St. Louis ($1.14\text{--}6.68 \text{ mg/kg-week}$) (Sorenson et al. 1974). Other surveys found Al dietary exposure was no greater than the 2 mg/kg-week PTWI for those living in the United States, Western Europe and the Canary Islands (ATSDR 2008, EFSA 2008, González-Weller et al. 2010), but it was

above the PTWI for toddlers living in the United Kingdom (2.4 mg/kg-week) (Rose et al. 2010), Japan (2.0–3.0 mg/kg-week) (Sato et al. 2014) and the EU (11.3–156 mg/kg-week) (EFSA 2013). The PTWI is based on studies with the highly bioavailable Al citrate (Benford et al. 2012, EFSA 2011); however, the oral bioavailability of the soluble and sparingly-soluble Al forms varies at least 10-fold (EFSA 2011) and insoluble Al silicates present in foods and beverages demonstrate essentially no uptake (Willhite et al. 2012). The validity of the assumption that the gastrointestinal bioavailability of all forms of ingested Al is equivalent to that of Al citrate (EFSA 2013) warrants further consideration.

Aluminum contamination of PN solutions continues to be of concern (Bohrer et al. 2010, Fanni et al. 2014, Hernández-Sandez et al. 2013, Poole et al. 2008, 2010, 2011, Popinska et al. 2010, Wier and Kuhn 2012). Recent reports (Fewtrell et al. 2009, 2011) confirm previous observations that Al contamination in PN solutions presents serious health risks for infants and neonates (Bates et al. 1985, Bishop et al. 1997, Fanni et al. 2014, Klein 1995, Klein et al. 1991).

The results of the present review support previous conclusions that there were no clear associations between vaccinations using Al adjuvants and serious adverse events (GACVS 2012, Kelso et al. 2012). Nevertheless, Al adjuvants increased injection site pain and tenderness (Table 4) and elicited sensitization to the metal (Table 5). The present review also identified controlled trials wherein vaccination without Al adjuvant provided equivalent response to vaccination with adjuvant and that vaccination with different Al forms produced a different response. Other recent studies found a limited immunogenic role for Al(OH)₃ adjuvant, or a diminished immune response to certain vaccines (Brady et al. 2009, Keitel et al. 2009, Manzoli et al. 2011, Liang et al. 2010, Yin et al. 2011, Zhu et al. 2009). Based on results with the relatively few published controlled trials with Al adjuvants it is not clear whether routine use of Al adjuvants represents best clinical practice. Where Al adjuvants provide demonstrable benefit, it is not clear which Al form(s) and dose(s) have the highest therapeutic ratio (Batista-Duharte et al. 2011).

Some (Byrne and Baugh 2008, Nel et al. 2006) have expressed concern that nanoparticles can be dangerous and that platelet and tubular Al nanoclays are cytotoxic (e.g., Lordan and Higginbotham 2012, Lordan et al. 2011, Verma et al. 2012, Wallace et al. 1985). However there is little correlation between Al nanoparticle toxicity in vitro and that observed in vivo, partly because the physical properties of the primary Al nanoparticles differ from the larger aggregates (Al nanoclusters) (Murdock et al. 2008) to which people are exposed. Acute oral (Prabhakar et al. 2011) and repeat exposure inhalation studies in rats (Pauluhn 2009a) and mice (Adamcakova-Dodd et al. 2012) with Al nanoparticles failed to identify adverse effects except at very high levels of exposure. Chronic occupational inhalation of nanoparticle-containing bauxite and other non-reactive Al dusts (Altekruse et al. 1984, Beach et al. 2001, Donoghue et al. 2014, Edling 1961, Gibbs and Pooley 1994, Hale et al. 1956, Lynch and McIver 1954, Oldham 1983, Rawlings et al. 1983, Sakula 1961, Taiwo 2014, Waxweiler et al. 1988) was associated with pneumoconiosis in exposed workers. These conditions are related to excessive particle loading of lung macrophages and impaired pulmonary clearance (Oberdörster 1995). Given the results with controlled inhalation of γ -AlO(OH) in rats, it appears preliminary estimates of health risk based on aggregate Al nanoparticle pulmonary

overload (Pauluhn 2011) are appropriate. The data suggest that the pulmonary response to inhaled engineered Al oxide nanoparticles will be similar to that seen after naturally-occurring bauxite nanoparticles are inhaled.

There is considerable variation in the OELs for metallic Al and the Al oxides under similar frequency and durations of exposure (Table 7). Both the Health Council of the Netherlands (2010) and the Nordic Expert Group (2011) concluded that existing data for metallic Al and its oxides are inadequate upon which to derive evidence-based OEL values. There remain concerns about reduced attention span, impaired cognition and deficits in fine motor skills among workers exposed to Al fume for many years (reviewed in Riihimäki and Aitio 2012). Nine studies (Akila et al. 1999, Bast-Petterson et al. 1994, 2000, Bowler et al. 2003, Flaten et al. 1996, Giorgianni et al. 2012, Hannien et al. 1994, Polizzi 2002, Riihimäki et al. 2000, Sjogren et al. 1990) identified adverse effects of Al fume on worker cognition, but four other studies (Buchta et al. 2005, Kiesswetter et al. 2007, 2009, Meyer-Baron et al. 2007) found no such changes. The reasons for these differences are unclear.

Of the many health risk issues discussed in this review, several in particular warrant further attention. These include consideration of relative bioavailability of different Al species in deriving human exposure guidelines, Al contamination of PN solutions, justification of the use of Al as vaccine adjuvants and the basis for and derivation of OELs for Al compounds. Resolution of these issues will require additional investigation, and the application of appropriate risk assessment methodologies to arrive at evidence-based risk management decisions (Landry and Sibbald 2001, Guzelian et al. 2005).

Abbreviations

Aβ	amyloid β peptide
ACH	aluminum chlorhydrate $\text{Al}_2\text{Cl}(\text{OH})_5 \cdot 2\text{H}_2\text{O}$
AChE	acetylcholinesterase
AD	Alzheimer's disease
AE	adverse events
AGD	anogenital distance
Al	aluminum
ALT	alanine aminotransferase
APP	β-amyloid precursor protein
apoE	apolipoprotein E
AST	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
AUC	area under concentration:time curve

BAT	Biologischer Arbeitsstoff-Toleranz-Wert
Bax	proapoptotic Bcl-2 associated protein
Bcl2	anti-apoptotic B-cell lymphoma-2-protein
BMC	bone mineral content
CA	chromosomal aberration
CAA	congophilic amyloid angiopathy
DBCP	double-blind placebo-controlled
DC	dendritic cells
DFO	desferrioxamine
DLB	dementia with Lewy bodies
DNEL	derived no effect level
DPT	diphtheria/pertussis/tetanus
DSB	double strand breaks
DTaP	diphtheria/tetanus acellular pertussis
EC	European Commission
EFSA	European Food Safety Authority
EPO	erythropoietin
ERER	erythrocyte rosette forming enhancing rate
ERIR	erythrocyte rosette forming inhibitory rate
FAO/WHO	Food and Agriculture Organization of the United Nations/World Health Organization
FDA	Food and Drug Administration
FOB	functional observational battery
FSH	follicle stimulating hormone
GD	gestational day
GFAAS	graphite furnace atomic absorption spectrophotometry
GLP	Good Laboratory Practice
GPx	glutathione peroxidase
GSH	reduced glutathione

GST	glutathione-S-transferase
HD	hemodialysis
HFT	hyperphosphorylated tau
ICP-AES	inductively-coupled plasma atomic emission spectroscopy
ICP-MS	inductively-coupled plasma mass spectrometry
IE	immunogenicity endpoints
IL	interleukin
im	intramuscular
ip	intraperitoneal
IPCS	WHO International Programme on Chemical Safety
Ire1β	serine/threonine-protein kinase/endoribonuclease 1
LDH	lactate dehydrogenase
LPO	lipid peroxidation
LTP	long-term potentiation
MAK	Maximale Arbeitsplatz-Konzentration
MDA	malondialdehyde
MEDI	maximum estimated daily intake
MN	micronuclei
MMF	macrophagic myofaciitis
MRL	minimal risk level
MMSE	Mini-Mental Status Examination
NSAID	non-steroidal anti-inflammatory drug
N2a	strain A mouse neuroblastoma
NDA	new drug application
NFT	neurofibrillary tangle
NFκB	anti-apoptotic nuclear factor kappa light-chain-enhancer of activated B cells
NLRP3	nucleoside binding domain, leucine-rich-repeat-containing family, pyrin domain-containing 3 inflammasome complex
OECD	Organisation for Economic Co-Operation and Development

OEL	Occupational Exposure Limit
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
PM	particulate matter
PN	parenteral nutrition
PND	postnatal day
PS	presenilin
RBC-C3bRR	erythrocyte C3b receptor rate
RCT	randomized control trial
PTWI	provisional tolerable weekly intake
RBC-ICR	erythrocyte C3B immune complex rosette rate
REL	recommended exposure limit
RfD	reference dose
ROS	reactive oxygen species
SALP	sodium aluminum phosphate
sc	subcutaneous
SCE	sister chromatid exchange
SEM	scanning electron microscopy
SOD	superoxide dismutase
T	testosterone
TBARS	thiobarbituric acid reactive substances
TEM	transmission electron microscopy
THGA	transversely heated graphic atomizer
TLV[®]	threshold limit value
TWA	time-weighted-average
TWI	tolerable weekly intake
UCL	upper confidence limit

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Table 1

Aluminum-induced neurotoxicity in laboratory animals.

Compound	Strain/Species/Sex	Exposure/Route/Frequency/Duration	Concentration/Dose	Response/Comment	References
AlCl ₃ (purity not specified)	Swiss mice ♂ (3–6 months of age)	Intraperitoneal Daily for 8 weeks	0 or 1.3 mg/kg-day	Duration-dependent ↑ Al in cerebellum, striatum, cortex, hypothalamus and brain stem Al measures by GFSAAS	Abd El-Rahman et al. (2011)
AlCl ₃ (purity and source not specified)	ICR mice (23.9 ± 1.96 g)	Dietary 100 days	0, 10, 50, or 300 mg/kg-day	Dose-dependent ↑ hippocampus and cortex MDA, ↑ mitochondrial 8-OHdG ↓ Hippocampus and cortex SOD	Rui and Yongjian (2010)
AlCl ₃	Kunming mice (20–25 g)	Intraperitoneal	0 or 40 mg/kg-day	No reduction body weight or abnormal clinical signs	Sun et al. (2009)
D-Galactose (chemical source and purity not specified)		Daily for 90 days	90 mg D-Galactose/kg-day	↑ Water maze escape latency at 90 days ↑ Hippocampus and cortex Aβ at 60, 75 and 90 days ↑ Hippocampus and cortex BACE ₁ at 45–90 days ↓ Hippocampus and cortex neprilysin (NEP) at 45–90 days	Foglio et al. (2012)
Al ₂ (SO ₄) ₃ with 10 or 86 mg/L silicic acid	C57BL/6 mice	Drinking water 12–15 months	0.04 M (pH 3.2–3.5)	Body weight gain, food and drinking water consumption not affected; duration-dependent ↓ nitergic neurons No concurrent Al control group	González-Muñoz et al. (2008a)
Al(NO ₃) ₃ • H ₂ O (Aldrich)	NMRI mice (gender not specified) (30 g)	Drinking water <i>ad libitum</i> 3 months	450 mg/L	No concurrent vehicle control group	González-Muñoz et al. (2008b)
Al(NO ₃) ₃ • H ₂ O (Aldrich)	NMRI mice (gender not specified) (30 g)	Drinking water <i>ad libitum</i> 3 months	450 mg/L	No concurrent vehicle control group	Sood et al. (2011)
AlCl ₃ (purity not specified)	Sprague-Dawley rat	Daily oral gavage 8 weeks	0 or 100 mg/kg-day	Cerebral cortex, midbrain and cerebellar ↓ATP levels, ↓ATP synthesis, ↑ATP hydrolysis, ↓succinate dehydrogenase, NADPH, cytochrome oxidase, NADH dehydrogenase	Sood et al. (2012)
AlCl ₃ (purity not specified)	Sprague-Dawley rat	Daily oral gavage 8 weeks	0 or 100 mg/kg-day	↑Focal inflammation and NO in cerebrum and cerebellum ↑Glial cell TNF-α, NF-κB, HSP70	Belaid-Nouria et al. (2012)
AlCl ₃ (purity not specified)	Wistar rat ♀	Gastric intubation daily for 1 month then drinking water <i>ad libitum</i> for 5 months	500 mg/kg-day 1600 mg/L	↑ Posterior brain, liver and plasma LPO ↑ LDH release	Ahmed et al. (2011)
AlCl ₃ (purity not specified)	Sprague-Dawley rat ♂ ♀	Gastric intubation daily for 4 months	0 or 100 mg/kg-day	↑ Whole brain AChE, LPO, homocysteine ↓ Whole brain folate, vitamin B12, GSH ↑ Plasma glucose, cholesterol, triglycerides and NO	Ahmed et al. (2011)

Compound	Strain/Species/Sex	Exposure/Route/Frequency/Duration	Concentration/Dose	Response/Comment	References
AlCl ₃ (purity not specified)	Wistar rat ♂	Oral intubation daily for 3 months	0 or 50 mg/kg-day	<ul style="list-style-type: none"> ↑ Necrosis and neurofibrillary tangles in both ♂ and ♀ ↓ Body weight ↑ Cerebral cortex neuronal loss, hemorrhage, gliosis, Bax expression ↑ Cerebral cortex AChE, SOD, MDA, protein oxidation ↓ Cerebral cortex Na⁺/K⁺-ATPase activity, GPx, GST, GSH ↓ ChAT, NGF-TrkA and muscarinic receptor M1 expression 	Bihaqi et al. (2009)
AlCl ₃ (source and purity not specified)	Sprague-Dawley rat ♂ (200–210 g)	Intraperitoneal injection once daily for 4 days	0 or 5.0 mg/kg-day	<ul style="list-style-type: none"> Rats killed 2 weeks after final injection ↑ Necrosis and mitochondrial degeneration in cerebral cortex and pyramidal neurons ↑ Perivascular edema in cerebral cortex 	Colak et al. (2011)
AlCl ₃ (source and purity not specified; fresh solution every 4 days)	Sprague-Dawley rat (gender not stated) (180 ± 10 g)	Intraperitoneal injection once daily for 90 days	0 or 40 mg/kg-day	<ul style="list-style-type: none"> ↓ Cerebral and cerebellar AChE, GSH-Px, GSH, SOD, catalase ↑ Cerebral and cerebellar LPO ↑ Cerebral and cerebellar Ca and Zn ↑ A disintegrin metalloprotease, P53, Bcl-2, IL-4, IL-2 ↓ AChE expression 	Elsaid et al. (2011)
AlCl ₃ (source and purity no specified)	Albino rat ♂	Intraperitoneal injection daily for 28 days	0 or 4.2 mg/kg-day	<ul style="list-style-type: none"> ↑ Cerebral cortex, cerebellum, hippocampus LPO ↓ Cerebral cortex, cerebellum, hippocampus GAS, SOD, GPx, GST, Na⁺/K⁺-ATPase 	Sumathi et al. (2011)
Al (chemical form, source and purity not specified)	Wistar rat ♂ (100–120 g)	Gastric intubation daily for 4 weeks	0 or 10 mg/kg-day	<ul style="list-style-type: none"> No change relative brain weight No change cerebral GSH, GSH-Px, SOD, glutathione reductase or catalase activities No change cerebral LPO 	Nayak et al. (2010)
Al (chemical form, source and purity not specified)	Wistar rat ♂ (100–120 g)	Gastric intubation daily for 4 weeks	0 or 10 mg/kg-day	<ul style="list-style-type: none"> ↓ Body weight gain No change absolute or relative brain weight, cerebrum acid or alkaline phosphomonoesterase or aspartate aminotransferase activities ↑ Cerebrum alanine aminotransferase No change cerebrum amino acid homeostasis 	Nayak et al. (2011)
Al(NO ₃) ₃ (chemical purity and source not specified)	Sprague-Dawley rat ♀ (160 ± 10 g)	Intraperitoneal injection daily for 60 days	0 or 27 mg/kg-day	<ul style="list-style-type: none"> ↓ Fore- and midbrain AChE activity ↑ Hindbrain ATPase activity ↑ Forebrain LPO ↓ Forebrain SOD, catalase; no change GSH ↑ Cerebral neurofibrillary and Purkinje degeneration 	Shrivastava 2012
AlCl ₃ (Sigma)	Wistar rat ♂ (500 ± 50 g)	Intrahippocampal injection Single dose	0 or 0.37 mg/kg	<ul style="list-style-type: none"> ↓ Hippocampus AChE at 10 min, 3 hr, 3 and 30 days post-injection 	Stevanovi et al. (2011)

Compound	Strain/Species/Sex	Exposure/Route/Frequency/Duration	Concentration/Dose	Response/Comment	References
$\text{Al}(\text{NO}_2)_3$	Wistar rat ♂	Single intraperitoneal injection	0 or 32.5 mg/kg	<ul style="list-style-type: none"> ↑ Hippocampus NO ↓ Number correct active avoidance responses at 28–30 days post-injection 	Bhadauria 2012
AlCl_3 (purity not stated)	Rabbit (strain and sex not specified)	Drinking water <i>ad libitum</i> 3 months	0 or 20 mg/L (5–6.6 mg AlCl_3 /day per 1 kg rabbit)	<ul style="list-style-type: none"> ↓ Forebrain, midbrain, hindbrain AChE ↑ Brain, liver, kidney LPO ↓ Brain, liver, kidney GSH 	Abd-Elghaffar et al. (2007)
AlCl_3 (source and chemical purity not specified)	New Zealand White Rabbit	Intracerebral injection Single dose per Klatzo et al. (1965)	0 or 1.4% aqueous	<ul style="list-style-type: none"> ↑ Total Al in brain ↑ Atrophy in cerebral cortex, hippocampus ↑ Brain perivascular edema ↑ Brain LPO Spectrophotometric Al measures ↓ 16% brain cytochrome c oxidase Vmax at 10 days post-exposure ↓ Mitochondrial O_2 consumption No clinical signs mentioned 	Alleyne et al. (2011)

Table 2

Neurobehavioral studies with aluminum in laboratory animals.

Compound	Strain/Species/Sex	Exposure/Route/Frequency/Duration	Concentration/Dose	Response/Comments	References
AlCl ₃	Wistar rat ♀	Drinking water during lactation	0, 200, 400, 600 or 800 mg/kg-day	Offspring tested in shuttle box for passive avoidance; no change at 600 mg/kg-day. Variable responses at 800 mg/kg-day	Ali et al. (2008)
10 mm Al ₂ O ₃ < 50 nm γ-Alumina	ICR mice ♂	ip injection (frequency and duration not specified)	0 or 100 mg/kg	Nano Al more potent than micro Al. No change swimming speed; ↑Escape latency; ↓target quadrant time, platform crossings Mice killed 10 days post-dosing ↓ Hippocampus mitochondrial membrane potential; ↑ ROS, apoptosis and necrosis	Zhang et al. (2011b)
AlCl ₃ (purity not specified)	Wistar rat ♂ (90–100 days of age)	ip injection Daily for 60 days	0 or 100 mg/kg-day	↑Body weight No change swimming speed ↑ Rearing, step-through latency ↑ Time to completion Morris Water Maze ↑ Errors on radial arm maze	Abdel-Aal et al. (2011b)
AlCl ₃ (source and purity not specified)	Wistar rat ♂	ip injection Daily for 60 days	0 or 4.2 mg/kg-day	↑ Escape latency; ↓ target quadrant time, ↓rotarod retention time ↓ Circulating hemoglobin ↑ Cerebral cortex and hippocampus pyknosis ↓ Serum and neuronal AChE ↑ Whole blood and whole brain SOD, G-6-P dehydrogenase, MDH	Chakrabarty et al. (2012)
AlCl ₃ (source and purity not specified)	<i>Drosophila melanogaster</i> 220 2U and mutants	Dietary 34–61 days	0, 0.5, 2, 5, or 10 mM	Dose-dependent ↓ lifespan Dose-dependent ↓ locomotion Dose-dependent ↓ learning ability ↑ Brain degenerative vacuoles at 10 mM ↑ Mitochondrial SOD No change lifespan or locomotion after 2 mM in AB42Arc overexpression flies or in human tauR406W—transfected flies	Wu et al. (2012a)
AlCl ₃ (source and chemical purity not specified)	Sprague-Dawley rat (3 day old) 16/group	ip injection daily for 14 days	0, 7 or 35 mg Al/kg-day	Dose-dependent ↑ hippocampus, diencephalon, cerebellar Al, and LPO ↓ Brain SOD No change body weight gain	Yuan et al. (2012)
AlCl ₃ (analytical grade)	Wistar rat ♂ (24 months old; 463 g)	Oral intubation daily for 90 days	0 (distilled water) or 100 mg/kg-day as aqueous gum acacia suspension	↑ Cerebellar Al LPO ↑ Purkinje cell damage ↓ Cerebellar weight ↓ SOD, catalase, GSHPx activity Prolonged righting reflex time ↓ Performance rota rod test	Tripathi et al. (2011)
AlCl ₃	APP/PS1 mice	Intracerebral injection		↓ Performance Morris water maze ↓ Neural cells	Zhang et al. (2012)

Table 3

Aluminum-induced cytotoxicity in vitro.

Compound	System	Exposure	Duration	Concentration	Response/Comments	References
Al glycinate (Tokyo Kasei Kogyo)	Cultured mouse primary cortical astrocytes	48 h or 6–12 h followed by 7 day control media culture		0.1 mM	No change anti-apoptotic Bcl2, pro-apoptotic Bax, IRE1 α , PERK, Bbc3/PUMA, ATF6 α , ATF6 β , CHOP/GADD15, OASIS, STC2 ↑ Irf β after 6–12 h indicates endoplasmic reticulum stress No concentration-response data	Aremu et al. (2011)
Al (C ₃ H ₅ O ₃) ₃	Synthetic A β ₁₋₄₂ SH-SY5Y Human neuroblastoma cells	48 h A β PP measures 72 h tau 181 measures		5 μ M Al 0.5 μ M A β -Al	↑ A β -Al annular protofibrils and fibril oligomers ↑ A β -Al spherical oligomers and extended β -sheet ↑ A β PP α at 48 and 72 h after A β -Al ↑ tau 181 at 72 h after A β -Al	Bolognin et al. (2011)
AlCl ₃ (Sigma) A β ₍₂₅₋₃₅₎	SH-SY5Y Human neuroblastoma cells	24, 48, 72 and 96 h		1, 10, 50, 100 and 300 μ M Al 2, 10, 20 and 100 μ M A β ₍₂₅₋₃₅₎	↑ Lethality at > 10 μ M A β ₍₂₅₋₃₅₎ No change mitochondrial activity 300 μ M Al Al dose-dependent ↑ death after co-treatment with 2 μ M A β ₍₂₅₋₃₅₎ ↓ β -secretase (BACE1 and BACE2) expression with 10 μ M Al and 2 μ M A β ₍₂₅₋₃₅₎	Castorina et al. (2010)
Al maltolate	SH-SY5Y Human neuroblastoma cells	24 h		50–800 μ M	No change viability or morphology at 200 μ M ↓ Cell bodies, neuritis and viability at 400 μ M ↓ Brain-derived neurotrophic factor (BDNF)-induced cytoskeleton-associated protein (Arc) expression at 200 μ M ↓ BDNF-enhanced phosphor-ERK expression at 200 μ M ↓ BDNF-induced phosphorylation, 4EBP, p70S6K, eIF-4E at 200 μ M	Chen et al. (2011a)
Al maltolate	Sprague-Dawley rat cortical neurons	1, 3, 5, and 7 days		5–200 μ M or 12.5 μ M for 7 days	↓ Viability at 7 days with 12.5 μ M No change sAPP α or full-length cellular A β PP Co-treatment with 25 μ M Rho-kinase inhibitor Y-27632 ↓ cytotoxicity and amyloid fibrils	Chen et al. (2010a)
AlCl ₃ • 6H ₂ O (Sigma)	Synthetic A β ₄₀ peptide	2–100 s		500 μ M – 20 mM	↓ A β oligomerization with Al at 50 μ M Zn ²⁺ and Cu ²⁺ ↑ A β oligomer formation ↑ Buffer acidity and ↑ A β amorphous aggregation at > 200 μ M ↑ A β hydrophobic cluster exposure at 500 μ M	Chen et al. (2011b)
Al ³⁺ (Perkin Elmer stock solution; chemical form not stated)	Synthetic human pro IAPP (1–48) (pancreatic islet amyloid polypeptide)	7–14 days		320 μ M	↓ ProIAPP (1–48) amyloid formation ↑ ProIAPP (1–48) spherulites	Esley et al. (2010)
KAl(SO ₄) ₃	10 nM Recombinant insulin-degrading enzyme Synthetic A β ₁₋₁₆ Synthetic A β ₁₆₋₂₈	0.5–5.0 h		100 μ M	No influence of Al ³⁺ on IDE activity	Grasso et al. (2011)

Compound	System	ExposureDuration	Concentration	Response/Comments	References
AlCl ₃ (source and chemical purity not specified)	Cell-free clarified rhodamine-conjugated 5 μm phosphorylated neurofilaments (NF) from adult C57/BalBc mouse spinal cord	30 min	1 μM – 4 mM	Dose-dependent ↑ neurofilament aggregation NF phosphorylation by cdk5 neurin inhibited AlCl ₃ – induced aggregation	Kushkuley et al. (2010)
Al lactate (source and chemical purity not specified)	Human CCF-STTG1 astrocytes Human HepG2 hepatocytes	24 h	0, 0.01–0.1 mM 0, 0.01–0.25 mM	Dose-dependent ↑ α-ketoglutarate and lipid accumulation ↓ γ-Butyrobetaine aldehyde dehydrogenase ↓ Butyrobetaine dioxygenase	Lemire et al. (2011)
K[Al (C ₇ H ₁₁ O ₆) ₃] (Al quinate)	Primary Sprague-Dawley rat hippocampal cells	3 or 24 h 96 h	10, 100 or 500 μM Al ³⁺	Dose-dependent ↓ neuron survival at 3 h ↓ Glial cell survival at 500 μM at 3 h	Nday et al. (2010)
Soluble Al ³⁺ (1% HCl, Sigma) with 50 μM Na citrate (Sigma)	Mouse N2a neuroblastoma cells expressing APP695 isoform 8.2 pg Aβ _(1–40) /ml negligible Aβ _(1–42)			Aβ _(1–40) ↑ neuronal and glial cell death No change cell survival after Aβ _(1–40) and 50 μM Al ³⁺ K[Al (C ₇ H ₁₁ O ₆) ₃] toxicity reduced compared to Al ³⁺	
Al ₂ (SO ₄) ₃	<i>Saccharomyces cerevisiae</i> BY4743	24 h	0–3.2 mM	↓ Concentration-dependent growth at 0.8–1.6 mM Disruption of Pdr5p detoxication pathway ↑ Al ³⁺ accumulation and ↑ cytotoxicity	Wu et al. (2012c)
AlCl ₃ Tridecameric Al polycationic sulfate (nano-Al ₁₃)	Porcine heart malate dehydrogenase	0–400 s	0 or 30 mM	↑ Malate dehydrogenase at pH 7.5	Yang et al. (2011)
Al maltolate AlCl ₃	Sprague-Dawley rat (3 day old neonate) primary cortical astrocytes	12, 24, 48 and 72 h	0, 200, 400, 800, 1600 μM	Concentration and duration-dependent ↑ apoptosis and lethality ↑ Beclin 1 ↑ LC3II ↓ LC3I Al maltolate was more potent than AlCl ₃	Zeng et al. (2011)
AlCl ₃ • H ₂ O	Human neuroblastoma SH-SY5Y	48 h	0 or 2–8 mM	Concentration ↑ apoptosis and necrosis Percentage of cells with necrosis was always higher than those with apoptosis Treatment with caspase-3 siRNA and Nec-1 reduced cell death	Zhang et al. (2010a)
AlCl ₃ • H ₂ O	Rat gliatoma C6	24 h	0 or 1–8 mM	↑ apoptosis ↑ necrosis ↑ cytochrome c release ↑ Bax expression	Zhang et al. (2010b)

Table 4

Human studies with intramuscular aluminum-adjunct vaccines.

Study design	Population/Sample	Substances	Outcomes studied	Results	References
DBPC*	Healthy adults, 18–40 years stratified by age ($n = 48-50/$ group)	AI (OH) ₃ in influenza inactivated whole virus A/H1N1 vaccine; 2 doses (0.5 ml per dose with 0.35 mg AI), 28 days apart 7.5 and 15 µg of hemagglutinin antigen (HA) with and without AI (OH) ₃ and 45 µg of HA without AI (OH) ₃ Control group received saline	<i>Immunogenicity endpoints (IEs):</i> hemagglutinin inhibition (HI) and neutralization assays were performed/ <i>Adverse events (AEs):</i> Subjects self-recorded their oral temperature and the presence and severity of injection site reactions (pain, tenderness, redness and swelling) and systemic symptoms (fever, malaise, myalgia, headache, and nausea) on a memory aid during the first 2 months after enrollment. SAEs were defined as life-threatening AEs, or AEs that resulted in significant or persistent disability, congenital anomalies, hospitalizations, or death and were reported during the 7-month study period	308 subjects were enrolled in the study, with 299 receiving both doses of vaccine. Baseline demographic characteristics and pre-immunization status did not differ among groups <i>IEs:</i> Increase in serum hemagglutination-inhibition (HAI) and/or neutralizing antibody after two doses was higher in participants received vaccine formulations without AI adjuvant (7.5 µg – AI and 15 µg – AI groups) compared to 7.5 µg + AI and 15 µg + AI groups (38 and 53% versus 16 and 38%, respectively) <i>AEs:</i> AI adjuvant- containing vaccine increased frequency of local reactions without increased systemic reactivity. Inclusion of AI adjuvant reduced immune responses and increased local reactions AI (OH) ₃ did not enhance HAI or neutralizing antibody responses, and contributed to increased injection site pain	Keitel et al. (2009)
DBPC*	Healthy participants ($n = 12,691$), stratified by age: (3 to < 12 years ($n = 2,828$); 12 to < 18 years ($n = 2,887$); 18–60 years ($n = 4710$); > 60 years ($n = 2,266$))	AI (OH) ₃ in influenza A (H1N1) split-virion (SV) and whole virion (WV) vaccines; 2 doses (0.5 mg AI/ml of SV vaccine and 1.2 mg AI/ml of WV vaccine), 21 days apart SV: 30, 15 or 7.5 µg HA per dose with and without AI (OH) ₃ ; WV: 10 or 5 µg HA per dose with AI (OH) ₃ Control group received sterile water or phosphate buffered saline injection	<i>IEs:</i> Geometric Mean Titre (GMT) of hemagglutination inhibition (HI) antibody and proportion of seroprotected AEs: Participants recorded any adverse events for 30 min after receipt of vaccine or control treatment and solicited adverse or any unsolicited events throughout the study Symptoms of Guillain-Barré syndrome were recorded. Information about serious adverse events (SAEs) ² and adverse events of special interest was obtained by diary cards, spontaneous reports, and hospital admission records throughout the study	All participants received the first dose on day 0, and 12,348 participants received the second dose on day 21 <i>IEs:</i> In groups that received SV formulations with similar antigen content (15 µg) with or without AI adjuvant, GMTs for non-adjunct formulations (167.8 and 225.0, respectively) were significantly higher than were those for adjunct formulations <i>AEs:</i> No immediate systemic allergic reactions, serious adverse events, or events suggestive of Guillain-Barré syndrome were reported in any group. The adjunct formulations had a higher rate of adverse events than non-adjunct formulations. Increased antigen dose and young age were associated with a higher frequency and severity of adverse effects. The authors mentioned that WV formulation was not given to children or adolescents because of concerns about adverse reactions	Liang et al. (2010)

Study design	Population/Sample	Substances	Outcomes studied	Results	References
Analysis of data from Liang et al. (2010) study	Healthy volunteers ($n = 3,520$), stratified by age (3–7, 8–12, 13–18, 19–40, 41–60 and 61 years)	A1 (OH) ₃ in influenza A (H1N1) split-virion (SV) vaccine formulations; 2 doses (0.5 mg Al/ml per dose), 21 days apart Control group received sterile water or phosphate buffered saline injection	IEs: Increase in GMT from day 0 (vaccination) to day 21, 35 and 42 compared to non-adjunctive vaccine	IEs: Reduced immune response after considering time post-vaccination, age and gender was reported in A1-adjunctive contained vaccine group. Peak immune response (GMT) was observed on day 35 in non-adjunctive group. Highest GMTs for adjunctive group were observed on day 41	Yin et al. (2011)
DBPC*	Healthy adults (males and females), 23–42 years ($n = 5-30$) randomly assigned for each group, stratified by gender with a 1:1 allocation ratio)	A1 (OH) ₃ in influenza A/H1N1 monovalent vaccine; 2 doses (0.25 mg per dose), 21 days apart 7.5 and 3.5 µg (HA) with Al (OH) ₃ (Group I and Group II, respectively) Control group received phosphate buffered saline	IEs ³ : Percentage seroconversion ⁴ at day 21 (%) after first and second vaccination, the proportion of seroprotected participants (with post-vaccination HI antibody titer 1:40) (%), increase in GMT measured before and 21 days after each vaccination AEs: Participants recorded the occurrence of unsolicited and solicited local (pain, bruising, redness, and swelling), and systemic (fever, chills, malaise, muscle aches, arthralgia, nausea, and headache) symptoms during three days after each vaccination	Of 357 subjects assessed, 266 underwent randomization. The age and gender distributions were similar among the groups. 100% ($n = 266$) received the first vaccination and 94.4% ($n = 251$) received the second vaccination. The age and gender distributions were similar among groups IEs: Seroconversion at day 21 (after first/second vaccination [mean (95% Confidence Interval (CI))]: Group I: 47.6(25.7–70.2)/60.0(36.1–80.9) Group II: 26.9(11.6–47.8)/48.0(27.8–68.7) Control group: 0(0–52.2)/0(0–52.2) Proportion of seroprotected participants (after first/second vaccination) [mean (95% Confidence Interval (CI))] Group I: 57.1(34.0–78.2)/70.0(45.7–88.1) Group II: 38.5(20.2–59.4)/52.0(31.3–72.2) Control: 0(0–52.2)/0(0–52.2) Increase in GMT (after first/second vaccination) [mean (95% Confidence Interval (CI))]: Group I: 36.2(22.6–58.0)/38.6(27.1–55.2) Group II: 21.7(15.2–31.0)/33.9(23.1–49.6) Control group: 10(5.4–18.4)/10(5.4–18.4) AEs: No deaths or other SAEs were reported. No local adverse events were reported by Group II participants and by 54% Group I participants. Mild and moderate pain (19 and 27%), moderate redness and swelling (4 and 4%, respectively) were the most frequent local events reported by participants from Group I. Only mild pain at the injection site was reported by Control group participants (10%) Systemic reactions: Malaise, nausea and headache were reported more often by	Precioso et al. (2011)

Study design	Population/Sample	Substances	Outcomes studied	Results	References
DBPC *	Healthy volunteers, 3–77 years, stratified by age (young children, 3–11 years of age, $n = 440$), adolescents, 12–17 years of age, $n = 550$), adults, 18–60 years of age, $n = 660$), and the elderly, 61 years or older, $n = 550$)	AI (OH) ₃ in influenza A/H1N1 monovalent, split-virus vaccine; 2 doses (administered volume not reported), 1.2 mg alum/ml of vaccine), 21 days apart AI (OH) ₃ , 7.5 µg of HA with AI (OH) ₃ Control group received phosphate-buffered saline	IEs: Proportions of seroprotected subjects (with an increase in the HI titer by a factor of 4 or more) on day 21 after the first dose and on day 35 (14 days after the second dose) AEs: The presence of any systemic reaction or injection-site reaction 30 min after injection and during 21 days after the first dose and 14 days after the second dose	participants from Group I than Group II (8, 8, and 23% versus 3, 3, and 7%, respectively) 2,200 subjects received one dose, and 2,103 (95.6%) received the second dose of vaccine or phosphate-buffered saline IEs: Reduced immune response was seen in younger and older subjects after first vaccination compared to adolescents and adults. Vaccine without adjuvant was associated with greater immune responses than was vaccine with adjuvant AEs: No serious vaccine-related adverse events were reported. A higher rate of local injection-site reactions was associated with AI adjuvant and the second dose ($p < 0.001$ and $p = 0.002$, respectively). A higher rate of systemic reactions was associated with age only. The most common injection-site reaction in all groups was injection site pain. In the AI adjuvant groups the proportion of systemic reactions was less than the control	Zhu et al. (2009)
RCT,**	Medically stable, 65 years and older ($n = 57$ –120/group)	AI (OH) ₃ in inactivated subvirion influenza A/H5N1 vaccine; 2 doses (0.25–0.5 ml per dose, 1.2 mg AI per ml), 28 days apart 3.75, 7.5, 15 and 45, µg of HA were formulated with or without AI (OH) ₃ Control group was not included in the study	IEs: Microneutralization (Neut) and HAI assays AEs: Nurses recorded acute events during 15 min after each immunization. Participants recorded their oral temperature and the presence and severity of injection site findings (pain, tenderness, redness, and swelling) and systemic symptoms (feverishness, malaise, myalgias, headache, and nausea) during 7 days after each immunization; nurses interviewed patients in the clinic on days 2 and 8 after each vaccination, follow up information was collected 28 days after each vaccination and 6 months after the second vaccination, the interim medical history was reviewed	600 subjects were enrolled in the study; 599 received the first vaccination and 545 received the second. No differences in gender, ethnicity, race, or age were noted between the vaccine groups. GMTs and Neut before vaccination were similar among all groups IEs: Significant dose-related increase in antibody response at 28 days after the second vaccination in both the adjuvant and non-adjuvant groups ($p < 0.01$) was observed. Antibody responses to the vaccine were not influenced by AI(OH) ₃ at any dose of HA AEs: Participants who received vaccine with AI(OH) ₃ had increased injection site tenderness with HA doses (except at 45 µg HA) during 7 days after the first and the second vaccinations ($p = 0.01$) and pain after the first vaccination only compared to vaccine without AI(OH) ₃ . In the 45 µg HA dose group, the frequencies of tenderness and pain increased after the first vaccination compared to the second vaccination. No gender-related differences in injection site reactions were noted. There were no HA dose-related increases in systemic reactions in	Brady et al. (2009)

Study design	Population/Sample	Substances	Outcomes studied	Results	References
RCT,**	Healthy children, stratified by age (0.5–3 years, 3–18 years, and 9–17 years ($n = 30$ participants per each group))	AI (OH) ₃ influenza monovalent A/H5N1 vaccine formulations; 2 doses (0.25–0.5 ml per dose with 1.2 mg AI/ml of vaccine), 21 days apart 30 and 15 µg of HA with and without AI adjuvant, respectively, and 7.5 and 3.5 µg of HA without AI adjuvant No control group	<i>IEs</i> : Increase in GMT from vaccination day 0 to day 21 <i>AEs</i> : Parents recorded adverse events occurring up to day 21 after vaccination. The daily occurrence of solicited systemic and injection site reactions were recorded up to day 7 following vaccination. During the following visit, investigators collected information from the children and their parents and assessed whether they were vaccine-related	either AI(OH) ₃ adjuvant or non-adjuvant groups <i>IEs</i> : The full dose (30 µg + AI) formulation was more immunogenic than the half dose (7.5 µg – AI) in all age groups. In the full dose (30 µg + AI) group, the proportion of subjects with GMTs 32 after the second vaccination was 60% (9–17 years), 70% (3–8 years) and 50% (0.6–3 years) and in the half-dose (15 µg + AI) group – 30% (0.5–3 years). In the full dose (30 µg + AI) group, neutralizing antibody response 21 days after two injections was 92% (9–17 years), 106% (3–8 years) and 72% (0.5–3 years); in the half dose (15 µg + AI) group, response was 60.2% (0.5–3 years) <i>AEs</i> : In group given 30 µg + AI(OH) ₃ pain was reported in 40% and 63% of 9–17 and 3–8 year old participants, respectively. Complaints of tenderness at the injection site in 44% of 0.5–3 years old participants. Pain was the most frequently reported event in children aged 0.5–3 years who received half-dose (15 µg + AI) formulation. Systemic reactions were headache 10% (9–17 years), myalgia 40% (3–8 years), vomiting 30%, irritability 30%, abnormal crying 50%, anorexia 36% (0.5–3 years). In the half dose (15 µg + AI) group, one child (2 years) had musculo-papule rash for 1 day and another (2 years old) had an injection site papule and mild itching that resolved after 2 days	Chopitayasunomdh et al. (2008)
RCT,**	Healthy females ($n = 960$), stratified by age: 9–14, 15–19, and 30–25 years ($n = 240$ –241/group)	AI (OH) ₃ in the human papillomavirus (HPV) – 16/18 ASO4 ⁶ adjuvanted vaccine 2 doses (0.5 ml) of 20/20 F ⁷ at 0, 6 months, 40/40F at 0, 6 months, 40/40 F ⁸ at 0, 2 months, or 3 doses of 20/20 F at 0, 1 or 6 months Control dose contained 0.5 mg AI(OH) ₃ .	<i>IEs</i> : Geometric mean antibody titer (GMT) one month after the last active dose: antibody concentrations to HPV-16 and HPV-18 were measured by the enzyme-linked immunosorbent assay (ELISA) and antibody concentrations greater than or equal to the lower limit of detection for each assay were pre-specified to indicate seropositivity ⁹ <i>AEs</i> : Parents or participants recorded solicited local symptoms (pain, redness or swelling at injection site) and general symptoms (fever,	961 girls and young women were enrolled into study; 960 received at least one vaccine injection <i>IEs</i> : The kinetics of antibodies against both HPV-16 and HPV-18 in the 2-dose vaccine groups for girls (9–14 years) were similar to those observed in the licensed 3-dose vaccine group for young women (15–25 years) <i>AEs</i> : No participants withdrew from the study due to an AE or SAE. Pain was the most frequently reported local symptom (81 to 86% of all doses across groups). No urticaria or rash was observed within 30 min after any vaccine dose in any group. Headache, fatigue and myalgia were the most frequently reported systemic complaints. In total cohort ($n =$	Romanowski et al. (2011)

Study design	Population/Sample	Substances	Outcomes studied	Results	References
RCT ^{*,**}	Healthy adolescents, 10–18 years of age, randomly assigned to three groups stratified by the received dose ($n = 209$ – 224 /group)	AI (OH) ₃ in combined diphtheria-tetanus-acellular pertussis (dTpa) vaccine; 1 dose (0.5 ml per dose with 0.133, 0.3 or 0.5 mg AI per 0.5 ml dose of vaccine) All three vaccine formulations were different only in their total AI content All antigens were fully adsorbed with AI (OH) ₃ Vaccine formulations were preservative-free No control group was included	headache, fatigue, gastrointestinal symptoms, arthralgia, myalgia, rash or urticaria) occurring 30 min and 7 days after each vaccination were recorded using a diary card. SAEs, other medically significant conditions (i.e., AEs prompting emergency room or physician visits that were not related to common diseases), new onset chronic diseases including new onset autoimmune diseases and pregnancies occurring through month 24 were documented. Pregnancies were followed until delivery. New onset chronic diseases and new onset autoimmune diseases (potential autoimmune events, which excluded allergy-related events or isolated signs and symptoms) were identified by comparing all reported AEs with a pre-defined list of potential chronic diseases derived from the Medical Dictionary for Regulatory Activities	721) through month 24, no adverse events leading to premature discontinuation of vaccine were reported. Medically-significant adverse effects and new onset autoimmune diseases were reported at a similar frequency across groups	Theeten et al. (2005)
			<i>IE_s</i> / <i>I₀</i> : Booster response rate to all vaccine antigens (diphtheria and tetanus or pertussis) and post-vaccination increase of geometric mean antibody concentration (GMC) induced by each of the formulations at 1 month after booster administration <i>AEs</i> : Patients self-monitored adverse events to record local redness, swelling and pain, systematic symptoms of fatigue, fever, headache, malaise and vomiting at the day of vaccination and during 14 days after vaccination; follow-up information on unsolicited symptoms. SAEs were collected from patients	647 subjects were vaccinated. 214 (33%) received the 0.133 mg AI formulation, 209 (32%) – 0.3 mg AI formulation and 224 (35%) – 0.3 mg AI formulation. All subjects were included in the safety analysis and 631 subjects – in immunogenicity analysis. The demographic profiles of the three groups were comparable. All groups were similar in their pre-vaccination serological status <i>IEs</i> : The booster immune response to diphtheria and tetanus was not significantly different among different groups. Post-vaccination anti-PT GMC was significantly higher in the 0.5 mg AI group compared to both groups with reduced AI content ($p < 0.0167$). Among the three dTpa formulations, the 0.5 and 0.3 mg AI doses produced a PT response within clinically acceptable limits	

Study design	Population/Sample	Substances	Outcomes studied	Results	References
Prospective observational study	Healthy children, 6–7 years old ($n = 243$)	AI (OH) ₃ in tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccines: single dose (0.33 mg AI (OH) ₃ /dose). All children received government-provided diphtheria-pertussis and tetanus (DPwT) vaccine for the first 3 doses. No control group was included	during 30 post-vaccination days	Initial serological status influenced the immune response in all groups. Among participants seronegative prior to booster vaccination, post-vaccination GMT concentrations were reduced and booster response rates were increased <i>AEs:</i> No significant differences among study groups in local or systemic effects were observed. The incidence of fever, headache, fatigue, and gastrointestinal distress had an onset within 2 days of follow up and were similar between groups. 65% in each group reported at least one systemic symptom. Systemic events tended to increase with increasing AI dose. Solicited general symptoms were rare but tended to increase with increased AI dose. A significant difference among study groups was found only for fatigue (grade 3) with onset within 14 days post-vaccination (number/percentage of subjects/95% CI) [4/1.9 (0.5–4.7), 9/4.3 (2.0–8.0), and 18/8.0 (4.8–12.4) for 0.133, 0.3 and 0.5 mg AI dose groups, respectively].	Wei et al. (2011)
Prospective observational study	Healthy adults, health care workers, from 30 to 50 years ($n = 207$)	All participants received the tetanus-diphtheria-acellular pertussis (Tdap) vaccine (no other details available)	<i>Post-vaccination AE</i> (up to 5 years after last vaccination): Local adverse events (pain, redness, and swelling) and systemic adverse events (e.g., fever, headache, and fatigue), as well as entire limb swelling were recorded. Unsolicited adverse events that occurred after Tdap vaccination were also recorded. Specific	A total 263 children were evaluated and 243 were enrolled in the study. <i>AEs:</i> Increased local skin redness 47 (19%) children, induration in 57 (23%), tenderness in 130 (53%), and fever in 12 (5%) children. Twenty-one (9%) participants reported itching around the injection site, with or without local redness and induration. Redness and induration resolved in 7 days and fever resolved on day 4. The adverse events were not associated with gender or BMI above the mean No seizures, major neurologic reactions or other rare events were observed; reported adverse events after Tdap vaccination were mild	Sandora et al. (2009)

Study design	Population/Sample	Substances	Outcomes studied	Results	References
Meta-analysis	12,375 children (up to 18 months and 10–16 years of age)	Al (OH) ₃ adjuvant-containing vaccines	Summary data from studies on adverse events following administration of Al (OH) ₃ -containing vaccines	<p>tetanus-diphtheria vaccine. Systemic adverse events were more common among those < 30 years age (OR, 4.15 [95% confidence interval, 1.94–8.86]). Limited details available regarding study design and outcomes</p> <p><i>AEs:</i> Vaccines with Al (OH)₃ increased erythema and induration compared to non-adjuvanted vaccines (OR) 1.87 [95% CI 1.57–2.24] and significantly fewer reactions of all types (OR 0.21 [95% CI 0.15–0.28]). Frequencies of local reactions of all types, collapse or convulsions, and persistent crying or screaming did not differ between the cohorts. There was no association between Al adjuvant-containing vaccines and onset of local induration or swelling. Increased local pain was reported up to 14 days (OR 2.05 [95% CI 1.25–3.38])</p>	Jefferson et al. (2004)
Meta-analysis	18 randomized clinical trials (<i>n</i> = 18,444)	Al adjuvant-containing vaccines	<p><i>IEs:</i> Seroreversion <i>I1</i> and seroresponse/ seroprotection <i>I2</i> <i>AEs:</i> Nurses and/or participants recorded fever, any systemic reaction, injection- site pain and any local reaction during the first 7–10 days after vaccination. Serious events (life-threatening events, or events resulting in persistent disability, hospitalization or death) were recorded separately</p>	<p><i>IEs:</i> Comparing Al adjuvanted to Al non-adjuvanted vaccines at equal dose, Al adjuvant vaccines were less immunogenic than non-adjuvant formulations at any age, especially after single dose injection <i>AEs:</i> Direct-comparison meta-analyses showed that Al adjuvanted vaccines at the same dose compared to the non-adjuvanted vaccines significantly increased the risk of local reactions, specifically injection site pain. <i>AEs</i> definition was not always fully standardized and similar across trials. Potential limitations to the database include some non-randomized trials that were used in the proportion meta-analyses</p>	Manzoli et al. (2011)
Integrated analysis	Integrated analysis of data contributed by > 68,500 participants	HPV Al adjuvant- containing vaccines	Immunogenicity endpoints and adverse events	<p><i>AEs:</i> At mean follow-up to 21.4 months the combined HPV-16/18, HSV and HBV vaccines and the separate HPV-16/18 vaccines failed to show increased relative risks for autoimmune disorders in participants receiving vaccines containing Al adjuvants compared with controls (relative risk of 0.98 for the HPV-16/18, HSV and HBV analysis and 0.92 for the HPV-16/18 analysis). No significant difference in neuroinflammatory disorders (relative risk of 1.00 for the HPV-16/18, HSV and HBV vaccine analysis, and 0.67 for the HPV-16/18 vaccine) were found.</p>	Verstraeten et al. (2008)

Study design	Population/Sample	Substances	Outcomes studied	Results	References
				According to study design, both participants who received AI adjuvant – containing vaccines and those that received AI(OH) alone were included in the control group ³	

* DBPC double-blind, placebo-controlled.

** RCT randomized controlled trial.

- 1 A significant antibody (sero-) response for both assays was defined as a 4-fold or greater increase in antibody titer after immunization (if antibody was detectable in the pre-immunization sample) or an increase in titer from < 10 before immunization to > 40 after immunization.
- 2 A serious adverse event (SAE) was defined as any untoward medical occurrence that resulted in death, life-threatening medical conditions, persistent or substantial disability or incapacity, admission to hospital, or extended length of an existing hospital admission.
- 3 Subjects with pre-vaccination hemagglutination-inhibition (HI) antibody titer were excluded from the analyses.
- 4 Seroconversion: Pre-vaccination hemagglutination-inhibition (HI) antibody titer < 1:10 and post-vaccination HI antibody titer 1:40, or pre-vaccination HI antibody titer 1:10 and a post-vaccination increase by a factor of four or more.
- 5 Participants with post-vaccination hemagglutination-inhibition (HI) antibody titer 1:40.
- 6 ASO4 adjuvant contained 0.5 mg of aluminum hydroxide and 0.05 mg of 3-O-desakyl-4-monophosphoryl lipid A.
- 7 20/20F-formulation containing 20 µg of HPV-16 and 20 µg of HPV-18 L1 protein virus-like particles.
- 8 40/40F-formulation containing 20 µg of HPV-16 and 20 µg of HPV-18 L1 protein virus-like particles.
- 9 8 ELISA units [EU]/ml for HPV-16 antibodies and 7 EU/ml for HPV-18 antibodies.
- 10 Booster response for diphtheria and tetanus antibodies was defined as: post-vaccination increase of at least four times the pre-vaccination antibody concentration or at least four times the cut-off in initially seronegative subjects. Booster response for pertussis antibodies was arbitrarily defined as: Post-vaccination increase of at least two times in case of pre-vaccination concentration > 20 EU/ml; post-vaccination increase of four times in case of pre-vaccination concentration > 5 and < 20 EU/ml; post-vaccination concentration at least four times the cut-off in initially seronegative subjects.
- 11 The proportion of subjects with a pre-vaccination hemagglutination-inhibition – HI – antibody titer (1:10 and a 3–4 week post-vaccination titer 1:40, or a pre-vaccination titer > = 1:10 and an increase in the titer by a factor of four or more after vaccination).
- 12 The proportion of subjects with post-vaccination HI titers 1:40.

Table 5

Human studies on sensitization by aluminum-containing vaccines.

Study design and size	Population/Sample	Substance/Exposure	Delivery route	Previously existing contact sensitivity	Outcomes	Comments	References
Case report	10 year old healthy girl with post-vaccinal granuloma nodule that appeared on the left upper arm 5 months after vaccination	Al(OH) ₃ (Diphtheria/Tetanus combination vaccine)	im	The girl was vaccinated according to the national childhood vaccination program. No history of previous allergic reactions to Al was not reported	Patch test not performed. Histological examination of subcutaneous granuloma revealed a normal epidermis with mild perivascular and periadnexal inflammatory infiltrates composed of lymphocytes, histiocytes, plasma cells, and a few eosinophils	Levels of Al in granuloma. Al contact sensitivity were not studied. The outcome was not conclusively associated with Al(OH) ₃	Avcin et al. (2008)
Case report and follow up to previous study (26 boys/38 girls)	Children/1.5–11 years (median age 3.3 years) with subcutaneous itching nodules (vaccination granulomas) that persisted for up to 12 years (<i>n</i> = 64) with median duration of 4.6 years (2.0–8.3 years, <i>n</i> = 44) and 6.3 years (<i>n</i> = 20)	Diphtheria-tetanus-pertussis (DTP) combination vaccines; 0.5–0.3 mg Al per dose	im	A previous Al contact sensitivity was reported for 11/63 children	Contact allergy to Al metal was epicutaneously tested in 63 children at the ages of 1.5–11 years (median, 3.3 years) with the interval between the appearance of the itching nodules and the testing 4 months to 10 years (median, 18 months). 60 of 63 children (95%) had positive reactions to the test (empty Finn Chamber) and AlCl ₃ ·6H ₂ O hexahydrate, 2% in petrolatum*	Persistent itching nodules and contact sensitivity can occur after vaccination with Al adjuvant vaccines	Bergfors and Trollfors 2012
Case report	6 months old girl with subcutaneous nodule at the injection site at 4-months with transformation into abscess	Al(OH) ₃ (routine vaccination program from birth to 6 months of age)	sc	No data	Results of immunodeficiency examination (a complete blood count, immunoglobulins and lymphocyte subsets, nitroblue-tetrazolium test) were negative or in the normal range Aluminum contact sensitivity to AlCl ₃ at 0.35, 1.7 and 3.5% aqueous solutions was 3 detected with a concentration-response	Case report levels of Al in the subcutaneous nodule were not studied. The outcome was not conclusively associated with Al(OH) ₃	Beveridge et al. (2011)
Case report	27 months old girl with draining abscess at the injection site after routine childhood vaccinations with diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed (DAPTACEL) and inactivated poliovirus	Al(OH) ₃ in the different vaccines	im or sc	No data	Aluminum contact sensitivity to 2% AlCl ₃ was examined at 72 h. A moderate reaction characterized as moderate erythema, multiple papules, and scattered vesicles were observed at the application site	Case report. Levels of Al in the abscess were not studied. The outcome could not be conclusively associated with Al(OH) ₃ . Formaldehyde, 2-	Lehman et al. (2008)

Study design and size	Population/Sample	Substance/Exposure	Delivery route	Previously existing contact sensitivity	Outcomes	Comments	References
	vaccine (IPO) (at 4 month), DAPTACEL and heptavalent pneumococcal conjugated vaccine (Prevnar) (at 6 months), Haemophilus b conjugate and hepatitis B vaccine (COMVAX) (at 2 years)					phenoxyethanol and thimerosal could not be excluded as possible causes associated the abscess formation in the patient	
Case report	11 year old girl with swelling, erythema and pruritis at the injection site and on arms and legs after vaccination	Al(OH) ₃ (influenza 3 DTaP)	im	Family history of atopic dermatitis and hay fever	Aluminum contact sensitivity was detected to AlCl ₃ hexahydrate	Case report Limited details regarding conducted patch test	Leventhal et al. (2012)
Case report	5 year old boy with erythema, and blistering at injection site	Al(OH) ₃ (influenza DTaP)	im	Personal history of atopic dermatitis, hay fever, and allergy to nuts, dogs, cats. Family history of atopy	Aluminum contact sensitivity was detected to AlCl ₃ hexahydrate (strongly positive reaction), and glutaraldehyde (mild reaction)	Case report Limited details regarding patch test	Leventhal et al. (2012)
Case report	4 year old boy with persistent indurated subcutaneous nodules, pruritus at the injection site. Recurrence of symptoms appeared during upper respiratory tract infections	Al(OH) ₃ in multiple vaccines (the most recent immunization was conducted at 18 months)	sc	Family history of asthma and hay fever	Aluminum contact sensitivity was detected to AlCl ₃ hexahydrate, neomycin and formaldehyde	Case report Limited details regarding patch test	Leventhal et al. (2012)

* Epicutaneous testing was performed according to recommendations of the International Contact Dermatitis Referral Group.

Table 6

Animal studies on immunotoxicity of aluminum after oral administration.

Test chemical	Species	Study design	Studied outcomes	Results/Comments	References
AIC ₃	Young Wistar rats (male, 5 weeks old, 110–120 g), n = 10 per group	<i>Dose:</i> low Dose Group (LD): 64.18 mg/kg bw/day (equal to 13 mg Al/kg bw/day) <i>Mid Dose Group (MD):</i> 128.36 mg/kg bw/day (equal to 26 mg Al/kg bw) <i>High Dose Group (HD):</i> 256.72 mg/kg bw/day (equal to 52 mg Al/kg bw/day) <i>Control group:</i> Non-treated animals <i>Route of exposure:</i> Oral (assuming gavage) with drinking water <i>Duration of exposure:</i> 4 months	Physical appearance, behavior, clinical signs of intoxication and mortality level (daily, during 4 months), body weight (every 10 days), levels of CD3+, CD4+, CD8 + T lymphocytes, acid non-specific activity esterase (ANAE+) in blood, interleukin-2 (IL-2) and tumor necrosis factor- α (TNF- α) in serum (at 4 months)	No deaths were reported but rats were less active (no other details available) ↓ Body weight at 1, 2, 3, and 4 months (LD, MD, HD) in a time- and dose-response manner ↓ Proportion of CD3+ (LD, MD, HD) and CD4 + T lymphocyte (MD, HD) in the blood in a dose-response manner ↓ Ratio of CD4+/CD8+ (MD, HD) in a dose-response manner ↑ Proportion of CD8 + T lymphocytes (MD, HD) in a dose-response manner ↓ level of ANAE+ in the blood (LD, MD, HD) in a dose-response manner ↓ Serum level of IL-2 (LD, MD, HD) and TNF- α (MD, HD) in a dose-response manner Comments: Details regarding administered test chemical (chemical structure, purity), pH of the administered solutions, particular method of AIC ₃ administration (gavage or free access to drinking water), data on food and water consumption – not provided; limited data available regarding treatment of control animals (was it done by the same route of exposure is not clear). Observed limitations decrease utility of reported findings for hazard identification and risk assessment	Zhu et al. (2012a)
			Physical appearance, behavior, clinical signs of intoxication and mortality level (daily, during 4 months), body weight (every 10 days), levels of immunoglobulin (Ig) G, IgA, IgM, IgE, complement factor (C3, and C4 (in serum (at 4 months)	No deaths were reported but rats were less active (no other details provided) ↓ Body weight at 1, 2, 3, and 4 months (LD, MD, HD) in a dose-response manner ↑ Serum IgG (HD), IgE (MD, HD) and IgA (LD, MD, HD) in a dose-response manner ↓ Serum IgM (LD, MD, HD) in a dose-response manner ↓ Serum C3 (MD, HD) and C4 (LD, MD, HD) in a dose-response manner	Zhu et al. (2011a)
			Physical appearance, behavior, clinical signs of intoxication and mortality level (daily, during 4 months), body weight (every 10 days), growth index of spleen (spleen weight \times 100/body weight), concentrations of Al, iron (Fe), copper (Cu), zinc (Zn), interleukin-2 (IL-2), tumor necrosis factor- α (TNF- α) in spleen (at 4 months)	Rats were less active compared to the control group (no other details provided); no deaths were observed among Al-treated or control animals ↓ Body weight at 1, 2, 3, and 4 months (IG, MD, HD) in a dose-response manner ↓ Growth index of spleen (LD, MD) ↑ Al levels in spleen (LD, MD, HD) in a dose-response manner ↑ Cu level (MD, HD) in spleen in a dose-response manner ↓ Fe (MD, HD) and Zn levels (MD, HD) in spleen in a dose-response manner ↓ IL-2 (MD, HD) and TNF- α in spleen (MD, HD) in a dose-response manner	Zhu et al. (2012b)
			Physical appearance, behavior, clinical signs of intoxication and mortality level (daily, during 4 months), body weight (every 10 days), levels of erythrocytes C3b receptor rate (RBC-C3bRR), erythrocytes C3b immune complex rosette rate (RBC-ICR), erythrocytes rosette forming enhancing rate	Rats were less active compared to the control group (no other details provided); no deaths were observed during the study ↓ Body weight at 1, 2, 3, and 4 months (LD, MD, HD) in a dose-response manner ↑ level of RBC-ICR in blood (LD, MD, HD) in a dose-response manner ↑ level of ERIR in blood (LD, MD, HD) in a dose-response manner ↓ level of RBC-C ₃ bRR in blood (LD, MD, HD) in a dose-response manner	Zhu et al. (2011b)

Test chemical	Species	Study design	Studied outcomes	Results/Comments	References
AlCl ₃ 6H ₂ O	Albino rats (females, 180-200 g.), n = 10 dams/offspring per group	<p><i>Dose:</i> Pregnant females: 345 mg/kg-day (≈ 40 mg Al/kg-day).</p> <p><i>Control group:</i> not treated animals</p> <p><i>Route of exposure:</i> Oral (gavage) with drinking water.</p> <p><i>Duration of exposure:</i> I. From gestation day (GD) 6 to lactation day (LD) 21. II. From GD15 to LD 21.</p>	<p>(ERER) and erythrocytes rosette forming inhibitory rate (ERIR) (at 4 months)</p> <p>Serum hemolysis antibody titer in dams and their offspring, diameter of skin delayed type hypersensitivity reaction 24 hours after intradermal injection of 0.5 ml of sheep red blood cells suspension in the hind food pad in both control and treated dams and their offspring, serum protein profile (concentration of total protein, total globulins (G) and globulins fractions (α, β, γ), albumin (A) and A/G ratio), histopathological examination of thymus, spleen and liver of both dams and their offspring</p>	<p>↓ level of ERER in blood (LD, MD, HD) in a dose-response manner</p> <p><i>Dams:</i> No differences in serum total protein or protein fractions No histopathological changes in thymus, spleen or liver of the AI- treated dams compared to control.</p> <p><i>Offspring:</i> ↓ Serum total globulins, albumin/globulin (A/G) ratio and δ-globulin fraction compared to the controls</p> <p>↓ Lymphoid cells in both thymus cortex and medulla and spleen white pulps</p> <p>↑ Hemosiderosis in the red pulps of spleen was observed in pups born from dams treated on GD6-LD21</p> <p>↑ Dilatation and congestion of hepatic central vein with hepatocytes degeneration</p>	Khalaf et al. (2008)

Table 7

Aluminum occupational exposure limits.

Country	8 h time-Weighted-Average (TWA)	15 min short-term exposure limit (STEL)	Comments	Source	References
Argentina	10	None	Total dust	http://infoleg.meccon.gov.ar/infolegInternet/anexos/30000-34999/3201/dto351-1979-anexo3.htm http://www.ilo.org/safework/areasofwork/WCMS_118291/lang-en/index.htm	Safe Work Australia 2012
Australia	5	None	Fume	http://hsis.safeworkaustralia.gov.au/ExposureStandards	Safe Work Australia 2012
Australia	10	None	Respirable dust	http://hsis.safeworkaustralia.gov.au/ExposureStandards	
Austria	10	20 (60 min)	Fume Dust	http://www.arbeitsinspektion.gv.at/NR/rdonlyres/F173280B-D4FB-44D2-8269-8DB2CB1D2078/0/GKY2007.pdf	
Belgium	1	None	Fume Powder (Fraction alvéolaire)	http://www.ilo.org/safework/areasofwork/WCMS_118291/lang-en/index.htm http://www.emploi.belgique.be/WorkArea/showcontent.aspx?id=23914	
Finland	1.5	None	Welding fume	http://pre20090115.stm.fi/hm1113394626349/passthru.pdf	
Denmark	5	10	Inhalable aerosol	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx	
Denmark	2	4	Respirable aerosol	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx	
France	10	None	Inhalable aerosol	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx	
France	5	None	Respirable aerosol	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx	
Germany	4 (under review)	None	Inhalable aerosol	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx http://www.dfg.de/download/pdf/dfg_im_profil/gremien/senat/arbeitsstoffe/mak_bat_werte_liste_2013.pdf	DFG (2007) IFA (2011a) DFG (2013)
Germany	1.5 (under review)	None	Respirable aerosol	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx http://www.dfg.de/download/pdf/dfg_im_profil/gremien/senat/arbeitsstoffe/mak_bat_werte_liste_2013.pdf	DFG (2007) IFA (2011a) DFG (2013)
Germany	10	None	Inhalable dust Fume	Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA)	IFA (2011b)
Germany	3	None	Respirable Dust Fume	Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA)	IFA (2011b)
Hong Kong	10	None	Metal dust	http://www.labour.gov.hk/te/public/oh/AirImpure.pdf	
Hong Kong	5	None	Welding fume	http://www.labour.gov.hk/te/public/oh/AirImpure.pdf	
Hungary	6	None	Respirable aerosol	http://www.emla.hu/prt/kembirt25_2000.pdf http://www.ilo.org/safework/areasofwork/WCMS_118291/lang-en/index.htm	
Malaysia	10	None	Metal dust	http://miosh.net/articles/OSH%20legislations/schedule1_II%26III.doc	Ministry of Manpower Permissible Exposure Limits Schedule 1 Regulation 6 and 7
Malaysia	5	None	Welding fume	http://miosh.net/articles/OSH%20legislations/schedule1_II%26III.doc	Ministry of Manpower Permissible Exposure

Metallic aluminum (mg/m ³)					
Country	8 h time-Weighted-Average (TWA)	15 min short-term exposure limit (STEL)	Comments	Source	References
Netherlands	None	None	Not assigned	http://www.gr.nl/sites/default/files/201005OSH.pdf http://www.healthcouncil.nl	Limits Schedule 1 Regulation 6 and 7 Health Council of the Netherlands. Aluminum and aluminum compounds. Publ. No. 2010/05OSH. ISBN 978-90-554 9-806-2
New Zealand	10	None	Metal dust	http://www.osh.dol.govt.nz/publications/booklets/wes-and-biological-indices-2013.pdf http://www.mbie.govt.nz	Ministry of Business, Innovation and Employment. Workplace Exposure Standards and Biological Exposure Indices, 7th ed. 2013
New Zealand	5	None	Welding fume	http://www.osh.dol.govt.nz/publications/booklets/wes-and-biological-indices-2013.pdf http://www.mbie.govt.nz	Ministry of Business, Innovation and Employment. Workplace Exposure Standards and Biological Exposure Indices, 7th ed. 2013
Norway	5	None	Al powder	http://www.arbeidsilsynet.no/artikkel.html?tid=78880	
South Africa	10	None	Metal dust Total inhalable	https://www.labour.gov.za/legislation/regulations/occupational-health-and-safety/regulation-ohs-hazardous-chemical-substances	
South Africa	5	None	Metal dust respirable	https://www.labour.gov.za/legislation/regulations/occupational-health-and-safety/regulation-ohs-hazardous-chemical-substances	
South Korea	10	None	Metal dust	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx	
Spain	10	None	Inhalable aerosol	http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_limite/GT-EPN024-07%20VIA%202008%20negro_2.pdf	Límites de Exposición Profesional para Agentes Químicos en España, 2008
Spain	5	None	Respirable aerosol	http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_limite/GT-EPN024-07%20VIA%202008%20negro_2.pdf	Límites de Exposición Profesional para Agentes Químicos en España, 2008
Sweden	5	None	Total dust	http://www.av.se/document/afs/AFS2005_17.pdf http://www.av.se/dokument/inenglish/legislations/eng0517.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Sweden	2	None	Respirable dust	http://www.av.se/dokument/inenglish/legislations/eng0517.pdf http://www.av.se/document/afs/AFS2005_17.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air

Metallic aluminum (mg/m ³)							
Country	8 h time-Weighted-Average (TWA)	15 min short-term exposure limit (STEL)	Comments	Source	References		
Switzerland	3	None	Respirable aerosol	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx	Contaminants, 13 June 2005		
United Kingdom	10	None	Inhalable dust/aerosol	http://www.hse.gov.uk/coshh/table1.pdf http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx	HSE (2011)		
United Kingdom	4	None	Respirable dust/aerosol	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx	HSE (2011)		
United States	10 (total) 5 (respirable)	None	Metal dust, powder, elemental Al	http://www.cdc.gov/niosh/npg/npgd0022.html	NIOSH REL		
United States	5	None	Welding fume	http://www.cdc.gov/niosh/npg/npgd0022.html	NIOSH REL		
United States	15	None	Total dust (as Al)	Federal Register 54 (12): 2508, 2554, 2589, 2621, Wednesday January 19, 1989	OSHA PEL		
United States	5	None	Respirable fraction	Federal Register 58(124): 35341, Wednesday, June 30, 1993	OSHA PEL		
United States	1	None	Respirable dust	Federal Register 58(124): 35341, Wednesday, June 30, 1993	ACGIH (2008)		
Australia	10	None		ACGIH TLV®	Safe Work Australia, 2012		
Austria	5	10	Respirable dust	http://hsis.safeworkaustralia.gov.au/ExposureStandards			
Belgium	1	None	Fraction alvéolaire	http://www.arbeitsinspektion.gv.at/NR/rdonlyres/F173280B-D4FB-44D2-8269-8DB2CB1D2078/0/GKY2007.pdf			
Germany	4 (under review)	None	Inhalable aerosol	http://www.ilo.org/safework/areasofwork/WCMS_118291/lang-en/index.htm http://www.emploi.belgique.be/WorkArea/showcontent.aspx?id=23914	DFG (2007) IFA (2011a) DFG (2013)		
Germany	1.5 (under review)	None	Respirable aerosol	http://www.dfg.de/download/pdf/dfg_im_profil/gremien/senat/arbeitsstoffe/mak_bat_werte_liste_2013.pdf	DFG (2007) IFA (2011a) DFG (2013)		
Germany	10	None	Inhalable dust Fume	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx	IFA (2011b)		
Germany	3	None	Respirable dust Fume	http://www.dfg.de/download/pdf/dfg_im_profil/gremien/senat/arbeitsstoffe/mak_bat_werte_liste_2013.pdf	IFA (2011b)		
Hong Kong	10	None	–	http://www.labour.gov.hk/te/public/oh/AirImpure.pdf			
Hungary	6	None	Respirable	http://www.emla.hu/prt/kembizt25_2000.pdf			
Malaysia	10	None	No asbestos; < 1% crystalline silica	http://www.ilo.org/safework/areasofwork/WCMS_118291/lang-en/index.htm	Ministry of Manpower Permissible Exposure Limits Schedule 1 Regulation 6 and 7		
Malaysia	10	None	–	http://niosh.net/articles/OSH%20legislations/schedule1.II%26III.doc			
Norway	10	None	–	http://www.arbeidsstilsynet.no/artikkel.html?tid=78880			
Poland	2.5	None	Total dust	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx			
Poland	2.5	None	Respirable dust	http://limitvalue.ifa.dguv.de/WebForm_ueliste.aspx			

Metallic aluminum (mg/m ³)					
Country	8 h time-Weighted-Average (TWA)	15 min short-term exposure limit (STEL)	Comments	Source	References
South Africa	10	None	Total inhalable dust Al ₂ O ₃ , Al(OH) ₃	https://www.labour.gov.za/legislation/regulations/occupational-health-and-safety/regulation-ohs-hazardous-chemical-substances	Límites de Exposición Profesional para Agentes Químicos en España, 2008
South Africa	5	None	Respirable dust Al ₂ O ₃ , Al(OH) ₃	https://www.labour.gov.za/legislation/regulations/occupational-health-and-safety/regulation-ohs-hazardous-chemical-substances	Límites de Exposición Profesional para Agentes Químicos en España, 2008
Spain	10	None	Inhalable aerosol	http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_limite/GT-IEPN024-07%20VIA%202008%20negro_2.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Spain	5	None	Respirable aerosol	http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_limite/GT-IEPN024-07%20VIA%202008%20negro_2.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Sweden	5	None	Total inhalable	http://www.av.se/document/afs/AFS2005_17.pdf http://www.av.se/dokument/inenglish/legislations/eng0517.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Sweden	2	None	Total dust	http://www.av.se/document/afs/AFS2005_17.pdf http://www.av.se/dokument/inenglish/legislations/eng0517.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Switzerland	3	None	Respirable aerosol	http://www.ilo.org/safework/areasofwork/WCMS_118291/lang--en/index.htm http://www.sapros.ch/images/supplier/220/pdf/01903_f.pdf http://firmitvalue.ifs.dguv.de/WebForm_uetliste.aspx	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
United Kingdom	10	None	Inhalable dust	http://www.hse.gov.uk/coshh/table1.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
United Kingdom	4	None	Respirable dust	http://www.hse.gov.uk/coshh/table1.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Argentina	2	None	Total dust	http://infoleg.meccon.gov.ar/infolegInternet/anexos/30000-34999/3201/dto351-1979-anexo3.htm http://www.ilo.org/safework/areasofwork/WCMS_118291/lang--en/index.htm	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Belgium	2.5	None	AlF ₃	http://www.ilo.org/safework/areasofwork/WCMS_118291/lang--en/index.htm http://www.emploi.belgique.be/WorkArea/showcontent.aspx?id=23914	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Belgium	2	None		http://www.ilo.org/safework/areasofwork/WCMS_118291/lang--en/index.htm http://www.emploi.belgique.be/WorkArea/showcontent.aspx?id=23914	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Finland	2	None		http://pre20090115.stm.fi/hm1113394626349/passthru.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Finland	1	None	Al ₂ (SO ₄) ₃ / AlF ₃	http://pre20090115.stm.fi/hm1113394626349/passthru.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Malaysia	2	None		http://mioosh.net/articles/OSH%20legislations/schedule1,1I%26III.doc	Ministry of Manpower Permissible Exposure

Metallic aluminum (mg/m ³)					
Country	8 h time-Weighted-Average (TWA)	15 min short-term exposure limit (STEL)	Comments	Source	References
Norway	2	None		http://www.arbeidsilsynet.no/artikkel.html?tid=78880	Limits Schedule 1 Regulation 6 and 7
New Zealand	5	None		http://www.osh.dol.govt.nz/publications/booklets/wes-and-biological-indices-2013.pdf http://www.mbie.govt.nz	Ministry of Business, Innovation and Employment. Workplace Exposure Standards and Biological Exposure Indices, 7th ed., 2013
South Africa	2	None		https://www.labour.gov.za/legislation/regulations/occupational-health-and-safety/regulation-ohs-hazardous-chemical-substances	
Spain	2	None		http://www.insht.es/InshtWeb/Contenidos/Documentacion/TextosOnline/Valores_limite/GT-IEPN024-07%20VIA%202008%20negro_2.pdf	Limites de Exposición Profesional para Agentes Químicos en España, 2008
Sweden	1	None	Total dust (as Al)	http://www.av.se/dokument/inenglish/legislations/eng0517.pdf	Provisions of the Swedish Work Environment Authority on Occupational Exposure Limit Values and Measures Against Air Contaminants, 13 June 2005
Switzerland	2	None	Inhalable aerosol		IFA (2011a)
United States	2	None	AlCl ₃ , Al ₂ (SO ₄) ₃	http://www.cdc.gov/niosh/npg/npgd0022.html	NIOSH REL
United States	2.5	None	Na ₃ AlF ₆	http://www.cdc.gov/niosh/npg/npgd0022.html	NIOSH REL