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Aluminum reproductive toxicity: a summary and interpretation of scientific reports

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ABSTRACT

Publications addressing aluminum (Al)-induced reproductive toxicity were reviewed. Key details were compiled in summary tables. Approximate systemic Al exposure, a measure of bioavailability, was calculated for each exposure, based on the Al percentage in the dosed Al species, Al bioavailability, and absorption time course reports for the exposure route. This was limited to laboratory animal studies because no controlled-exposure human studies were found. Intended Al exposure was compared to unintended dietary Al exposure. The considerable and variable Al content of laboratory animal diets creates uncertainty about reproductive function in the absence of Al. Aluminum-induced reproductive toxicity in female mice and rats was evident after exposure to ≥25-fold the amount of Al consumed in the diet. Generally, the additional daily Al systemic exposure of studies that reported statistically significant results was greater than 100-fold above the typical human daily Al dietary consumption equivalent. Male reproductive endpoints were significantly affected after exposure to lower levels of Al than females. Increased Al intake increased fetus, placenta, and testes Al concentrations, to a greater extent in the placenta than fetus, and, in some cases, more in the testes than placenta. An adverse outcome pathway (AOP) was constructed for males based on the results of the reviewed studies. The proposed AOP includes oxidative stress as the molecular initiating event and increased malondialdehyde, DNA and spermatozoal damage, and decreased blood testosterone and sperm count as subsequent key events. Recommendations for the design of future studies of reproductive outcomes following exposure to Al are provided.

Abbreviations: ACP: acid phosphatase; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CAT: catalase; FSH: follicle stimulating hormone; GD: gestation day; GPx: glutathione peroxidase; GR: glutathione reductase; GSH: glutathione; GST: glutathione s-transferase; i.g.: intragastric; i.m.: intramuscular; i.p.: intraperitoneal; i.v.: intravenous; LDH: lactate dehydrogenase; LH: luteinizing hormone; MDA: malondialdehyde, the product of the thiobarbituric acid-reactive substances assay for lipid peroxidation; NO: nitric oxide; PND: post-natal day; s.c.: subcutaneous; SOD: superoxide dismutase

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Focus

This review focuses on the pre-natal effects of aluminum (Al) exposure on female and male reproduction, the embryo/fetus, and offspring up to the time of birth. It does not include developmental effects.

Value of this review

It has been some time since an extensive review and assessment of the literature assessing Al effects on female and male reproduction was published. Many studies on this topic have been published recently. There is considerable current interest in the potential for Al to produce reproductive toxicity, fueled in part by the controversy concerning its safety as an adjuvant in vaccines. This has been addressed by the proposed Cochrane Library assessment of the benefits and harms of Al adjuvants used in vaccines versus placebo or no intervention (Djurisic et al. 2017; Weisser et al. 2017).

Search strategy and literature reviewed

Prior reviews of this topic were obtained and the reports cited therein reviewed (Tariq 1993; Domingo 1995; Domingo et al. 2000; Domingo 2005; Krewski et al. 2007; ATSDR 2008; Domingo 2011; Pandey and Jain 2013; Willhite et al. 2014; Berihu 2015). A SciFinder search for "aluminum reproductive toxicity" (no qualifiers) and SciFinder and PubMed searches for "aluminum reproduction human" were conducted. English-language reports of mammalian organisms, excluding nanoscale Al forms, were reviewed. The introduction and discussion of reports cited herein were reviewed to identify citations to other reports that were reviewed.

Descriptions of female and male reproduction, including illustrations, are available in physiology textbooks, such as Ganong's (Barman et al. 2019). The summaries below were prepared to focus on and include the endpoints of the reviewed studies.

Female reproduction as it relates to reported Al effects

The development of an oocyte begins as a primordial germ cell. Early in embryonic development these cells migrate into the future site of the ovaries, undergo meiotic cell division, and multiply, resulting in primary oocytes (primordial follicle) within the ovary. Their development is arrested until puberty, when follicle stimulating hormone (FSH) produced by the pituitary gland stimulates some to begin to mature, developing through follicle stages (primary, secondary, and if fertilized tertiary (Graafian) follicles), in the process of folliculogenesis. Most die (atresia) during these stages. During the resumption of cell division, the oocyte's nucleus (germinal vesicle) breaks down and the first polar body (that forms concomitantly during oocyte division) is extruded. Follicle cells secrete and release estrogen that feeds back to the pituitary gland to decrease FSH release and increase luteinizing hormone (LH) release. This causes the follicle to rupture, resulting in release of the egg (ovulation), that migrates into the fallopian tubes where it can be fertilized by sperm. The ruptured follicle forms a corpus luteum, a transitory endocrine organ that secretes estrogen and progesterone. The latter feeds back to the pituitary gland to decrease LH release. The fertilized oocyte forms a mature egg cell (ovum). When the oocyte and sperm chromosomes combine, it becomes a zygote, which divides as it migrates into the uterus, creating the pregnant (gravid) state.

In animal species that give birth to multiple offspring at the same time (multiparous), the fetuses are implanted evenly down the uterine horns, where the fallopian tubes and uterus meet. The zygote develops into an embryo then a fetus. If fertilization does not occur, decreasing estrogen feeds back to the pituitary gland to increase FSH to repeat the cycle. FSH and LH act on their receptors. In addition to estrogen, which effects ovarian follicle growth and development, and progesterone, which effects embryo development and implantation, the ovary synthesizes testosterone that serves as a precursor to estrogen, promotes follicular growth, and corpus luteum formation.

Male reproduction as it relates to reported Al effects

The testes (singular testis) have two primary functions, to produce sperm and hormones including testosterone. The testes are composed of multiple seminiferous tubules and interstitial tissue, housed within a fibrous covering, the tunica albuginea. During embryonic development within the seminiferous germinal epithelium, Sertoli cells, which surround the developing germ cells, associate with the latter to form seminiferous tubules after birth. The seminiferous tubules are coiled masses that produce sperm cells through spermatogenesis, the maturation of germ cells to haploid spermatozoa. At birth, the seminiferous tubules contain spermatogonial stem cells. During the first round of spermatogenesis, Sertoli cells join to form tight junctions that compartmentalize the seminiferous epithelium into basal and luminal compartments. Spermatogonia, which are in the basal compartment, divide into type A spermatogonia that remain to replenish the precursor cells or type B spermatogonia. The latter, through meiosis in the luminal compartment, become (primary) spermatocytes. These divide to form secondary spermatocytes which meiotically divide to from spermatids, which are initially round. Multinucleated giant cells in the seminiferous tubules are degenerating germ cells. Spermatids become spermatozoa during late spermatogenesis.

Spermatozoa travel from the seminiferous tubule lumen through efferent ductules to enter the head of the epididymis, a long, coiled tube (duct) on the backside of each testis that transports and stores the spermatozoa. The epididymis is composed of its initial segment and head (caput) which is characterized by its thick epithelium, body (corpus), and tail (cauda), where spermatozoa are stored. Within the epididymis, sperm mature while gaining mobility. During sexual arousal, contractions force the sperm into the vas deferens.

The vas deferens is a long, muscular tube that travels from the epididymis into the pelvic cavity to transport mature sperm to the urethra in preparation for ejaculation. Seminal vesicles are sac-like pouches attached to the vas deferens. They produce fructose that provides sperm with an energy source and assists the sperms' motility. Seminal vesicle fluid provides most of the ejaculate volume.

The prostate gland is composed of many secretory acini that contain epithelial cells, which produce prostatic fluid, and line a central lumen that is filled with fluid. Fibromuscular stromal tissue surrounds the acini. The seminal vesicles and prostate gland produce seminal fluid which mixes with sperm to form semen. The accessory organs are internal organs (in contrast to the penis and scrotum containing the testes) of the male reproductive system, including the vas deferens, seminal vesicles, prostate gland, and bulbourethral glands. The bulbourethral glands produce a clear, slippery fluid that empties into the urethra. It lubricates the urethra and neutralizes acidity from urine in the urethra.

Testes interstitial tissue contains connective tissue and Leydig cells. LH and FSH, produced by the pituitary gland, stimulate Leydig cells to release androgens, including testosterone, synthesized from cholesterol. Testosterone stimulates the testes and prostate gland during embryological development to adulthood and, with FSH and other factors, regulates spermatogenesis. Estradiol, synthesized by Leydig and Sertoli cells and mature spermatocytes, modulates spermatogenesis in a complex manner. Testosterone acts on the androgen receptor.

Aluminum exposure

Aluminum is ubiquitous, quantifiable in all exposure sources and biological materials. The main source of exposure for humans and laboratory animals is food. Additional sources for humans include beverages, air-borne particulates and fumes, pharmaceuticals such as antacids and cosmetics, and vaccines with Al as an adjuvant. Typical exposures from these sources, estimated percentage absorbed, and resulting daily Al absorbed are summarized in a mini-review (Yokel and McNamara 2001). The calculation of daily Al absorption is applied in this review.

Bioavailability expressed as approximate systemic Al exposure

A challenge in relating the results of studies that used different routes of exposure/administration is the different percent of Al that enters systemic circulation (bioavailability) and, therefore, potentially enters the reproductive organs or other sites affecting reproduction. It has been suggested that testing in animals to determine the effects and human risks of environmental toxicants could be improved if test substances were administered to achieve pharmacokinetically equivalent serum levels in the animal and the human (Brent 2004). To relate Al uptake from different routes of administration, calculation of approximate systemic Al load was based on the extent of absorption from the site of absorption and absorption time course (WHO 2012). For this review, an approximate systemic Al load was determined for the exposure and administration routes used in studies assessing Al reproductive toxicity. This approach goes beyond the typical report of Al exposure, that is often the amount added to drinking water or the diet without documentation of actual intake; normalizes the amount of Al in the different chemical species of Al studied that can have Al content varying by 6-fold; and takes into account absorption from the exposure route, that can vary by 500-fold; to generate systemic exposures that can be compared. Assumptions had to be made in some cases, such as when the chemical species was ambiguously reported or actual consumption was not reported. Bioavailability was based on reported values, for which there is often a range. For oral exposure, values were usually obtained under conditions that have some differences from the study to which the value is applied, e.g. a different Al species was studied, in a different dose, in a different mammalian strain or species, in a different status of gastric contents, and/or in a different dosing schedule. Nevertheless, this approach advances the ability to compare the cited studies. The values used are in Table 1 and are based on the following.

After orogastric intake or intragastric delivery of aqueous solutions 0.2% of Al was assumed to enter into systemic circulation (the blood stream) in the first 24 h, based on reports of oral Al bioavailability (Hohl et al. 1994; Drüeke et al. 1997; Jouhanneau et al. 1997; Priest et al. 1998; Stauber et al. 1999; Yokel et al. 2001; Zhou et al. 2008). Studies we conducted found oral bioavailability of ^{26}Al incorporated into acidic SALP in a biscuit or 1.5% basic SALP in cheese to be ~0.1% (Yokel and Florence 2006; Yokel et al. 2008). Comparison of normal urinary Al excretion to daily Al intake (the vast majority being in the diet) resulted in estimated Al absorption of 0.1 to 0.3% (Ganrot 1986), ~0.1% (Priest 1993), and ~0.1% (Nieboer et al. 1995). Therefore, the percent of Al entering systemic circulation from food was assumed to be 0.1%. No

Table 1. Approximate systemic Al exposure for the first 24 h and total for the exposure/administration routes cited in this article.

Exposure/administration route	Approximate systemic Al exposure for the first 24 h	Total approximate systemic Al exposure for the exposure/administration
Oral, intragastric (i.g.)	0.2% from solutions, 0.1% from food	0.2% from solutions, 0.1% from food
Intramuscular (i.m.) aluminum hydroxide	0.5%	0.5% daily up to 100% of the dose
Intramuscular (i.m.) aluminum phosphate and amorphous aluminum hydrophosphate sulfate in Merck aluminum adjuvant	1.8%	1.8% daily up to 100% of the dose
Intraperitoneal injection (i.p.)	100%	100%
Subcutaneous injection (s.c.)	21%	21%
Topical application	0.01%	0.01%

The generation of these values is described in the text.

absorption from oral intake was assumed after 24 h. Al exposure assessment for the orogastric route did not consider possible accumulation following multiple day dosing.

Many studies using the *in situ* rat gut preparation and determination of Al in animal and human urine and plasma and animal organs showed higher Al concentrations when citrate was co-administered with Al, suggesting citrate increased Al absorption from the gastrointestinal tract. The increase, and number of demonstrations, with co-administered citrate was greater than co-administration of other carboxylic acids (Yokel and McNamara 1988; Domingo et al. 1993; Gómez et al. 1994; Cunat et al. 2000; Poirier et al. 2011). Using the preferred method to quantitate oral bioavailability, comparison of area under the curve after oral versus intravenous (i.v.) administration of the test substance, it was shown that Al citrate absorption was twice that of the Al ion (Zhou et al. 2008). Therefore, the percent of Al assumed to enter into systemic circulation in the presence of citrate was assumed to be 2-fold that in its absence.

It has been shown, with presumably similar daily Al intake over time, mouse brain Al concentration increased several-fold from 1 to 4 weeks of age, was then fairly constant until ~1 year of age, then declined several-fold from 1 to 2 years of age. Similar changes were not seen in rat brain (Takahashi et al. 2001). Results of studies of Al concentration in humans that presumably represent the general public showed lung, liver, and kidney Al concentration in 1–12-year olds were ~4-, 1.5-, and 2-fold of that in 0 to 3-month-olds (Stitch 1957). Serum Al increased with age from 20 to 80 years in healthy humans (Zapatero et al. 1995). Brain Al was ~2.3-fold higher in 80–99 year olds compared to premature infants to 6 month olds (Markesbery et al. 1984). Bone Al increased > 4-fold from the first to fourth quartile of 16–98-year-olds (Hellström et al. 2005). No reports of longitudinal studies of Al concentration in male or female reproductive organs were found. The duration of increased Al exposure in most studies that assessed its effect on reproductive function was much shorter than the test subject's life span. Expressing orogastric route Al exposure on a daily basis without consideration of sex organ Al accumulation over time when there is continued Al exposure perhaps underestimates the resultant reproductive organ Al concentration.

The approximate systemic Al exposures after intramuscular (i.m.) injection of Al hydroxide (0.5%) and aluminum phosphate and amorphous aluminum hydrophosphate sulfate in Merck aluminum adjuvant (1.8%) are based on a study in rabbits (Flarend et al. 1997). The time course of Al absorption from the injection site appears to depend on its chemical species. In their, albeit limited, study addressing the rate and extent of Al absorption after injection, Flarend et al. (1997) gave i.m. injections of ^{26}Al-labeled aluminum hydroxide and aluminum phosphate adjuvants to rabbits and determined the area under the curve (blood concentration x time) for ^{26}Al compared to i.v. injection (which delivers 100% into the blood) of ^{26}Al-labeled aluminum citrate. After i.m. ^{26}Al-labeled aluminum hydroxide adjuvant injection, 17% appeared in the blood within 28 days. After the initial burst of blood ^{26}Al at ~10 h, blood ^{26}Al was fairly constant for 28 days, suggesting a relatively stable absorption rate. This would equate to ~0.5% of the dose per day. After i.m. ^{26}Al-labeled aluminum phosphate adjuvant injection the amount in the blood was fairly constant for 28 days, representing a total of 51% of the injected ^{26}Al, equating to 1.8% of the dose per day. The daily approximate systemic Al exposure after i.m. injection was assumed to be 0.5 or 1.8%, to a maximum of 100% if there was sufficient time.

After intraperitoneal (i.p.) injection 100% absorption in the first 24 h was assumed, because absorption from the peritoneal cavity is typically quite rapid and complete (Lukas et al. 1971; Bräunlich et al. 1988; Suzuki et al. 1995). This is supported by a study showing liver had ~13% of an i.p. dose 5 days later. Extrapolation to $t = 0$ from the near linear liver Al concentration at days 5, 10, and 25 suggests ~29% in the liver (Kobayashi et al. 1990); this exceeds the percentage of the human Al body burden in the liver (Krewski et al. 2007), suggesting efficient Al absorption from the peritoneal cavity.

Absorption in the first 24 h after subcutaneous (s.c.) injection was taken to be 21%, based on Al lactate (Yokel and McNamara 1985). After s.c. injection, no absorption from the injection site was assumed after the first day based on the ~92% of injected Al (as the lactate) in the carcass (Al not accounted for in 7 soft organs that did not include the skeleton, the major site of Al accumulation) after 20 injections over 2 weeks (Melograna and Yokel 1984).

Following topical application, 0.01% of Al was assumed to be absorbed based on reports of dermal Al absorption from Al chlorohydrate in humans (Flarend et al. 2001; de Ligt et al. 2018).

Once Al enters tissues and organs, it is slowly cleared. Estimated half-lives for the rabbit liver, lung, and spleen were 74, 44, and 113 days, respectively (Yokel and McNamara 1989) and ~150 days for rat brain (Yokel et al. 2001). After human i.v. injection of ^{26}Al citrate, approximately 50% of the ^{26}Al was eliminated in the first day, 70% in the first 5 days, and 98% after approximately 3,000 days. Estimated whole body ^{26}Al half-lives were 1.4, 40, and 1700 days, with a possible fourth half-life of approximately 50 years (Priest et al. 1995). Given these long half-lives and the short interval between completion of Al exposure and termination of subjects in the studies cited herein, the reduction of organ Al due to clearance would be negligible and was not considered.

Animal diet Al content and daily food and water consumption

Non-purified laboratory animal diets contain more Al than the typical human diet due to their high grain content. Table 2 contains the reported Al concentration in laboratory animal diets. Fifteen of the studies cited in Tables 3 and 6 reported the source of the diet and its Al concentration (Table 2). Some studies cited the diet source, but not its content or Al concentration.[1] A few studies reported the diet contents but not the Al concentration (McCollum et al. 1928; Myers and Mull 1928; Yousef 2004; Yousef et al. 2005; Yousef et al. 2007; Sakr et al. 2017). The rest of the studies cited in this report did not state the diet source, contents, or Al concentration.

Table 2. Reported Al concentration of laboratory animal diets, as mg/kg diet.

Species	Al (mg/kg)	Source	Reference[a]
Mouse			
	160–180	Larsen diet	Ondreička et al. (1966)[a]
	100	Standard mouse chow	Golub et al. (1987)[a]
	25	Dyets semi-purified diet	Donald et al. (1989)[a]
	200	Purina laboratory mouse chow	Golub et al. (1992)
	209–280	Panlab	Domingo et al. (1993)
	Essentially Al free	Purified diet	Fosmire et al. (1993)
	134	Commercial rodent chow	Fosmire et al. (1993)
	7	Dyets purified diet	Golub et al. (1996) and Golub and Germann (2001)[a]
	257	Panlab	Colomina et al. (1998)
	350	Purina 5001C	Oteiza et al. (1993)
	3	Purified diet	Oteiza et al. (1993)
	64.5	Commercial mouse chow	Długaszek et al. (2000)
	370	Purina 5001 rodent chow	Guo et al. (2001, 2002, 2005b, 2006, 2009)[a]
	3.2	AIN-76 A purified diet for mice and rats	https://altromin.com/products/specialdiets/aindiets/AIN-76A
Rat			
	119	Lab Blox	McCormack et al. (1979)[a]
	100		Gupta et al. (1986)
	8300	Purina Rodent Chow 5001	Fleming and Joshi (1987)
	190	Altromin 1320	Gawlik et al. (1987)
	270	Sniff diet	Gawlik et al. (1987)
	7.3	Altromin C	Gawlik et al. (1987)
	66	Purina Certified 5002 rodent chow	Hicks et al. (1987)
	60	Panlab	Domingo et al. (1987b)[a]
	100	Wayne Lab Blox	Fulton et al. (1989)
	121 and 135	Purina rat chow	Provan and Yokel (1990)
	10.5	AIN-76 rat diet with lactalbumin as protein source	Greger and Powers (1992)
	103	Nohrlin	Wilhelm et al. (1992)
	27.9	AIN-76 rat diet	Hsu and Hsu (1994)
	110	Ralston Purina Rodent Chow	Kandiah and Kies (1994)
	5	Semi-synthetic feed	Glynn et al. (1995)
	50	Animal diet	Deng et al. (1998)
	7–10	Semi-purified AIN-76 diet with lactalbumin (Teklad Test Diet)	Sutherland et al. (1996) and Sutherland and Greger (1998)
	20	Purified diet	Deng et al. (2000)
	227	Agway rat chow	Yokel et al. (2001)
	<9		Poirier et al. (2011)
	22–29	Standard rat diet (CRF-1; Oriental Yeast Co., Ltd.)	Hirata-Koizumi et al. (2011a, 2011b)[a]
	988		Wu et al. (2012)
	203	R/M-H, extruded (V1536)	Weisser et al. (2019)
Guinea pig			
	$\sim$60	Proprietary chow	Owen et al. (1994)
	10	Special diet services, Ltd.	Owen et al. (1994)
	47	Purina guinea pig chow 5025	Golub et al. (1996)
Rabbit			
	1215	Purina rabbit chow	Yokel (1985)[a]
	5.4	Wayne rabbit feed	Du Val et al. (1986)[a]
	297	Purina rabbit chow	Fulton and Jeffery (1990)
	7–9	Bio-Serv purified rabbit diet	Yokel and McNamara (1990)

[a]Aluminum reproduction studies that are summarized in this review.

Unless a semi- or purified diet was used, the diet may have contained $\geq$ 100 mg Al/kg.

Typical daily food consumption for both male and female mice is 0.2 kg/kg body weight/day. Daily food and water intakes are based on the average default values for rats and mice (TERA). Assuming 100 mg Al/kg food and consumption of 0.2 kg food/kg/day, a mouse would take in 20 mg Al/kg/day from dietary sources. If absorption from the gastrointestinal tract is 0.1%, 20 μg Al/kg would enter systemic circulation daily. An assumption that oral Al bioavailability from grain-based laboratory animal feed is comparable to other Al sources is based on the fate of orally consumed Al. It is assumed to be solubilized at low gastric pH to a common species that is then precipitated in the upper intestine due to its pH being close to that of the nadir of Al solubility (Reiber et al. 1995; Harris et al. 1996). It was speculated that metal bioavailability from a purified diet would be considerably greater than from commercial grain-based chows that contain metal ligands (Donald et al. 1989). There are no reports of Al bioavailability from grain or purified animal diets to verify either assumption.

For rats, typical daily food consumption by males and females is 0.09 and 0.1 kg/kg body weight/day, respectively (TERA). Assuming 100 mg Al/kg food and consumption of 0.1 kg food/kg/day, a rat would take in 10 mg Al/kg/day from the diet. This is consistent with calculations conducted in two studies that estimated daily Al intake from drinking water (which provides $\sim$5% of daily Al intake in humans and would represent $<$1% in laboratory animals due to much higher dietary Al content) and food (containing 22–29 mg Al/

kg) to be ~2 mg Al/kg bw/day (Hirata-Koizumi et al. 2011a, 2011b). If absorption from the gastrointestinal tract is 0.1%, this would produce a systemic Al intake (approximate systemic Al exposure) of 10 μg/kg/day in the rat.[2]

The primary source of Al intake in the general human population is from foods and beverages, with over 95% most commonly from food. Daily Al intake by adults from 70 English-language published studies since 1990 averaged 7.4 mg, with a median of 5.3 mg (calculated by the author). Assuming 70 kg body weight, 7.4 mg/day results in a daily intake of 106 μg/kg. Assuming 0.1% Al absorption, the daily systemic Al exposure would be ~0.1 μg/kg, or 0.5 to 1% of that calculated for the mouse and rat. However, some people consume much more dietary Al than these averages. The highest average reported in these studies is 28.5 mg/day (Gharib 2004) and one individual's daily consumption was reported to be 176 mg (Aung et al. 2006). Major contributors to Al in food are the approved food additives acidic sodium aluminum phosphate as a leavening agent, resulting in high Al levels in baked goods; basic sodium aluminum phosphate as an emulsifying agent in cheese; and sodium aluminosilicate as an anticaking agent, in non-diary creamer and single packets of salt (Yokel 2013). In China, fried bread, and in Japan jellyfish treated with alum, often contain very high Al levels. Tea beverage typically contains 1–4 mg/L and can significantly increase daily Al intake. Consumption of Al-containing pharmaceuticals, such as antacids/phosphate binders, can result in ingestion of up to 5000 mg Al/day (Yokel and McNamara 2001). Because >90% of Al is eliminated by the kidneys, reduced renal function and end-stage renal disease can increase Al accumulation and the risk of Al-induced adverse effects.

The average age of first-time mothers and fathers in the United States is 26 and 31 years, respectively. Typical total dietary Al intake in the first 26 years of life for a female is ~1500 mg/kg and for a 31-year old male ~1700 mg/kg. Assuming 0.1% absorption, total systemic Al exposures would be approximately 1500 and 1700 μg/kg, respectively. Some of the studies assessing Al reproductive toxicity in mice and rats provided calculated Al exposures during gestation that exceeded these values.

Introduction to the tables of study summaries

The reports of studies assessing Al reproductive toxicity often included some measure of variability. For this review, only average (mean) values are reported. Endpoint-specific responses of Al-treated subjects were calculated as a percentage of control subjects by the author, when not provided in the report, from the report tables and/or figures. All indications of statistical significance are from the original reports. In studies of Al in drinking water and other exposure/administration routes, concentration/dose entries of 0 indicate no added Al. Daily Al exposure was calculated from the added Al concentration in the food, water, or as administered by another route to the subject; times the mass of Al/mass of the Al species when the exposure was expressed as mass or moles of Al species; and adjusted for body weight when the Al exposure was expressed as mass of feed or volume of consumed water. The ratios of Al mass/Al species mass are in a footnote to Table 3. Systemic Al exposure was calculated from the daily Al exposure times the Al mass/Al species mass times the fraction absorbed, as described in a footnote to Table 3.

Addition of Al to drinking water can decrease water intake, possibly due its astringent property (Marcussen et al. 2013). For example, control mice consumed 6 ml water daily whereas mice consuming 750 mg/L $Al_2(SO_4)_3{\cdot}18H_2O$ (providing 61 mg Al/mL) in the drinking water consumed 4.4 ml water daily (Clayton et al. 1992). Addition of 3000 ppm $Al_2(SO_4)_3$ decreased water consumption ~30–35% (Hirata-Koizumi et al. 2011b). As most studies did not report fluid consumption, it was assumed that the target dose was delivered.

All available literature was included in the tables, without inclusion/exclusion or ranking based on quality. Some studies were conducted following more rigorous protocols, providing more confidence in their results. The European Union enacted a chemical regulation (REACH; Registration, Evaluation, and Authorization of Chemicals) that includes requirements for reproductive toxicology for substances manufactured in or imported into the European Union at ≥10 metric tons/year (Scialli 2008). The requirements for such high production volume chemicals include screening tests for reproductive toxicity (OECD Test Guideline 421 or 422) in one animal species and for importation of 100–1000 metric tons/year an extended one-generation reproductive toxicity test (OECD Test Guideline 443) or a 2-generation reproductive study if it was initiated before 13 March 2015 (OECD Test Guideline 416). Three studies were conducted following an OECD Test Guideline (Beekhuijzen 2007; Hirata-Koizumi et al. 2011a, 2011b). Four studies were conducted following good laboratory practice (GLP) (Beekhuijzen 2007; Wise et al. 2008; Hirata-Koizumi et al. 2011a, 2011b). When studies included several treatment conditions, the results are presented in the same order as the treatment conditions.

Studies and experimental conditions that did not appreciably increase Al exposure above that provided by the diet

There were many studies that included added Al exposures that, by calculation, contributed less to systemic Al exposure than the diet (20 and 10 μg Al/kg/day for mice and rats, respectively). These exposures are marked in italics in Tables 3 and 6. None of the female exposure studies using added Al exposures that contributed less to the approximate systemic Al exposure than the diet resulted in statistically significant differences from controls, with the exception of the two reports by Trif et al. (2008, 2010) and some significant differences in the Miska-Schramm et al. (2017) report. These low additional Al exposures raise doubt about results that were reported as significantly different from control (no added Al) exposure.

Table 3. Results of studies of females exposed to additional Al.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a,b]	Study results*	Reference
Rats, 45–55 g, females and males	0, 0.067, or 0.063% Al as $AlCl_3 \cdot 6H_2O$ or baking powder in the diet started as young rats and raised to maturity	45 (∼945)	The growth, reproduction, external appearance, and autopsy of rats on the Al-added diets were the same as controls	McCollum et al. (1928)
A mixture of pied and albino rats, females and males	0 or 2 mg of Al as $KAl(SO_4)_2$ added to the stock diet daily for ≥100 days that delivered an average of 8 mg Al/kg bw/day	*9* (800)	Four generations were raised consuming the diet. Average litter size of the first and second litters was 120 and 112% of controls. No gross abnormalities were seen at autopsy	Myers and Mull (1928)
Mice	Bread estimated to deliver 10.5–30 mg Al/day (Lyman and Scott 1930)	∼85–240 daily	Decreased number of offspring (fertility), ovarian atrophy, and histological changes in the ovaries	Schaeffer and Fontes (1928)
Albino rats,4 weeks, 30 to 50 g, females and males	Fed several generations a diet containing 2–4% sodium Al sulfate baking powder for 2 years	∼220–468 daily	No appreciable effect on reproduction	Lyman and Scott (1930)
Rats, 50 to 100 g, females and males	Fed three generations a diet containing 2 to 3.4% sodium Al sulfate baking powder	∼235–400 daily	No effect on fertility	Mackenzie(1932)
Dobrá Voda strain mice, females and males	0 or 19.3 mg/kg/day Al as $AlCl_3$ in the drinking water and 170 ppm Al in the diet for 180–390 days	*7.8* (1403 over 180 days)	No significant differences in number of litters or offspring between treated and control mice. Al-dependent growth retardation was seen in the second and third generation. No pathological tissue changes were seen.	Ondreička et al. (1966)
Holtzman rats, 200–240 g, females	Single treatment: 0 or 40 mg/kg $AlCl_3$ i.p. on GD 9 or 13 Repeated treatment: 0, 75, 100, or 200 mg/kg on GDs 9–13 or 14–18	8080–40,400 (8080–210,080)	After the single injection on GD 9 or 13 GD 20 fetal weight was 104 and 103% of controls. The number of (a) implantations, (b) resorptions, and (c) normal fetuses from GD 9 or 13 injection was (a) 122 and 134, (b) 43 and 267, and (c) 111 and 100% of controls. Repeated treatment with 100 and 200 mg/kg caused some maternal death, with ascites, adhesions between organs, and periheptic granulomas. Fetal weight after (a) 75 mg/kg GDs 9–13 or 14–18, (b) 100 mg/kg GDs 9–13 or 14–18, or (c) 200 mg/kg GDs 9–13 or 14–18 was (a) 83* and 98, (b) 110 and 106, and (c) 87* and 53%* of controls. Fetal crown-rump length was (a) 92* and 99, (b) 98 and 98, and (c) 91* and 69%* of controls. Implantations were (a) 110 and 81, (b) 60 and 93, and (c) 60 and 11% of controls. Resorption percent was (a) 17 versus 0 and 3 versus 2, (b) 1 versus 3 and 10 versus 0, and (c) 37 versus 0 and 12 versus 5 compared to controls. Malformation percent was (a) 0 and 0, 0 and 0; (b) 1 and 0, 8 and 1; and (c) 0 and 0, and 0 and 0 compared to controls	Benett et al. (1975)
Sprague Dawley rats, females	119 ppm Al in the diet supplemented with 0, 500, or 1000 ppm Al as $AlCl_3$ on GD 6, 9, 12, 15, and 18	16 or 32 (80 or 160)	Live and resorbed or dead fetuses were 93 and 93, and 200 and 213% of controls. Fetal body weight and crown-rump length were 101 and 104, and 100 and 103% of controls. There were no statistically significant increases of any abnormalities	McCormack et al. (1979)
Sprague Dawley rats and New Zealand white rabbits, females	74 or 1600 mg/kg Zeolite (20.1% Al) by gavage GD 6–15 (rats) or 74, 345, or 1600 mg/kg by gavage GD 6–18 (rabbits)	30 or 643 (297 or 6432) 30, 139, or 643 (387, 1803, or 8362)	There were no adverse effects on the dam, embryo, or fetus	Nolen and Dierckman (1983)
Beagle dogs, 7–9 months, females and males	112, 361, or 1087 mg sodium aluminum phosphate/kg/ day in the diet for 6 months	*9.5*, 30, or 92 (1738, 5600, or 16,862)	Gross autopsy and histopathological exam showed the normal range of variations of the gonads	Katz et al. (1984)
NMRI strain mice, 6–8 weeks, 24–26 g, females	0.1 ml of 50 or 100 mM $AlCl_3 \cdot 6H_2O$ on GD 3 or 50 mM on GD 8 i.v.	621 or 1242 (621 or 1242)	On GD 17 the % of injected mice with implantations was 130, 106, and not reported; % resorptions 114, 214, and 86%; fetal body weight 98, 94, and 97; fetuses with less mature skeletons 147, 57, and 180*; and fetuses with internal hemorrhage 18, 424*, and 200% of controls	Wide (1984)
Rats, females	1:4 mixture of Maalox TC and water starting GD 2		Pilot study showed 40% failed to deliver pups. Offspring weighed 91%* of controls	Anderson et al. (1985)
New Zealand white rabbits, 3.3–5.5 kg, females	0, 25, 100, or 400 μmol Al/kg as Al lactate s.c. GD 2–6, 9–13, 16–20 and 23–27	142, 567, or 2268 per injection (2268, 9072, or 36,288)	The percentage of does bred producing offspring were 86, 90, and 108; number of offspring 95, 90, and 80; and % of stillborn or dead offspring within 2 days postpartum 57, 171, and 828% of controls	Yokel (1985)
BALB/c mice, 43–50 days, females	0, 100, 150, or 200 mg/kg $AlCl_3$ i.p. or 200 or 300 mg/kg i.g. GD 7 to 16	20,200, 30,300, 40,400, 81, or 121 (202,000, 303,000, 121,200, 808, or 1212)	Does died on the third day of 200 mg/kg/day i.p. dosing. Placental and fetal weight was 53, 107, no result, 112, and 108; and 62, 90, no result, 83, and 90% of controls. Resorptions were 291,1609, no result, 581, and 939% of controls	Cranmer et al. (1986)
Sprague Dawley rats, 240–280 g, females and males	0, 180, 360, or 720 mg/kg $Al(NO_3)_3 \cdot 9H_2O$ i.g. daily for 60 days before mating (males) and 14 days before and throughout mating (females)	26, 52, or 104 (700, 1400, or 2800 through GD 13)	The fertility index was 78, 111, and 111; corpora lutea 93, 87, and 80*; total implants 96, 91, and 102; early resorptions 700, 100, and 800; late resorptions 60, 93, and 73; live fetuses 92, 89, and 89; and dead fetuses on GD 13 400, 200, and 300% of controls	Domingo et al. (1987a)
Sprague Dawley rats, 240–280 g, females	0, 180, 360, or 720 mg/kg/day $Al(NO_3)_3 \cdot 9H_2O$ i.g. GD 14 through lactation day 21	26, 52, or 104 (207, 415, or 829 through GD 21)	Number of living offspring/litter after 1 day of nursing was 100, 69, and 88% of controls. Number of dead offspring/litter after 1 day of nursing was 0, 0.3, 1.1, and 1.6. Offspring body weight was 99, 96, and 81*; body length 100, 98, and 91*; and tail length 104, 100, and 84%* of controls	Domingo et al. (1987b)
Swiss Webster mice, 6–8 weeks, 30 g, females	81–90 (100) [control], 413 (500), or 844 (1000) ppm Al as Al lactate in diet from GD 0 to PND 21 0, 10, 20, or 40 mg Al/kg as Al lactate s.c. GD 3, 5, 7, 9, 11, 13, and 15	84, 171, 2100, 4200, or 8400 (1425, 2913, 14,700, 29,400, or 58,800)	Diet Al did not affect fertility. Pup weights and crown-rump lengths at birth in 500 and 1000 groups were significantly lower than controls. Completed pregnancies of s.c. injected females were 89, 71, and 31% of controls. Al treatment did not affect fetal resorption; number of fetuses; or fetal, placental, or uterine weight. No major	Golub et al. (1987)

(*continued*)

Table 3. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a,b]	Study results*	Reference
			malformations were seen. Minor abnormalities in 10 and 20 mg/kg offspring were 192 and 275% of controls. Fetal crown-rump length was lower* in the 20 mg/kg offspring	
Sprague Dawley rats, 240–280 g, females	0, 180, 360, or 720 mg/kg $Al(NO_3)_3 \cdot 9H_2O$ i.g. GD 6–14	26, 52, or 104 (233, 467, or 933)	On GD 20 doe gestational weight gain was 81*, 80*, and 81%* and placental weight was 101, 78*, and 85%* of controls. The number of litters was 80, 70, and 80; corpora lutea 96, 108, and 106; implants 82, 106, and 107; resorptions 150, 250, and 250; and live fetuses 76*, 102, and 109% of controls. There were 0, 0.7, 0.2, and 0.1 dead fetuses/doe. The percent of litters with runt fetuses was 0, 25, 43, and 62. The fetal weight was 86*, 84*, and 66*; body length 86, 84, and 66*; and tail length 88*, 90*, and 85%* of controls. Of 19 assessed malformations and variations, significant Al effects were seen in micrognathia (360 mg/kg); and decreased supraoccipital bone ossification, hypoplastic deformed ribs, vertebral alterations, and sternebral variations (all 3 groups). Significant hematomas were seen in the 768 mg/kg in the abdominal area, thorax, and limbs	Paternain et al. (1988)
Wistar rats, ~200 g, females	0, 96, 273 or 399 mg Al/kg/day as $AlCl_3$ or 0, 96, 195, or 378 mg Al/kg/day as Al lactate in the diet from GD1 to parturition	96, 273, or 399 (2016, 5733, or 8379) 96, 195, or 378 (2016, 4095, or 7938)	Litter size at birth was 123,123, and 131; and 93, 96, and 96% of controls. Mortality PND 1 was 177, 1986*, and 1470*; and 46, 31, and 520%* of controls. Pup weight PND 1 was 97, 84*, and 78*; and 101, 100, and 85%* of controls.	(Bernuzzi et al. (1989)
Swiss mice, 28–32 g, females	0, 66.5, 133, or 266 mg/kg/day $Al(OH)_3$ i.g. GD 6–15	46, 92, or 184 (460, 920, or 1841)	On GD 18 the number of litters was 90, 95, and 90; implantations 108, 103, and 97; resorptions 775, 625, and 350; live fetuses per litter 85, 83, and 88%; male/female sex ratio 71, 76, and 84; fetal body weight 101, 102, and 101; and fetal body length 100, 104, and 100% of controls. There were no remarkable external malformations, internal soft-tissue defects, or skeletal abnormalities	Domingo et al. (1989)
Swiss Webster mice, 8–12 weeks, females	25 (control), 500, or 1000 mg Al/kg diet as Al lactate from GD 0 through lactation	102 or 203 (2030 or 4060)	There were no differences in pregnancy rate, litter size, sex ratio, birth weight, body length, or perinatal mortality. Gestation length was shorter or longer than the controls in 4 of 17 litters.	Donald et al. (1989)
Wistar rats, females	0, 192, 384, or 768 mg/kg/day as $Al(OH)_3$ i.g. GD 6–15	133, 266, or 531 (1329, 2657, or 5315)	Gravid uterine weight was 99, 101, and 95; number of litters 95, 95, and 100; corpora lutea/doe 109, 113, and 108; implants/litter 107, 111, and 111; preimplantation loss 113, 104, and 94; live fetuses/litter 103, 96, and 105; post-implantation loss 662, 2269*, and 900; non-viable implants/litter (early and late resorptions and dead fetuses) 675, 2375, and 1025; fetal body weight 90, 95, and 93; and male/female sex ratio were 85, 119, and 89% of controls.	Gomez et al. (1990)
Wistar rats, ~220 g, females	0 or 400 mg Al/kg/day as Al lactate in the diet GD 1–7, 1–14, or GD 1–parturition	400 (2800, 5600, or 8,000)	The litter size was 93, 89, and 81; post-natal mortality 212, 288, and 154; and fetal body weight one day after parturition were 91, 91 and 93% of controls. There were no significant effects on the number of dead pups or offspring sex	Muller et al. (1990)
Humans	88 pregnant women exposed to excess Al in the drinking water	Excess $Al_2(SO_4)_3$ in the drinking water raising the maximum recorded Al concentration to 600 mg/l. The EU guideline is <0.1 mg/l	Births up to 42 weeks after the contamination showed a significant reduction of the percentage with spontaneous onset of labor among the exposed compared to unexposed, but no difference in percentage of premature rupture of membranes, mean gestation, pregnancies estimated to be < 37 weeks, or miscarriages in hospital. Newborns showed no difference in mean birth weight; percentage with low birth weight, admitted to special care baby unit, or congenital defects; head circumference, male/female ratio, or Apgar score among the exposed compared to unexposed	Golding et al. (1991)
Sprague Dawley rats, 230–260 g, females and males	0 or 133 mg Al/kg as $Al(OH)_3$, Al citrate, or $Al(OH)_3$ with citric acid (62 mg/kg) i.g. GD 6–15	266 (2660) as $Al(OH)_3$ 532 (5320) as Al citrate, or $Al(OH)_3$ with citric acid	GD 20 percent pregnant rats was 106, 88, and 112; gravid uterine weight 106, 90, and 100; number of litters 106, 88, and 112; corpora lutea/doe 101, 99, and 102; implantations/litter 101, 84, and 103; preimplantation loss/litter 105, 185, and 100; viable implants/litter 102, 81, and 96; nonviable implants/litter 83, 150, and 250; post implantation loss/litter 95, 203, and 276; male/female sex ratio 108, 99, and 94; and fetal body weight were 103, 104, and 94%* of controls. Fetal a) parietal, b) occipital, and c) sternebrae delayed ossification; and d) absence of xiphoids indicating delayed ossification were a) 100, 80, and 109; b) 70, 161, and 213*; c) 109, 107, and 134*; and d) 85, 165*, and 155%* of controls	Gomez et al. (1991)
CBA mice, 25 g, females	0 or 200 mg/kg $Al_2(SO_4)_3 \cdot 18H_2O$ i.p GD 10–13 or 0 or 750 mg/l $Al_2(SO_4)_3 \cdot 18H_2O$ i.g. GD 10–17	648,000 (2,592,000) 4860 (38,880)	Al exposure did not affect gestation length, litter size, or sex ratio. Pups born to does that received i.p. Al weighed ~95%* of controls. Weight of pups born to does that received oral Al were not significantly different from controls	Clayton et al. (1992)
Swiss albino mice, 28–32 g, females	0 or 57.5 mg Al/kg as $Al(OH)_3$ or Al lactate, or $Al(OH)_3$ with lactic acid (570 mg/kg) i.g. GD 6–15	115 (1150)	GD 18 gravid uterine weight was 91, 89 and 80% of controls. The number of litters was 85, 77, and 100; implantation sites/litter 86, 99, and 82; resorptions 121, 106, and 186; post-implantation loss 141, 138, and 240; live fetuses/litter 84, 97, and 77; male/female sex ratio 106, 101, and 98; and fetal body weight/litter 102, 84*, and 102% of controls. The number of dead fetuses was 0, 0, 1, and 1. Cleft palate, dorsal hyperkyphosis, and parietal, delayed ossification, not seen in controls, were produced, mostly in Al lactate-exposed offspring	(Colomina et al. (1992)

(*continued*)

Table 3. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a,b]	Study results*	Reference
THA strain rats, females	0, 90, 180, or 360 mg/kg $AlCl_3$ i.g. GD 8 to 20	36, 73, or 145 (473, 945, or 1891)	There were no differences in the mean number of implantation sites, birth rate, or mean litter size.	Misawa and Shigeta (1992)
THA strain rats, females	0, 900, or 1800 mg/kg $AlCl_3$ i.g. GD 15	364 or 727 (364 or 727)	There were no differences in the mean number of implantation sites, birth rate, or mean litter size. Female and male offspring weight was 76* and 66*; and 73* and 64%* of controls	Misawa and Shigeta (1993)
Wistar rats, ~260 g, females	0 or 400 mg Al/kg/day as Al lactate in the diet GD 1–19	400 (7600)	Litter size was 103% of controls. GD20 fetus body weight was 97 (upper uterine horn) and 101% of controls (lower uterine horn). GD20 fetus calcium was 115*, phosphorus 104, Al 286, copper 48, zinc 103, and magnesium were 90%* of controls	Muller et al. (1993)
CBA/T6 mice, 10–12 weeks old	0 or 200 mg/kg $Al_2(SO_4)_3$ i.p. GD10 to 13	31,600 (126,400)	Offspring birth weights were 88%* of controls.	Rankin and Manning (1993)
Swiss albino mice, 28–32 g, females	0 or 103.8 mg Al/kg as $Al(OH)_3$ or $Al(OH)_3$ with ascorbic acid (85 mg/kg) i.g. GD 6–15	208 (2076)	There were no significant effects on GD 18 doe body and uterine weight, number of implantation sites, post-implantation loss %, resorptions/litter, live and dead fetuses/litter, fetal body weight, or fetal sex ratio. No fetal gross external, visceral, or skeletal malformations were seen	Colomina et al. (1994)
B6C3F1 mice, 4 weeks old, females and males	1, 2.5, 5, and 10% $KAl(SO_4)_2{\cdot}12H_2O$ in the diet for 20 months	114, 285, 570, or 1140 (69,312, 173,280, 346,560, or 693,120)	Vaginal mucosal epithelium keratinization was 113, 94, 104, and 98% of controls. Vaginal lymphocytic infiltration was 95, 127, 18, and 108% of controls.	Oneda et al. (1994)
Charles River CD rats, females	0, 5, 25, 50, 250, 500, or 1000 mg/kg Al lactate i.g. GD 5–15	*0.92*, *4.6*, *9.2*, 46, 92, or 184 (10, 51, 101, 506, 1012, or 2024)	Female offspring weight was 101, 112, 103, 100, 99, and 101 and anogenital distance 100, 96, 99, 105, 95, and 93% of controls. Male offspring weight was 99, 105, 98, 94, 94* and 98; anogenital distance 93*, 94*, 96, 97 and 90*, 98 and 93*, and 97; and testicular weight 105, 112*, 92*, 99 and 110*, 119 and 102, and 96% of controls	Agarwal et al. (1996)
SPRD rats, 240–280 g, 7 weeks, females	0, 2.45, 4.9, or 9.8 mg/kg Al lactate s.c. GD 7–15	47, 95, or 189 (473, 947, or 1893)	The number of offspring/litter was 95, 111, and 111 and their weights were 98, 96, and 93% of controls	Gonda et al. (1996)
SPRD rats, 240–280 g, females	0, 2.45, 4.9, or 9.8 mg/kg Al lactate s.c. GD 7 to 15	47, 95, or 189 (473, 947, or 1893)	The number of offspring/litter was 86, 105, and 112 and their weights were 100, 100, and 98% of controls.	Gonda and Lehotzky (1996)
SPRD rats, 240–280 g, females	0 or 9.8 mg/kg Al lactate s.c. GD 7 to 15	189 (1893)	The number of pups/litter and their weights were 112 and 93% of controls	Gonda et al. (1997)
CBA/T6 and C57/BL/6J mice	0, 750, 1000, or 1250 mg/l $Al_2(SO_4)_3$ in the drinking water GD 10–17 or 200 mg/kg i.p. GD 10–13	64, 86, or 107 (516, 688, or 860) 31,300 (126,400)	There were no effects on gestation length, litter size, sex ratio, or pup mortality. Offspring weights of CBA pups exposed to 750 or 1000 weighed less than controls. C57/BL/6J pups exposed to 1250 mg/l weighed 5% less than controls. Pups of both strains exposed to i.p. Al *in utero* weighed less than controls	Alleva et al. (1998)
Swiss albino mice, 28–32 g, females	0, 37.5, or 75 mg/kg $AlCl_3$ i.p. GD 6–15	7575 or 15,150 (75,750 or 151,500)	GD 18 gravid uterine weight was 89 and 79*, implants/litter 83 and 82, live fetuses/litter 91 and 87, early resorptions/litter 0 and 438, dead fetuses/litter 875 and 125, post-implantation loss 368 and 521, % male sex 86 and 96, and fetal body weight was 87* and 82%* of controls. Al exposure did not increase fetal morphologic defects	Colomina et al. (1998)
Charles River CD-1 mice, 25–30 g, females	0, 60, 120, or 240 mg/kg $AlCl_3$ i.p. GD 6–15	12,120, 24,240, or 48,480 (121,200, 242,400, or 484,800)	GD 18 percentage of dead fetuses was 0, 0, 15*, and 50*; abortions 0, 9, 30*, and 43*; early deliveries 0, 0, 0, and 0; resorbed litters 0, 0, 5, and 0; and does with live fetuses 100, 91*, 50* and 0%*. For the 60 and 120 mg/kg exposed does gravid uterine weight was 84 and 76*, implants/litter 104 and 98, live fetuses/litter 94 and 91, non-viable implants/litter 192 and 154 , early resorptions 36 and 55, late resorptions 950 and 600, male/female sex ratio 100 and 93, and fetal body weight 79* and 79%* of controls. There was an exposure-dependent increase in fetal asymmetrical sternebrae and frontal bone reduced ossification	Albina et al. (1999)
Charles River CD-1 mice, 25–32 g, females	0 or 398 mg/kg $Al(NO_3)_3{\cdot}9H_2O$ i.g. GD 6–15	57 (573)	Al caused 56%* doe mortality, abortion in 3% and early delivery in 6%* compared to 0% in controls. The doe body, gravid uterine, and fetal weights were 67*, 49*, and 58%* of controls. Implants, live fetuses, and non-viable implants per litter were 95, 82, and 727% of controls. Of the non-viable implants Al increased early and late resorptions and dead fetuses. Male/female sex ratio was 112% of controls. Significant fetal effects were internal alterations and reduced and delayed ossification of multiple bones	Bellés et al. (1999)
Mouse oocytes	Al nitrate, 30 or 60 mg/l		First polar body extrusion was inhibited and viability affected, but there was little effect on germinal vesicle breakdown	Shen et al. (1999)
Swiss mice, 5–6 weeks, 30–35 g, females	0 or 200 mg/kg $AlCl_3$ i.g. for 30 days	81 (2424)	Ovarian protein was 69*, uterine protein 59*, ovarian 3β-hydroxysteroid dehydrogenase 44*, and 17β-HSD activities (enzymes involved in steroid [estrogen and progesterone] production) 46*, ovarian cholesterol 198*, uterine glycogen 164*, phosphorylase 43*, and serum estradiol 66% of controls	Chinoy and Patel (2001)
Swiss Webster mice, 8 weeks, females	0, 100, 500, or 1000 mg Al/kg diet as Al lactate GD 0 to PND 35	20, 102, or 203 (609, 3045, or 6090)	There were no differences in the number of does completing pregnancy, gestation length, or litter size at birth	Golub and Germann (2001)
Naval medical research institute mice, 24–33 g, females	0 or 150 mg/kg $AlCl_3$ i.p. on GD 10, 11, or 12	30,300 (30,300)	Resorption rates were 25.5, 21.2, and 23.3% and 0% in vehicle-exposed does. GD 18 fetus body weights were 88*, 90*, and 93%* of controls. Crown-rump length was not affected.	Malekshah et al. (2005)

(*continued*)

Table 3. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a,b]	Study results*	Reference
			Percent of Al-exposed offspring with fetal anomalies was 29*, 20*, and 13%*. Percent of vehicle-exposed offspring with fetal anomalies: 3.4, 4.3, and 4.1	
Wistar rats, females (∼11 weeks), males (∼9 weeks)	0, 40, 200, or 1000 mg/kg/day $AlCl_3$ i.g. from 2 weeks prior mating to ≥ 3 PNDs	20, 98, or 494 (554, 2744, or 13832)	The mating index was 100, 90, 100, and 100; number of pregnant females/number of females paired 100, 90, 90, and 100; fecundity index 100, 90, 90, and 100; and fertility index 90, 100, 100, and 100%. Gestation duration (number of days between confirmation of mating and the beginning of parturition) was 100, 100 and 100%; implantation sites 95, 84, and 98; and corpora lutea 98, 81, and 91% of controls. PND 1 male offspring weight was 93, 97, and 98; female offspring weight 100, 104, and 100; and live offspring 102, 103, and 99% of controls. There were 0, 1.3, 0.1, and 0 dead offspring/litter. Microscopic assessment of cervix, clitoral gland, ovaries, uterus, and vagina showed no significant difference from controls	Beekhuijzen (2007)
Wistar rats, 3 weeks, females	0 or 3 mg Al as $Al(OH)_3$ gel s.c.	10,161 (10,161)	Ovary weight 3 days later was 104% of controls	Kimura et al. (2007)
Japanese black cows, 411 kg, females	15 or 30 mg Al as $Al(OH)_3$ gel i.m. once. 48 h later luteolysis induced, then artificially inseminated 0 or 15 mg Al i.m. once 15 mg Al i.m. on 5 occasions every 2 to 3 months over 1 year All with porcine FSH (pFSH) to induce super-ovulation	A) *0.18* or *0.36* (1.3 or 2.6 after 7 days) B) *0.18* (1.3 after 7 days) C) *0.18* (182 after 1 year)	A). Seven days after 30 mg Al the number of corpora lutea, total ova recovered, transferable embryos, or large follicles was 115, 83, 78, and 243%* of those given 15 mg. B) Corpora lutea, large follicles, total ova recovered, and transferable embryos were 105, 98, 108, and 108% of controls. C) The number of corpora lutea was 111, 73, 79, and 97%; total ova recovered 105, 57, 63, and 95%; and transferable embryos 91, 58, 42, and 91% after the 2nd, 3rd, 4th, and 5th injection compared to the 1st	
Swiss mice, 50 days, females	0, 75, 94, or 117 mg/kg/day $AlCl_3$ in the drinking water for 12 weeks	30, 38, or 47 (2545, 3190, or 3971)	Body 82*, 90*, and 83*; uterus 100, 100, and 119*; and ovary weight was 72*, 89, and 89% of controls after the 12 weeks. GD20 number of pregnant females was 50*, 50*, and 44*; viable fetuses 91, 52*, and 83; implantation sites 107, 81, and 116; and resorptions/implantation sites 1303*, 2481*, and 1945%* of controls. Histology of ovarian sections showed highly congested blood vessels throughout the ovary, with a large number of atretic follicles at different stages of development	Mohammed et al. (2008)
	0, 19, or 38 mg/kg/day $AlCl_3$ i.p. GD 0–6	3838 or 7676 (26,866 or 53,732)	38 mg/kg/day resulted in sluggishness, paralysis, decreased body weight, diarrhea, and death in 40% of the does. GD20 doe body weight was 48, 35*, and 28* g; placental weight 0.17, 0.15, and 0 g; fetal weight 1.2, 1.0 and 0 g; viable fetuses 8.3, 5.17*, and 0; implantation sites 8.3, 6.7, and 3.0*; resorptions/implantation sites 0, 23* and 100%*; and pregnant females 100, 60* and 17%*. The highest Al dose caused highly congested blood vessels over the ovaries with a large number of atretic follicles at different developmental stages	
Wistar rats, females	50 (control), 200, 400, or 1000 ppb Al as $Al_2(SO_4)_3$ in the drinking water for 6 months	*0.24, 0.48, or 1.2* (44, 87, or 218)	Sexual cycle duration was 108, 116, and 114% of the control group. The percent normal proestrous was 100, 94*, 100, and 97*; estrous 62, 29*, 31*, and 41*; diestrous I 62, 56*, 62, and 47*; and diestrous II (estrous cycle phases) 97, 62*, 81*, and 94%*	Trif et al. (2008)
Sprague Dawley rat, ∼5 weeks, females	0 or 0.1125 mg Al as Merck Al adjuvant i.m. into each hindlimb premating weeks 5 and 2 and GD 6. F0 females bred at 12 weeks of age	48.6 at GD21 (450 at GD21)	No significant effect was seen on F0 female body weight. Fecundity index was 101, GD21 corpora lutea/pregnant female 100, peri-implantation loss 104, implantations/pregnant female 100, resorptions/implants 112, post-implantation loss 112, live fetuses/pregnant female 99, female fetal weight 101, and male fetal weight 101% of controls. No significant differences in fetal morphology were seen. F1 generation showed no significant reproductive effects	Wise et al. (2008)
Humans giving 76,788 births, females	Mean exposure to 0.042 $\mu g/m^3$ in $PM_{2.5}$ captured Al in Connecticut for 3.5 years	0.00021[c] (0.27)	The interquartile range gestational exposure (0.03 $\mu g/m^3$) was associated with a 5% decrease in birthweight (95% confidence interval) and 11% increase in risk of small-at term birth (95% confidence interval).	Bell et al. (2010)
Wistar rats, females and males	0, 200, 400, or 1000 ppb $Al_2(SO_4)_3$ in the drinking water for 3 months before mating F0 generation. F1 offspring had same exposure to sexual maturity	*0.24, 0.48, or 1.2* (22, 44, or 109)	The authors saw severe structural changes in F0 and F1 ovary and uterus of Al-exposed rats, summarized as congestive and degenerative changes. The ovary had vacuolar epithelial cells, follicles with large oocytes, edema of the parenchymatosa zone, and follicle and parenchyma destruction. The uterus showed necrosis, uterine epithelium lining destruction, vascular congestion, connective tissue necrosis and reduction, and uterie epithelium detachment.	Trif et al. (2010)
Sprague Dawley rats, 5 weeks, females and males	0, 120, 600, or 3000 ppm $Al_2(SO_4)_3$ in the drinking water for 10 weeks before mating and throughout the lactation period for F0 and F1 generation rats, resulting in mean 14.4, 71.5, or 316 mg/kg bw/day $Al_2(SO_4)_3$ intake by F0 females and 15.3, 74.2, or 338 mg/kg bw/day $Al_2(SO_4)_3$ intake by F1 females	F0 females *4.6*, 23, or 100 (319, 1582, or 6990 over 10 weeks) F1 females *4.8*, 23, or 107 (338, 1641, or 7477 over 10 weeks)	The mating index was 95.8, 100, 100, and 100% in the F0 generation and 100, 95.8, 100, and 95.8% in the F1 generation. Fertility was 95.7, 91.7, 100 and 95.8% in the F0 generation and 91.7, 82.6, 91.7, and 91.3% in the F1 generation. There were no treatment-related differences in the number of pups delivered. There were no treatment-related alterations in the histopathology of female reproductive organs or number of primordial follicles in the ovary of F1 females between the control and highest Al exposure group. There was no significant effect of Al treatment on ovary weight of F1 females.	Hirata-Koizumi et al. (2011b)

(*continued*)

Table 3. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a,b]	Study results*	Reference
			Uterus weights of Al-treated F1 weanlings were 105, 84*, and 78%* of controls and 102, 87, and 87% of controls normalized to body weight. Ovary weights of Al-treated F2 weanlings were 95, 97, and 95%* of controls and 97, 98, and 93% of controls normalized to body weight. Uterus weights of Al-treated F2 weanlings were 105, 107, and 81%* of controls and 106, 105, and 90% of controls normalized to body weight	
Sprague Dawley rats, 5 weeks, females and males	0, 50, 500, or 5000 ppm $NH_4Al(SO_4)_2$ in the drinking water for 10 weeks before mating and throughout the lactation period for F0 and F1 generation rats, resulting in mean 6.52, 58.6, or 500 mg/kg bw/day $NH_4Al(SO_4)_2$ intake by F0 females and 6.65, 61.9, or 517 mg/kg bw/day $NH_4Al(SO_4)_2$ intake by F1 females	F0 females *1.5*, 13.4, or 114 (104, 935, or 7980 over 10 weeks) F1 females *1.5*, 14, and 118 (106, 988, or 8251 over 10 weeks)	The mating index was 100, 100, 100, and 100% in the F0 generation and 100, 95.8, 100, and 100% in the F1 generation. Fertility was 100, 87.5, 100 and 100% in the F0 generation and 91.7, 78.3, 95.8, and 95.8% in the F1 generation. There were no significant differences in the number of implantations, pups delivered, sex ratio, or pup viability on delivery. There were no treatment-related alterations in the histopathology of female reproductive organs or number of primordial follicles in the ovary of F1 females between the control and highest Al exposure groups. There was no significant effect of Al treatment on ovary weight of F1 females. Ovary weights of Al-treated F2 weanlings were 101, 98, and 83%* of controls and 98, 100, and 92% of controls normalized to body weight. Uterus weights of Al-treated F2 weanlings were 94, 82, and 75%* of controls and 92, 85, and 84% of controls normalized to body weight	Hirata-Koizumi et al. (2011a)
Sprague Dawley rats, females	100 μl saline or AS04 (GSK Biologicals proprietary Adjuvant System that contains 500 μg $Al(OH)_3$ salt and 50 μg of a lipopoly-saccharide derivative per 500 μl) i.m. 30 days before pairing with a male and on GD 6, 8, 11, and 15	*3.1 from each injection* (280 on GD 20)	The mating index was 102, fecundity 100, fertility index 100, post-implantation survival 105, live birth 101, and viability index 101% of controls. GD 20 corpora lutea were 91, implantations 94, pre- and post-implantation losses 82 and 108, live young 94, placental weight 104, litter weight 95, female and male fetal weights 102 and 100, and minor visceral abnormalities 108% of controls	Segal et al. (2011)
C57BL/6 and BALB/c mice, 10 weeks, females	2% $Al(OH)_3$ in 0.2 ml as an adjuvant in tetanus toxoid s.c. 3 times at 2-week intervals. Mated one day after the last dose	14,532 for the 1 day after one injection (44,596)	Fecundity index and fertility were 60 and 88% in C57BL/6 mice and 87 and 59%* in BALB/c mice compared to saline-treated controls	Zivkovic et al. (2011)
Swiss-Webster mice, 10–12 weeks, females	0, 300, or 600 mg/kg $AlCl_3$ in the drinking water throughout pregnancy	121 or 242 (2424 or 4848)	Al exposure non-statistically significantly decreased newborn body weight	Abu-Taweel et al. (2012)
Wistar rats, 5 weeks, 110-120 g, females	0, 64, 128, or 257 mg/kg $AlCl_3$ in the drinking water for 120 days	26, 52, or 104 (3103, 6205, or 12,459)	Blood estrogen was 96*, 34*, and 15*; progestogen 91*, 69* and 42*; LH 77*, 22*, and 4*, and FSH 59*, 16*, and 12%* of controls. Blood testosterone increased ~2-, 8-, and 12-fold of controls.	Wang et al. (2012)
C57BL/6 mice, 10 weeks, females	0 or 2% alhydrogel ($Al(OH)_3$ wet gel suspension) in 0.2 ml s.c. 3 times at 2- week intervals	14,532 for the 1 day after one injection (44,596)	Fecundity was 56%* in Al-injected mice and 83% in controls. Fertility was 7.3 offspring in Al-injected mice and 7.0 in controls	Zivkovic et al. (2012)
Albino rats, 150–200 g	0 or 200 mg/kg $AlCl_3$ i.g. GD 6 to 15	80.8 (808)	Implantations, resorptions, live fetuses, and dead fetuses were 52/60, 11/0*, 37/60, and 3/0* compared to controls	Hussein and Mahmoud (2013)
Wistar rats, 5 weeks, 110–120 g, females	0, 64, 128, or 256 mg/kg $AlCl_3$ in the drinking water for 120 days	26, 52, or 103 (3103, 6205, or 12,411)	Ovary ACP activity was 96*, 84*, and 78*; ALP 94*, 83*, and 78*; Mg-ATPase 97*, 93*, and 82*; Na-K-ATPase 7*, 84*, and 81*; and Ca-ATPase 93*, 83* and 78%* of controls. Ovary FSH receptor expression was 104*, 107*, and 110* and LHR 102*, 105*, and 109%* of controls. Ovary zinc was 90, 77*, and 68*; copper 103, 120*, and 131*; and iron 89, 70*, and 59%* of controls. Ovary ultrastructural changes in the highest exposure group included: Margination and concentration of nuclear chromatin showed ovary granulosa cell apoptosis. Irregular nuclear envelope structure. Swollen mitochondria. Disintegrated and vacuolated cristae. Dilated rough endoplasmic reticulum with lost ribosomes. Disordered Golgi body structure. Much higher electron density in nuclear and cytoplasmic substances	Fu et al. (2014)
Humans	Urine Al above (26% of subjects) and below 9 μg/L with fetus at gestational age > 22 weeks and birth weight > 500 g		Median cell proliferation, as a measure of oxidative stress, of erythrocytes in umbilical cord blood was 2.3-fold in those with higher Al. Newborns with cell proliferation above the median were more likely to be diagnosed as small-for-gestational age and weighed less.	Karakis et al. (2014)
Humans			Umbilical cord blood averaged 10.9 μg/L. There was no correlation with birth weight, crown-heel length, head circumference, Apgar scores or gestational age	Rahbar et al. (2015)
Humans	Mean exposure to 0.040 and 0.042 $\mu g/m^3$ Al in $PM_{2.5}$ captured in Florida during the first trimester and entire pregnancy, respectively	0.0002[c] (0.018 and 0.054)	Adjusted odds ratio risk of placental abruption was 1.10* (95% C.I. 1.02–1.18) in the first trimester and 1.06* (95% C.I. 0.94–1.19) in the entire pregnancy	Ibrahimou et al. (2017)
Wistar rats, 250 g, female	0 or 1 mg $Al(NO)_3)_3$ i.p every other day for 7 doses	508 (3556)	Electron-dense material was seen in endometrial, myometrial, ovary internal theca, and granulosa cell cytoplasmic lysosomes. Increased number of endometrial and myometrial cell cytoplasmic lysosomes, with varied shapes and sizes. Endometrial cell swollen mitochondria with no visible cristae, containing a very electron lucent matrix. Some endoplasmic	Marwa et al. (2017)

(*continued*)

Table 3. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a,b]	Study results*	Reference
			reticulum alterations. Myometrium cells had relatively dense, compact cytoplasm. There were collagen fibers in the extracellular matrix, some cells had altered mitochondria, dilated endoplasmic reticulum, and many eosinophils as signs of inflammation produced by the damaged cells. Ovary internal theca cells had lysosomes of various shapes and sizes. Nuclei were elongated, polymorphous, with random heterochromatin distribution. Mitochondria were round, sometimes swollen, with decreased or altered endoplasmic reticulum. Granulosa cells had euchromatic, indented nuclei; intercellular vacuolations; cytoplasmic organelles with degenerative ultrastructural changes; polymorphous or swollen mitochondria with abnormal, altered cristae and electron lucent matrix; and enlarged endoplasmic reticulum	
Bank voles, 4 weeks, females and males	0, 1.5, or 100 mg Al/kg/day as $AlCl_3·6H_2O$ in the drinking water for 12 weeks	*3* or 200 (252 or 16,800)	Uterine weights were 155* and 124% of controls. Total number of type 6 (355–418), type 7 (527–595), and type 8 (717-867 μm diameter) uterine follicles was 112 and 93% of controls. The number of type 6, 7, and 8 follicles was 100 and 102; 153* and 75*; and 90 and 69% of controls. Mouse follicle classification goes up to type 8 (the largest and preovulatory follicle). (Pedersen and Peters 1968)	Miska-Schramm et al. (2017)
Slc: ICR mice, females	0, 108, or 207 mg/kg Al as $AlCl_3·6H_2O$ in the drinking water from GD 6–PND 21	216 or 414 [3456 or 6624]	One animal in each Al-treatment group had an abortion. The number of implantation sites, live offspring, and male/female ratio were 104 and 103, 98 and 106, and 96 and 107% of control	Inohana et al. (2018)
Wistar rats, 180–200 g, females	0 or 500 mg/l $AlCl_3$ in the drinking water from GD 6 to the end of lactation	28 [441]	The gestation period, litter number, males, females, and weight were 102, 87*, 83, 94, and 107% of controls	Kinawy and Al-Eidan (2018)
Sprague Dawley rats, ~8 weeks, females	0 or 0.25 mg Al as Al hydroxy-phosphate sulfate (in Merck's aluminum adjuvant) i.m. in each hindlimb muscle 5 and 2 weeks prior to cohabitation with untreated males and GD 6	142 at GD 21 (5021 at GD 21)	Mating index was 100%. Fecundity was 96 to 100%. Mated and pregnant females were 100 and 95% of controls. Corpora lutea were 102, peri-implantation loss 175, implants 100, resorptions 119, post-implantation loss 120, live fetuses 99, and female and male fetal weights 98 and 98% of controls. GD 21 live fetus/litter was 104% of controls. Fetuses with external malformations were 2/271 versus 0/275 in controls, visceral malformations and visceral abnormalities 1/142 and 1/142 versus 0/143 in controls; coronal malformations 1/131 versus 1/132 in controls; skeletal variations 18/142 versus 17/143 in controls; and incomplete ossification 6/142 versus 1/143 in controls	Wise et al. (2018)
Gerbils, 3 to 4 months old, females	0 or 20.2 mg Al/kg/day as $AlCl_3$ orally GD 17 versus24	40.4 [323]	Offspring body weight, anogenital distance; and prostate epithelial buds, mesenchyme, and smooth muscle were 85*, 53*, 126*, 9*, and 105% of controls. Androgen receptor, estrogen receptor alpha, and proliferating cell nuclear antigen in the prostate epithelial buds, mesenchyme, and smooth muscle was 57*, 86, and 75; not reported, 244*, and 290*; and 371*, 260*, and 209%* of control. The results suggest Al acts as an endocrine disruptor	Gomes et al. (2019)
Humans			Maternal urinary Al concentration during the second and third trimester positively correlated with increased umbilical cord mitochondrial DNA number, suggesting increased reactive oxygen species exposure	Liu et al. (2019)

The approximate systemic Al exposure from the additional Al was calculated as described in the text. Daily exposures that did not add more Al than expected from the diet are in italics.

[a]Percentage of Al in $Al(OH)_3$ 34.6%, $AlCl_3$ 20.2%, $AlCl_3·6H_2O$ 11.5%, $Al_2(SO_4)_3$ 15.8%, $Al_2(SO_4)_3·16H_2O$ 8.6%, $Al_2(SO_4)_3·18H_2O$ 8.1%, $Al(NO_3)_3$ 12.7%, $Al(NO_3)_3·9H_2O$ 7.2%, $NH_4Al(SO_4)_2$ 11.4%, $KAl(SO_4)_2$ 10.5%, $KAl(SO_4)_2·12H_2O$ 5.7%, $NaAl_3H_{14}(PO_4)_8·4H_2O$ 8.5%, Al lactate 9.2%, and Al acetate 13.2%.

[b]The fraction absorbed from i.g. solutions was taken to be 0.002, from food 0.001, $Al(OH)_3$ i.m. 0.005 daily, Al phosphate and amorphous aluminum hydrophosphate sulfate i.m. 0.018 daily, i.p. 1, s.c. 0.21, and topical 0.0001, as described in the text.

[c]The fraction absorbed for inhalation was taken to be 0.015–0.02, resulting in daily absorption of 0.001 μg/kg for air containing 0.2 $\mu g/m^3$ (Yokel and McNamara 2001).

*Results that are statistically significantly different from controls.

Assessment of Al reproductive toxicity in female animals

The assessment of Al reproductive toxicity focused on studies in animals due to the lack of prospective or controlled-dose human studies that provide insight into potential Al-induced reproductive toxicity. Table 3 summarizes results of studies of Al reproductive toxicity in females. The cited studies do not consistently use the terms fecundity or fertility or their indexes. The author could not find generally accepted descriptions of these terms related to laboratory animals, as noted in a review of non-clinical fertility study design (Lerman et al. 2009). Four endpoints are used, following published guidelines (Wolterbeek et al. 2004), and the reported results categorized accordingly, irrespective of the definition used by the authors. Mating (copulation) was defined as positive mating (typically determined as sperm in the vagina (vaginal smear) or a vaginal plug) and mating index (%) as positive matings/cohabitated females. Fecundity (conception) was defined as a pregnant female and fecundity index (%) as pregnant females/successfully mated females. Fertility was defined as the number of live offspring and fertility (gestation) index (%) as the number of live offspring/litter.

The results of all studies are categorized as to whether they showed significant toxicity and the daily and total

Table 4. Studies conducted in females categorized according to study report of significant findings and approximate systemic Al exposure.

	Daily approximate systemic Al exposure (μg/kg)	Total approximate systemic Al exposure (μg/kg)
A. GLP compliant studies conducted following an OECD Test Guideline showing no statistically significant toxicity		
Beekhuijzen (2007)	20, 98, or 494	554, 2744, or 13,832
Hirata-Koizumi et al. (2011b)	*4.6*, 23, or 100	319, 1582, or 6990
Hirata-Koizumi et al. (2011a)	*1.5,* 13.4, or 114	104, 935, or 7980
B. No statistically significant effects from exposures similar to A. above		
McCollum et al. (1928)	45	∼945
Schaeffer and Fontes (1928)	∼85–240	
Lyman and Scott (1930)	∼220–468	
Mackenzie (1932)	∼235–400	
McCormack et al. (1979)	16 or 32	80 or 160
Nolen and Dierckman (1983)	30 or 643	297 or 6432
Nolen and Dierckman (1983)	30, 139, or 643	387, 1803, or 8362
Katz et al. (1984)	*9.5*, 30, or 92	1738, 5600, or 16,862
Yokel (1985)	142, 567, or 2268	2268, 9072, or 36,288
Donald et al. (1989)	102 or 203	2030 or 4060
Muller et al. (1990)	400	2800, 5600, or 8,000
Misawa and Shigeta (1992)	36, 73, or 145	473, 945, or 1891
Colomina et al. (1994)	208	2076
Gonda et al. (1996) and Gonda and Lehotzky (1996)	47, 95, or 189	473, 947, or 1893
Gonda et al. (1997)	189	1893
Alleva et al. (1998)	64, 86, or 107	516, 688, or 860
Golub and Germann (2001)	20, 102, or 203	609, 3045, or 6090
Wise et al. (2008)	48.6	450
Segal et al. (2011)	*3.1*	280
Abu-Taweel et al. (2012)	121 or 242	2424 or 4848
Inohana et al. (2018)	216 or 414	3456 or 6624
Wise et al. (2018)	142	5021
C. Study found some statistically significant results from exposures similar to A. above		
Domingo et al. (1987a)	26, 52, or 104	700, 1400, or 2800
Domingo et al. (1987b)	26, 52, or 104	207, 415, or 829
Paternain et al. (1988)	26, 52, or 104	233, 467, or 933
Bernuzzi et al. (1989)	96, 273, or 399; 96, 195, or 378	2016, 5733, or 8379; 2016, 4095, or 7938
Domingo et al. (1989)	46, 92, or 184	460, 920, or 1841
Gomez et al. (1990)	133, 266, or 531	1329, 2657, or 5315
Gomez et al. 1991)	266 or 532	2660 or 5320
Colomina et al. (1992)	115	1150
Misawa and Shigeta (1993)	364 or 727	364 or 727
Muller et al. (1993)	400	7600
Agarwal et al. (1996)	*0.92, 4.6, 9.2,* 46, 92, or 184	10, 51, 101, 506, 1012, or 2024
Gonda et al. (1996)	47, 95, or 189	473, 947, or 1893
Gonda and Lehotzky (1996)	47, 95, or 189	473, 947, or 1893
Gonda et al. (1997)	189	1893
Bellés et al. (1999)	57	573
Chinoy and Patel (2001)	81	2424
Kimura et al. (2007) (cows)	*0.18* or *0.36*	1.3, 2.6, or 182
Mohammed et al. (2008) (i.g.)	30, 38, or 47	2545, 3190, or 3971
Trif et al. (2008)	*0.24, 0.48, or 1.2*	44, 87, or 218
Trif et al. (2010)	*0.24, 0.48, or 1.2*	22, 44, or 109
Wang et al. (2012)	26, 52, or 104	3103, 6205, or 12,459
Hussein and Mahmoud (2013)	80.8	808
Fu et al. (2014)	26, 52, or 103	3103, 6205, or 12,411
Miska-Schramm et al. (2017)	*3* or 200	252 or 16,800
Kinawy and Al-Eidan (2018)	28	441
Gomes et al. (2019)	40.4	323
D. Study found some statistically significant results from higher exposure		
Wide (1984)	621 or 1242	621 or 1242
Golub et al. (1987)	84, 171, 2100, 4200, or 8400	1425, 2913, 14,700, 29,400, or 58,800
Clayton et al. (1992) i.p.	648,000	2,592,000
Rankin and Manning (1993)	31,600	126,400
Colomina et al. (1998)	7575	75,750
Albina et al. (1999)	12,120, 24,240, or 48,480	121,200, 242,400, or 484,800
Malekshah et al. (2005)	30,300	30,300
Mohammed et al. (2008)	3838 or 7676	26,866 or 53,732
Zivkovic et al. (2011)	14,532	44,596
Zivkovic et al. (2012)	14,532	44,596
Marwa et al. (2017)	508	3556
E. Study found no statistically significant results from exposures similar to D. above		
Clayton et al. (1992) i.g.	4860	38,880
Oneda et al. (1994)	114, 285, 570, or 1140	69,312, 173,280, 346,560, or 693,120
Kimura et al. (2007) (rats)	10,161	10,161
F. Study found statistically significant results associated with maternal mortality		
Benett et al. (1975)	8080–40,400	8080–210,080
Mohammed et al. (2008)	3838 or 7676	26,866 or 53,732

calculated systemic Al exposure (Table 4). Overall, these studies suggest limited additional Al exposure above what would enter systemic circulation from the diet did not affect female reproduction. The 4 studies that were GLP compliant and 3 studies conducted following an OECD Test Guideline are notable in that they reported no significant effects following daily Al exposures that, by calculation, would increase the systemic Al exposure by up to 25-fold (Table 4, Category A and Table 3). Additionally, there are numerous studies that utilized comparable Al exposures that did not report any statistically significant effects (Table 4, Category B and Table 3). In contrast, several studies utilizing calculated added Al exposure that was in the range of the above studies showed some significant effects, although most of the studied endpoints were not significantly altered (Table 4, Category C and Table 3). With seven exceptions (Bernuzzi et al. 1989; Gomez et al. 1990; Gomez et al. 1991; Muller et al. 1993; Wang et al. 2012; Fu et al. 2014; Miska-Schramm et al. 2017), the total calculated systemic Al exposure of these 25 studies was less (up to 3,971 μg Al/kg) than the studies in Table 4, Category A (6990–13,832 μg Al/kg), suggesting that the occasional significant results are not a product of greater overall Al systemic exposure. Daily systemic Al exposures greater than the highest of the Beekhuijzen 2007 study generally demonstrated significant effects (Table 4, Category D and Table 3), with three exceptions. The lack of toxicity reported after gestation day (GD) 10–17 i.g. exposure (Clayton et al. 1992) is consistent with the lower susceptibility to Al toxicity in the latter stages of gestation, as noted by Benett et al. 1975, who stated that GD 9–13 are critical for organogenesis and 14–18 for bone formation. With the exception of one study that employed increased Al exposure starting at GD 14 (Domingo et al. 1987b) and a single exposure on GD 15 (Misawa and Shigeta 1993), all other studies in rats and mice in Table 4 category C increased Al exposure before mating or starting from GD 3 Misawa 7. The lack of significant toxicity in one study may be due to its limited endpoint (Kimura et al. 2007). Much higher daily and total calculated systemic Al exposures (Table 4 category F) resulted in significant toxicity associated with maternal morbidity or mortality (Benett et al. 1975; Mohammed et al. 2008).

The most sensitive endpoint to Al-induced toxicity in the pregnant female was resorption, and in the fetus death. Overall, these results suggest a positive exposure level-adverse response relationship, as would be expected. One study is notable for having a wide exposure range from less Al than would be expected to reach systemic circulation from the diet to well beyond that, with exposure throughout most of the period of fetal susceptibility (Agarwal et al. 1996). With the exception of the two lower exposures in the Agarwal et al. (1996) study, the two-Al-dose comparison in cows (Kimura et al. 2007), the two studies reported by Trif et al. (2008, 2010), and the lower dose of the Miska-Schramm et al. (2017) study, the additional daily Al systemic exposure of all other studies that reported statistically significant results was greater than 100-fold above the typical human daily Al consumption equivalent (0.1 μg/kg).

Assessment of Al reproductive toxicity in female humans

The accidental addition of Al to the drinking water of some residents in Camelford, Cornwall, England in July 1988 (Coggon 1991) did not result in documented reproductive effects (Golding et al. 1991). Epidemiological studies suggest Al in airborne particulates, although resulting in an approximate daily systemic Al exposure that is 1000-fold lower than from the typical human diet, is associated with smaller newborns and increased risk of placental abruption (Bell et al. 2010; Ibrahimou et al. 2017). Newborns of mothers who had higher urine Al concentrations, and whose umbilical cord blood showed greater evidence of oxidative stress, were more likely to be smaller (Karakis et al. 2014; Liu et al. 2019). These results are consistent with animal studies showing smaller newborn weight after much higher Al exposures. However, there remains a lack of correlation between umbilical cord Al concentration and newborn size (Rahbar et al. 2015). The results of these studies do not provide consistent evidence of Al-induced reproductive toxicity or enable exposure-response determination.

Assessment of Al reproductive toxicity in male animals

Many endpoints were quantified in the studies of Al reproductive toxicity in males (Table 5). Table 6 summarizes reports of the assessment of Al reproductive toxicity in males. Quantitative endpoint results are presented in the order presented in Table 5. Two studies sought to model Al intake from drinking water (Trif et al. 2007; Mouro et al. 2018). However, as water would provide <1% of daily total Al intake in laboratory animals, the additional Al exposure in water in the Trif et al. (2007) and two lowest exposures in the Mouro et al. 2018 studies were insignificant compared to the basal exposure from feed.

The results of all studies are categorized as to whether they showed significant toxicity and the daily and total approximate systemic Al exposures (Table 7). Four studies are notable because they were GLP compliant, and/or were conducted following an OECD Test Guideline, and included males and females (Beekhuijzen 2007; Wise et al. 2008; Hirata-Koizumi et al. 2011a, 2011b). Two reported no statistically significant toxicity at their lower (<20 μg/kg/day; <200 μg/kg total) Al exposures, but statistically significant toxicity at their higher (>50 μg/kg/day, >500 μg/kg total) Al exposures, delineating NOAEL and LOAEL exposures (Beekhuijzen 2007; Wise et al. 2008; Hirata-Koizumi et al. 2011b, 2011a) (Table 7, Categories A and C and Table 6). Six other studies reported no significant effects from exposures <60 μg/kg/day (<10,000 μg/kg total), but did find some significant effects from higher within-study exposures (≥20 μg/kg/day, >600 μg/kg total) (Pettersen et al. 1990; Roy et al. 1991; Hichem et al. 2013; Kumar and Singh 2015, 2016; Falana et al. 2017). Comparing Tables 4 and 7 suggests males are more susceptible to Al-induced reproductive toxicity than females. The GLP compliant studies that showed statistically significant toxicity after their higher exposures (Table 7,

Table 5. Endpoints quantified in the studies of Al reproductive toxicity in males.

Testis	
	• Testis (and accessory gland) (testis tunica albuginea and parenchyma) weight
	• Protein content
	• Leydig cells/interstitial space or/testis, cell proliferation, proliferating cell area, epithelial wall thickness, nuclear diameter, nuclear percentage, cytoplasm percentage, and visual field percentage
	• Non-Leydig cell visual field percentage
	• Calcium, copper, iron, magnesium, sodium, and zinc concentrations
	• MDA/reactive oxygen and nitrogen species, H_2O_2, and antioxidant capacity
	• SOD, CAT, GSH, GST, GPx, GR, thioredoxin reductase, and thiol groups
	• Protein carbonyls and lipid peroxides
	• AST, ALT, ALP, ACP, LDH, LDH isoenzyme, phosphorylase, succinate dehydrogenase, nucleotidase, gamma-glutamyltransferase, gamma glutamyl transpeptidase, and 17-ketosteroid reductase
	• cAMP, total ATPase (ATPases), Na^{+}-K^{+}-ATPase, Mg^{2+}-ATPase, and Ca^{2+}-ATPase activity
	• Vitamins C and E
	• Cholesterol, triglycerides, and phospholipids
	• Bax and Bcl-2 expression
	• Activated macrophages
	• NO content; iNOS, tNOS, cNOS activity and expression; and NO products
	• Putrescine, spermidine, and spermine
	• Testosterone, LDH, and FSH
	• Androgen receptor mRNA, follicle stimulating hormone receptor, and luteinizing hormone receptor expression
	• 3- and 17-beta-hydroxysteroid dehydrogenase, steroidogenic acute regulatory protein, cytochrome P450 cholesterol side chain cleavage enzyme, caspase-3, and proliferating cell nuclear antigen protein
Seminiferous tubules and sperm	
	• Seminiferous tubule diameter, duct diameter, luminal diameter, epithelial thickness/height, visual field percentage, and interstitial space diameter
	• Sertoli cell count (number)
	• Spermatogenesis
	• Spermatogonia count (number)
	• Primary spermatocyte count (number)
	• Secondary spermatocyte count (number)
	• Spermatid (round) count (number)
	• Elongated spermatid count (number)
	• Spermatozoa count (number) and daily production
	• Testicular sperm production (count)
	• Motile sperm cell count (number)
	• Sperm mobility
	• Normal or abnormal sperm cell count (number)
	• Dead sperm or viability
	• Sperm plasma and acrosomal membrane intactness
	• Sperm MDA, SOD, CAT, AST, ALT, and ACP
Epididymis	
	• Weight
	• Protein content
	• Percent epithelium
	• Caput epithelial height
	• Tubular diameter
	• Luminal diameter
	• Lumen with sperm
	• Empty efferent ducts
	• NO products
	• MDA/reactive oxygen and nitrogen species and antioxidant capacity
	• SOD, CAT, GST, GPx, and GR
	• ALP
	• Vitamins C and E
	• Putrescine, spermidine, and spermine
	• Nucleotidase and gamma glutamyl transpeptidase
	• ATPase
	• Sialic acid
	• Sperm/spermatozoa count/number
	• Sperm transit time
	• Cauda sperm count/number
	• Cauda sperm transit time
Vas deferens	
	• Weight
	• Spermatozoa count/number
Seminal vesicle	
	• Seminal vesicle and secretion weight
	• Fructose concentration
Prostate and semen	
	• Weight
	• Prostate MDA, reactive oxygen and nitrogen species, and antioxidant capacity
	• Semen pH, MDA, GST, AST, ALT, and ACP

(*continued*)

Bulbourethral gland	• Weight
Blood/serum/plasma	• Testosterone, FSH, LH, prolactin, and estradiol
Male sex performance	• Time to and number of mounts, time to and number of intromissions, time to ejaculation, and copulatory efficiency
Female response	• Percent of pregnant females, fecundity, and fertility • Corpora lutea/female • Implantations • Post-implantation loss • Resorptions
Fetus and offspring	• Fetal weight • Dead or live fetuses

Category C.) and other studies showing significant results from lower exposures (2/3 $\leq$ 20 μg/kg/day) (Table 7, Category D.) suggest Al-induced reduction of reproductive function in males after exposure to additional daily Al systemic exposure less than 100-fold the typical human daily Al consumption equivalent (0.1 μg/kg). The most common male reproduction endpoints from the summaries in Table 6 were tested for adherence to a normal distribution and then correlation with daily and total systemic Al exposure. (The number in brackets is the number of values from Table 6.) Testes weight [69], sperm number [51], abnormal sperm [37], motile sperm [34], sperm viability [20], testes MDA [41], testes SOD [22], testes CAT [20], and blood/serum/plasma testosterone [34] were tested. Sperm number and SOD values compared to the daily and total doses were normally distributed, but correlated significantly, and negatively, only with the total Al dose ($p = 0.0076$ and 0.0235, respectively). Abnormal sperm were not normally distributed but were correlated with the daily and total Al dose (0.044 and 0.049, respectively). MDA was consistently above, and testosterone consistently below values from subjects not given additional Al but they did not correlate with Al exposure. These results suggest sperm number, sperm SOD, and abnormal sperm are the more sensitive indicators of Al-induced male reproductive toxicity and that prolonged exposure has a greater effect than short-term exposure. More prolonged exposure is more likely to inhibit the entire process of spermatogenesis that has a duration of ~35, 50, and 64 days in the mouse, rat, and human, respectively (Adler 1996).

Assessment of Al reproductive toxicity in male humans

A study of human semen showed sperm viability decreased as semen Al concentration increased from averages of 18 to 101 μg/L (Table 10) (Dawson et al. 1998). A study by the same group reporting an average semen Al concentration among control subjects of 460 μg/L (Table 10) (Dawson et al. 2000). Other reported comparable values (540 in factory workers and 870 μg/kg in sperm donor candidates (Hovatta et al. 1998) and 299 in normal semen (Klein et al. 2014)) raises some doubt about the findings of Dawson et al. (1998).

Sperm exposed to 0.125–30 mM $AlCl_3$ showed concentration-dependent decreased motility and increased MDA (Table 6) (Jamalan et al. 2016), but these Al concentrations (3375–810,000 μg/L) are greatly in excess of reported human semen Al concentrations. The suggestion from animal and these human studies of possible Al-induced reduced reproductive function in males is supported by the reduction in normal and mobile sperm and sperm concentration of refinery and polyolefin factory employees and positive correlations between high spermatozoa Al concentration and decreased sperm motility and normal morphology (Hovatta et al. 1998).

Fetal, placental, amniotic fluid, meconium, and testes Al concentrations

Al distribution into the fetus was reported in many studies (Table 8). The additional maternal Al exposures are not normally distributed. The log of the fetal Al concentration as a multiple of the Al concentration in fetuses that did not receive additional maternal Al exposure was normally distributed. Correlation analysis of the log of the additional maternal Al exposure dose and the fetal Al concentration multiple resulted in a non-significant Pearson correlation ($p = 0.21$). Consequently, no relationship between the approximate added total systemic Al exposure and fetal Al concentration incorporating all studies was concluded. Individually, the studies show the ability of Al to enter the fetus in an exposure-dependent manner. Added Al exposure ranged from that ~ equal to exposure from the diet that did not significantly increase fetal Al concentration (McCormack et al. 1979) or increased it up to 2-fold in some organs (Yokel 1985) to exposures that were $\geq$1000-fold above the dietary exposure that increased fetal Al concentration up to ~6-fold in some organs and were associated with adverse fetal effects (Cranmer et al. 1986; Mestaghanmi et al. 2003). The highest Al concentrations were seen in the bone of both controls and animals exposed to additional Al.

Placental Al has been quantified in several studies (Table 9). As in the fetus, the available studies show an

Table 6. Results of studies of males exposed to additional Al.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
Rats, 45–55 g, males and females	0, 0.067, or 0.063% Al as $AlCl_3·6H_2O$ or baking powder in the diet started as young rats and raised to maturity	45 (∼945)	The growth, reproduction, external appearance, and autopsy of rats on the Al-added diets were the same as controls	McCollum et al. (1928)
Rats, 100–120 g Swiss strain mice, 20–30 g	One intra-testicular injection of 0.08 mmol/kg $Al_2(SO_4)_3$ (rat) or 0.08 mmol/kg total in 30 daily s.c. doses (mouse)	30, s.c. (907)	Rat testes weight 2 and 7 days after intratesticular injection was 98 and 50% of controls, with focal (2 days) and partial (7 days) necrosis, and spermatozoa destruction. After s.c. injections mouse testes weight 30 days later was 30% of controls. Necrosis was not seen. Tubular shrinkage and spermatogenic arrest were seen but there was no effect on the interstitium	Kamboj and Kar (1964)
Sprague Dawley rats, males	0, 44.8, 448, or 4476 mg/l $AlCl_3·6H_2O$ in the drinking water for 90 days then housed serially with a different virgin rat for 7-day periods up to 70 days	*1.5*, 15, or 149 (135, 1350, or 13,410)	Fertility results showed no significant effects on the number of implantation sites or average litter size	Dixon et al. (1979)
Rats, guinea pigs, and rabbits, males	0, 6, 17, or 50 mg/kg Al as $AlCl_3$ orally to rats and guinea pigs for 20–30 days; 0, 3, 9, or 27 mg/kg Al orally to rabbits for 20–30 days; 0, 0.0025, 0.25, or 2.5 mg/kg orally to rats for 6–12 months	12, 34, or 100; *6,* 18, or 54; *0.005, 0.5, or 5* (300, 850, or 2500; 150, 450, or 1350; 1.35, 135, or 1350)	After 6–12-month exposure a decreased spermatozoa number (to 74*% of controls) was only seen with the highest dose. The tubular basal membrane was thickened with a layer of Sertoli cells. The tubular lumen had some pathological forms of spermatogenic epithelium. There was a substantial proliferation of Leydig cells. There was increased Leydig cell oxidizing enzyme activity and ATPase in seminiferous tubule basal membranes and a tendency for decreased RNA with the highest dose	Krasovskiĭ et al. (1979)
Beagle dogs, 7–9 months, females and males	118, 317, or 1034 mg sodium aluminum phosphate/kg/day in the diet for 6 months	10, 27, or 88 (1830, 4917, or 16,040)	Gross autopsy and histopathological exam showed normal range of variations of the gonads and prostate.	Katz et al. (1984)
New Zealand white rabbits, 2.9–4.3 kg	0 or 600 μmol/kg Al as the lactate 5 days weekly for 4 weeks s.c., sacrificed 2 weeks later	3400 (68,000)	Testis weight was 168% of controls	Melograna and Yokel (1984)
Sprague Dawley rats, 48 days, males	5 (control), 67, 141, or 288 mg Al/kg/day as sodium aluminum phosphates or 302 mg Al/kg day as $Al(OH)_3$ in the diet for 28 days	67, 141, 288, or 302 (1876, 3948, 8064, or 8456)	Testes calcification, degeneration with atrophy, and edema were not significantly increased above controls	Hicks et al. (1987)
Human sperm	Exposed for 0, 10, 30, or 60 min to bovine estrous cervical mucus that had been in contact with 10, 100, or 200 μM/ml $AlCl_3$		Al exposure inhibited sperm entry into the mucus. The effect was not contact time or Al concentration (including 0 min exposure) dependent, shedding doubt on the validity of these results	Kaur (1988)
Rats, 120–160 g, Leydig cells	0, 1, 10, or 100 μM $AlCl_3$		Cell viability (trypan blue exclusion indicating live cells) was not affected. LH-stimulated testosterone production was 104, 90, and 104% of controls	Ng and Liu (1990)
Beagle dogs, male and female	0, 4, 10, 27 or 75 mg/kg/day of Al as basic sodium aluminum phosphate in the diet for 26 weeks	*8*, 20, 54, or 150 (1456, 3640, 9828, or 27,300)	High dose males had a decrease (no details reported) in testis weight and moderate seminiferous tubule germinal epithelial cell degeneration and atrophy	Pettersen et al. (1990)
Albino rats, 120–150 g, about 2 months old, males	0, 212, 265, 355, 530, 1060, or 2120 mg/kg $Al_2(SO_4)_3·18H_2O$ or 503 or 765 mg/kg $KAl(SO_4)_2·12H_2O$ by gavage for 7, 14 or 21 days	34.4–343 (240–7203) or 57.2 or 87.2 (401–1831)	No testes histological damage up to the 530 mg/kg $Al_2(SO_4)_3·18H_2O$ or 765 mg/kg $KAl(SO_4)_2·12H_2O$ dose. Some spermatogonial cell decrease after 21 days of 1060 mg/kg or 14 days of 2120 mg/kg $Al_2(SO_4)_3·18H_2O$	Roy et al. (1991)
B6C3F1 mice, 4 weeks old, females and males	1, 2.5, 5, and 10% $KAl(SO_4)_2·12H_2O$	114, 285, 570, or 1140 (69,312, 173,280, 346,560 693,120)	Testes weight was 102, 102, 101, and 99% of controls. Testes relative weight was 88*, 88*, 100, and 114%* of controls. Ductus epididymis hyperplasia was 93, 107, 103, and 84% of controls. Epididymis atrophy was 120, 95, 98, and 43% of controls	Oneda et al. (1994)
Swiss mice, 30–32 g, male	0, 50, 100, or 200 mg/kg $Al(NO_3)_3·9H_2O$ i.p. 5 days/week for 4 weeks	3600, 7200, or 14,400 (72,000, 144,000, or 288,000)	At the end of dosing: (1) testes weight was 88, 88, and 76*; and epididymis weight 89*, 97, and 79%* of controls, but not significantly different when normalized to body weight; (2) seminiferous tubule diameter was not affected, the two higher doses significantly increased spermatocyte/spermatid necrosis but did not affect giant cells, germ cell hypoplasia, or Leydig cell vacuolization; (3) spermatid count was 97, 56*, and 59%* and spermatozoa count 100, 86, and 50%* of controls, but there were no significant effects on the % of motile cells or abnormal morphologic forms. GD 10–14 percentage of pregnant females was 120, 40*, and 30%* of controls. The number of total implantations, early or late resorptions, dead or live fetuses, or post-implantation loss was not significantly different	Llobet et al. (1995)
Human sperm			Refinery and polyolefin factory employee ($n = 27$) normal sperm was 85, mobile sperm 97, and sperm concentration 82% of sperm donor candidate ($N = 45$) values. Regression analysis showed a correlation between high spermatozoa Al concentration (Table 10) and decreased sperm motility and normal morphology	Hovatta et al. (1998)
Human semen	*In vitro* incubation in 0, 2.5, 5, or 7.5% $KAl(SO_4)_2·12H_2O$		Time to sperm immobility was 3.4*, 2.4*, and 1.4%* of controls. Alum is a spermicide	Singh et al. (1998)
Sprague Dawley rats, ∼300 g, males	0 or 1000 ppm $AlCl_3·6H_2O$ in the drinking water for 12 weeks	33 (2800)	Testis weight was 68* and seminal vesicle weight 70%* of controls. The time to first mount was 57, number of mounts 60*, intromission latency 254*, number of intromissions 41*, ejaculatory latency 104, and copulatory efficiency 88%* of controls.	Bataineh et al. (1998)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
			The percent of pregnant females was 108, number of implantations 96, number of viable fetuses 96, and percentage resorptions 50%* of controls	
CD-1 mice, 8 weeks, males	0, 13, or 35 mg Al/kg as $AlCl_3$ i.p. for 12 or 16 days	13,000 or 35,000 (182,000 or 490,000)	One day after 12 injections testis weight was 101 and 101, nitric oxide products 422* and 1028*, and testosterone 60* and 42%* of controls. Fifteen days after 16 injections testis weight was 97 and 96, nitric oxide products 118* and 168*, and testosterone 91* and 73%* of controls	Guo et al. (2001)
CD-1 mice, males	0, 13, or 35 mg Al/kg as $AlCl_3$ i.p. for 14 days	13,000 or 35,000 (182,000 or 490,000)	Testis weight was not significantly affected. Testis zinc was 95 and 65*, iron 130* and 180*, copper 148* and 127*, MDA 125* and 121*, and angiotensin-converting enzyme activity 68* and 58%* of controls.	Guo et al. (2002)
New Zealand white rabbits, 7 months, 2.9 kg, males	0 or 34 mg Al/kg as $AlCl_3$ orally every other day for 16 weeks	68 every other day (3808)	Testis MDA was 148*, GST 69*, sulfhydryl groups 77*, AST 60*, ALT 78*, ALP 75*, ACP 69*, LDH 124*, and phosphorylase 74%* of controls	Yousef (2004)
Sprague Dawley rats, 130–150 g, males	0 or 34 mg/kg $AlCl_3$ orally every other day for 30 days	14 every other day (206)	Testis MDA was 144*, GST 81*, sulfhydryl groups 80*, AST 71*, ALT 76*, ALP 80*, ACP 73*, LDH 126*, and phosphorylase 69%* of controls	El-Demerdash (2004)
ICR (CD-1-derived) mice, 32–35 g, males	0 or 35 mg Al/kg/day as $AlCl_3$ i.p. for 12 days	35,000 (420,000)	Testis weight was 104, nitric oxide products 421*, cholesterol 166*, cAMP 27* and testosterone 41%* of controls	Guo, et al. 2005a)
CD-1 mice, 8–9 weeks, males	0, 7, or 13 mg Al/kg/day, as $AlCl_3$ s.c. for 14 days, then housed with 3 non-treated females. Mated females replaced with new virgins, for 9 weeks	1470 or 2730 (20,580 or 38,220)	Testis, epididymis, and seminal vesicle weights were 94 and 87*, 97 and 87*, and 99 and 77%* of controls 5 weeks after dosing. Testes showed slight, dose-dependent damage 2 weeks after dosing. Seminiferous tubule spermatid cell and spermatozoa necrosis was seen 5 weeks after dosing. Tubular diameters and epididymis were not affected. The percentage of mated females significantly decreased from 1 to 10 weeks after dosing, to a nadir of 68* and 53%* of controls 5 weeks after dosing. The fecundity index significantly decreased 4 weeks to 83* (13 mg/kg/day dose) and to 86* and 75%* 5 weeks after dosing. From weeks 3 to 5 there were no significant effects on corpora lutea/female or implantations per female. The 13 mg dose increased pre-implantation dead embryos to 148* and 162* of controls 3- and 5-weeks post dosing. Resorptions per female 4 weeks after dosing were 227* and 186%* and at 5 weeks 254* and 313%* of controls. Dead fetuses/female were 520* and 760%* of controls 5 weeks after dosing. Survivals/female were 88%* of controls 5 weeks after 13 mg/kg/day dosing. Day 16 fetal weights 3–7 weeks after dosing were 88* and 88*, 96* and 94*, 94* and 94*, 95* and 92*, and 92* and 94%* of controls	Guo, et al. (2005b)
Swiss mice, 50 days, males	Ingestion of 0, 1000, 1200, or 1400 ppm $AlCl_3$ in the drinking water for 12 weeks, then housed for 10 days with an untreated virgin female, that was killed GD20	104, 125, or 145 (8755, 10,507, or 12,258)	Testes weight as a percentage of body weight was not affected. Seminal vesicle weight as a percentage of body weight was 58*, 43*, and 59%* of controls. Testicular sperm production efficiency (sperm/g testes/day) after 6, 9, and 12 weeks averaged 70*, 58*, and 76%* of controls. Epididymal sperm count after 3 weeks was 88, 115, and 57*; 6 weeks 87, 74*, and 63*; 9 weeks 54*, 50*, and 62*; and 12 weeks 85, 81, and 69%* of controls. Mice exposed to 1200 and 1400 ppm had congested testes blood vessels and increased interstitial connective tissue. Mice exposed to 1200 ppm showed seminiferous tubule and tubule arrangement destruction. Mice exposed to 1400 ppm had many spermatids in the center of their seminiferous tubular lumen with few or none in the periphery and absence of spermatozoa in the epididymis. The percent of pregnant females was 95, 75, 80, and 56%*. There was no difference in the number of implantation sites or viable fetuses. The percentage of resorptions was 0, 15*, 10*, and 17* and the percentage of animals with resorptions 0, 67*, 62*, and 70*	Mayyas et al. (2005)
New Zealand white rabbits, 7 months, 2.9 kg, males	0 or 34 mg Al/kg as $AlCl_3$ orally every other day for 16 weeks	68 every other day (3808)	Testes and epididymis body weight were 73* and 68%* of controls. Weekly measurements of ejaculate volume averaged 87*, reaction time (mounting to complete ejaculation) 210*, packed sperm volume 89*, sperm concentration 87*, total sperm output 76*, sperm motility 91*, total motile sperm 72*, dead sperm 141*, normal sperm 95*, total functional sperm fraction (sperm output × motility × normal morphology) 86*, and initial fructose concentration 86%* of controls. Semen pH was 8.08* versus 7.66 for controls. Seminal MDA was 119*, GST 88*, AST 91*, ALT 88*, and ACP 91%* of controls	Yousef et al. (2005)
CD-1 mice, males	0, 7, or 35 mg Al/kg/day, as $AlCl_3$ s.c. for 14 days	1470 or 7350 (20,580 or 102,900)	Testes and left epididymis weight as a percentage of body weight were not affected. Right epididymis weight as a percentage of body weight was 82 and 68%* of controls.	Guo et al. (2006)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
			Testicular and epididymal nitric oxide products were 165* and 282* and 119 and 179%* of controls. Testis putrescine was 87 and 79*, spermidine 97 and 97, and spermine 97 and 91%* of controls. Epididymal putrescine was 100 and 86, spermidine 98 and 97, and spermine 99 and 94% of controls	
Sprague Dawley rats, males	0 or 50 mg $AlCl_3$ i.p. for 20 days	10,100 (202,000)	Blood testosterone was 53*, FSH 84, and LH 60%* of controls	Reza and Palan (2006)
Wistar rats, males (~ 9 weeks), females	0, 40, 200, or 1000 mg/kg/day $AlCl_3$ i.g. 2 weeks prior to and during mating for a total of 28 days	20, 98, or 494 (554, 2744, or 13832)	Testes weight was 99, 103, and 102; and epididymis weight 104, 106, and 103% of controls. Microscopic assessment of testes, epididymis, prostate gland, and seminal vesicles showed no significant difference from controls	Beekhuijzen (2007)
Albino rats, 100–150 g, males	0, 15, or 30 mg/kg $AlCl_3$ i.p. every other day for 5 weeks	3030 or 6060 every other day (53,025 or 105,050)	Low dose: Seminiferous tubules had thickened basement membrane with fibrous connective tissue. Spermatogenic epithelium and Sertoli cell cytoplasm had focal areas of vacuolar degenerative changes. Abnormal spermatozoa distribution in the seminiferous tubule lumina. Swollen and vacuolated spermatogonia mitochondria. Primary spermatocytes smaller with dilated endoplasmic reticulum and Golgi apparatus and condensed mitochondria. High dose: Severe seminiferous tubule damage and cell vacuolation, spermatid level arrest, germinal cell degenerative changes, a few fragmented sperm in the lumen, and a thick, irregular basement membrane. Spermatogenesis arrest at the spermatid level with germ cell degenerative changes. Spermatogonia, spermatocytes, and spermatids more affected than after the low dose. Sertoli cells more damaged than the spermatogonia. Nuclear membrane distortion and some rupturing and chromatin accumulation. No spermatozoa in the seminiferous tubules	Khattab (2007)
Wistar rats, males	0 or 5 mg/kg $Al_2(SO_4)_3$ i.p. 3 times weekly for 2 weeks	790 3 times weekly (4790)	The germinal epithelium was thinner in places where spermatids were absent. Some germinal cells lost their cytoplasm. Cells with pyknotic nuclei were necrotic. The tight junctions were broken down. Some enlarged Sertoli cell mitochondria. Enlarged Sertoli cell rough endoplasmic reticulum. Their cisternae had fewer ribosomes. Increased lysosome number and nuclear membrane irregularities Some primary spermatocyte mitochondria showed size and shape variations with tubular or vesicular appearing cristae. Decreased luminal sperm numbers. Spermatogonia were only seen on the basal membrane. There were no luminal sperm. Low spermatid numbers. There were free cells in the lumen. Increased rough endoplasmic reticulum in spermatocyte cytoplasm	Kutlubay et al. (2007)
Albino mice, 60 days, 25 g	Dosing (route not stated, assume oral) of 0, 1, 2, or multiple doses aluminum acetate 3.5 mg/kg	*0.92*	Testes ATPase activity was 74, 50, and 34% of controls at an unstated time after injection	Sushma and Rao (2007)
Wistar rats, males	50 (control), 200, 400, or 1000 ppb $Al_2(SO_4)_3$ in the drinking water for 6 months	0.002 the control, *0.009*, *0.018*, or *0.045* (0.4, 1.7, 3.3 or 8.4)	Weights of the testes were 96, 86*, and 70%*; epididymis 91*, 82*, and 75%*; seminal vesicle 79*, 63*, and 59%*; prostate 97, 90, and 84%*; and bulbourethral gland 87, 78*, and 69%* of controls. Seminiferous tubule diameter was 96, 73*, and 66%* of controls	Trif et al. (2007)
New Zealand white rabbit sperm	Incubation with 0, 1, 5, 10, 15, or 20 mM $AlCl_3$ for 2 or 4 h		Sperm mobility after 1–2 min was 100, 97, 94*, 76*, and 64*; 2 h 98, 86, 83*, 35*, and 19*; and 4 h 94, 79*, 62*, 18*, and 8%* of controls. Sperm viability after 1–2 min was 98, 94, 88*, 80*, and 70*; 2 h 98, 90, 78*, 57*, and 40*; and 4 h 94, 87, 64*, 35*, and 22%* of controls. Sperm MDA after 2 h was 101, 108, 114*, 119*, and 143*; SOD 100, 96, 94, 87*, and 74*; CAT 96, 92, 84*, 75*, and 53*; AST 127, 146*, 198*, 238*, and 272*; ALT 103, 110, 114, 126* and 162*; and ACP 96, 94, 89, 82* and 70%* of controls. Sperm MDA after 4 h was 109, 118, 124*, 134*, and 148*; SOD 98, 93, 88, 77*, and 65*; CAT 89*, 84*, 78*, 69*, and 45*; AST 128*, 149*, 186*, 224*, and 285*; ALT 110, 115, 131*, 142*, and 182*; and ACP 86*, 84*, 78*, 60*, and 46%* of controls	Yousef et al. (2007)
Sprague Dawley rats, 235–347 g, males	0 or 4.125 pmole $AlCl_3$ (pH 3.4) lateral ventricle injection twice daily for 20 days		Testis, epididymis, and vas deferens weights were 89, 88, and 89% of controls. Epididymis and vas deferens spermatozoa counts were 76 and 74% of controls. Serum testosterone was 43, FSH 59, and LH 76% of controls	Shahraki et al. (2008)
Albino rats, 230–250 g, males	0 or 0.5 mg/kg as $AlCl_3{\cdot}6H_2O$ i.g. for 30 days	*0.12* (3.4)	Testis MDA was 368*, lipid hydroperoxides 145*, GSH 38*, SOD 62*, and CAT 45%* of controls	Al-Hashem (2009)
KM mice, males	0, 50, 75, or 100 mg/kg $AlCl_3$ i.p. for 2 consecutive days with a 1-day interval for 2 weeks	7214, 10,821, or 14,428 (72,140, 108,210, or 144,280)	Dose dependent increase of DNA damage and sperm nucleus immaturity rate	Cui et al. (2009)
Albino rats, 3–4 months, 190–215 g, males	0, 40, or 80 mg/kg $AlCl_3$ i.g. for 30 or 60 days	16 or 32 (485 or 970 for 30 days, 970 or 1940 for 60 days)	Testis weight after 40 mg/kg for 30 or 60 days was 102 and 88%, and after 80 mg/kg for 30 or 60 days 81* and 73%* of controls.	Entissar et al. (2009)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
			Epididymis head (caput), body, and tail weights after 40 mg/kg for 30 or 60 days were 99 and 86, 106 and 88, and 90 and 92% of controls. Epididymis head, body, and tail weights after 80 mg/kg for 30 or 60 days were 81* and 80*, 105 and 91, and 97 and 97% of controls. Seminal vesicle weight after 40 mg/kg for 30 or 60 days was 114 and 82%, and after 80 mg/kg for 30 or 60 days 97 and 88% of controls. Prostate gland weight after 40 mg/kg for 30 or 60 days was 99 and 94%, and after 80 mg/kg for 30 or 60 days 96* and 77% of controls. Sperm counts after 40 mg/kg for 30 or 60 days were 60* and 62%*, and after 80 mg/kg for 30 or 60 days 33* and 33%* of controls. Live sperm % after 40 mg/kg for 30 or 60 days was 83* and 65%*, and after 80 mg/kg for 30 or 60 days 51* and 47%* of controls. Abnormal sperm % after 40 mg/kg for 30 or 60 days was 157 and 133%, and after 80 mg/kg for 30 or 60 days 176* and 175%* of controls. Al exposure caused congested testes, hyperemic blood vessels, interstitial edema, and multiplication of interstitial Leydig cells. Seminiferous tubules showed germinal epithelium hyperplasia and decreased tubular lumen sperm bundles. There was desquamation and sloughing of spermatogonia into the tubular lumen. There was spermatogenic epithelial coagulative necrosis, extensive sloughing into tubular lumen, absence of sperm bundles, and inflammation cell infiltration as lymphocytic infiltration	
CD-1 mice, males	0, 7, or 35 mg/kg $AlCl_3$ i.p. for 14 days	1414 or 7070 (19,796 or 98,980)	Testes MDA was 121* and 144*; GPx 88* and 78*, GR 87* and 77*; and thioredoxin reductase 89 and 93% of controls	Guo et al. (2009)
Wistar rats, 180–200 g, males	0 or 34 mg/kg $AlCl_3$ orally for 70 days	14 (962)	Testes, epididymis, seminal vesicle, and prostate weights were 81*, 70*, 57*, and 88% of controls. Testes protein content was 79%* of controls. Sperm concentration was 70*; and percent motile 70*, dead 179*, and abnormal 146%* of controls. Testicular CAT activity was 43*, GST activity 55*, MDA 273*, reduced GSH 67*, and testicular 17-ketosteroid reductase activity 70%* of controls. Plasma testosterone was 76%* of controls. Interstitial space blood vessels were markedly dilated and congested. Some germ cells had small, darkly stained nuclei. There was vascular degeneration of the spermatogenic and Sertoli cell cytoplasm. There were irregularities in the nuclear membrane, some damaged mitochondria, a decrease of ribosomes, an increase of lysosomes in the Sertoli cell cytoplasm, and an increase of rough endoplasmic reticulum in the primary spermatocyte cytoplasm. Seminiferous tubule architecture was disorganized, with intratubular accumulation of exfoliated germ cells, maturation arrest, thinner germinal epithelium, near absence of spermatids, and absence of sperm in the lumen. There was Leydig cell hyperplasia in the interstitial tissue and clumps of Leydig cells surrounding most seminiferous tubules	Yousef and Salama (2009)
Sprague Dawley rats,160 g, males	0 or 20 mg/kg $AlCl_3$ i.g. daily for 70 days	*8* (566)	Testis, seminal vesicle, and prostate weights were 53%*, 93, and 91%* of controls. Sperm count was 46*, motility 51*, viability 58*, and abnormalities 279%* of controls. Testicular SOD and MDA were 46* and 157%* of controls. Serum testosterone was 50%* of controls. Testes interstitial blood vessels were congested, there was marked degeneration and necrosis of seminiferous tubule lining germ cells, and interstitial edema and testicular degeneration with germ cell absence	Hala et al. (2010)
Wistar rats, males	0 or 100 mg/kg $AlCl_3$ orally for 90 days	40 (3636)	Testis GSH and lipid peroxides were 43* and 155%* of controls. There was arrest at the spermatid level, germinal cell degenerative changes, a few fragmented sperm in the lumen, and a thick, irregular basement membrane	Thirunavukkarasu et al. (2010)
Sprague Dawley rats,10 weeks, males	0 or 0.125 mg Al as Merck aluminum adjuvant i.m. into each hind limb 6 and 3 weeks and 3 days prior to cohabitation with females	34 at cohabitation (745 at cohabitation)	Sperm count was 107, sperm motility 99, and testis weight 99% of controls ~ 4 weeks after the last injection. Testis and epididymis histomorphology were not remarkable. There was no effect on the number of mated or pregnant females	Wise et al. (2010)
Swiss Webster mice, 25 g, males	0, 300, or 600 mg/kg $AlCl_3$ in the drinking water for 20 days	121 or 242 (2424 or 4848)	Blood testosterone was 52* and 6%* of controls	Abu-Taweel et al. (2011)
Sprague Dawley rats, 5 weeks, males and females	0, 120, 600, or 3000 ppm $Al_2(SO_4)_3$ in the drinking water from 10 weeks before mating to lactation for F0 and F1 generation rats, until parturition of paired	F0 males *2.7*, 13, or 59 (247, 1179, or 5406 over 13 weeks) F1 males	There were no significant differences in the number of testis sperm, percentage of motile sperm, progressively motile sperm, swimming speed and pattern, or percentage of morphologically abnormal sperm between treated and control groups in F0 or F1 adults.	Hirata-Koizumi et al. (2011b)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
	females, resulting in mean 0, 8.6, 41, or 188 mg/kg bw/day $Al_2(SO_4)_3$ intake by F0 males and 0, 10.7, 50.2, or 232 mg/kg bw/day $Al_2(SO_4)_3$ intake by F1 males.	*3.4*, 16, or 73 (308, 1444, or 6671 over 13 weeks)	Cauda epididymal sperm number in 3000 ppm F0 adults was 11%* of controls, but the number/gram epididymal cauda was not significantly changed. No changes were observed in F1 adults. The mating index was 91.7, 91.7, 100, and 91.7% in the F0 generation and 95.8, 91.3, 95.8, and 87.5% in the F1 generation. Fertility was 95.5, 90.9, 100 and 95.5% in the F0 generation and 91.3, 81.0, 91.3, and 95.2% in the F1 generation. There was no significant effect on testis weight of F1 or F2 weanlings. Epididymis weight of Al-treated F1 weanlings was 94, 94, and 88%* of controls, and 91, 94, and 101% of controls normalized to body weight. Epididymis weight of Al-treated F2 weanlings was 104, 100, and 94%* of controls, and 103, 100, and 104% of controls normalized to body weight	
Sprague Dawley rats, 5 weeks, males and females	0, 50, 500, or 5000 ppm $NH_4Al(SO_4)_2$ in the drinking water from 10 weeks before mating to lactation for F0 and F1 generation rats, resulting in mean 0, 8.6, 41, or 188 mg/kg bw/day $NH_4Al(SO_4)_2$ intake by F0 males and 0, 10.7, 50.2, or 232 mg/kg bw/day $NH_4Al(SO_4)_2$ intake by F1 males.	F0 males *0.9*, *8*, or 70 (78, 695, or 6328 over 13 weeks) F1 males *1.0*, 10, or 85 (95, 867, or 7718 over 13 weeks)	There were no significant differences in the number of testis sperm, cauda epididymal sperm, motile sperm, progressively motile sperm, swimming speed and pattern, or percentage of morphologically abnormal sperm between control and Al-treated groups. The mating index was 100, 91.7, and 91.7% in the F0 and 91.7, 91.7, 91.3, and 95.8% in the F1 generation. Fertility was 100, 91.3, 100 and 100% in the F0 and 90.1, 77.3, 95.2, and 100% in the F1 generation. Testis weight of Al-treated F1 weanlings was 97, 97, and 90%* of controls, and 100, 100, and 104% of controls normalized to body weight. Epididymis weight of Al-treated F1 weanlings was 94, 98, and 84%* of controls, and 94, 98, and 84%* of controls normalized to body weight. Epididymis weight of Al-treated F1 weanlings was 104, 100, and 84%* of controls, and 98, 101, and 98% of controls normalized to body weight. There was no significant of Al treatment on testis or epididymis weight of F2 weanlings	Hirata-Koizumi et al. (2011a)
Wistar rats,190 g, males	0 or 34 mg/kg $AlCl_3$ in the drinking water for 70 days	14 (962)	Serum testosterone was 45%* of controls. Testes exhibited interstitial blood vessel congestion, decreased carbohydrates, disorganized germinal epithelium, and degenerative germinal cells. Seminiferous tubules had thick basal lamina with fibrous connective tissue, irregular basement membrane, fragmented spermatozoa in their lumen, and germinal cell spermatogenesis arrest at the spermatid level with reduction in sperm density. Spermatogonia type A and B cell cytoplasm had swollen vacuolated mitochondria, vascular endoplasmic reticulum, and periphery clumped chromatin particles. Primary spermatocytes were small. There was condensed, periphery chromatin and some nuclear membrane irregularity. Cell cytoplasm was vacuolated with lipid droplets. Golgi apparatus cisternae and smooth endoplasmic reticulum were dilated with vacuolated swollen mitochondria. Spermatids had dilated vascular smooth endoplasmic reticulum. Golgi apparatus cisternae were elongated and joined in groups with mitochondrial fragmentation	Mahran et al. (2011)
Wistar rats, 4 weeks, 75–95 g, males	0, 64, 128, or 257 mg/kg $AlCl_3$ in the drinking water for 120 days	26, 52, or 104 (3103, 6205, or 12,459)	Testis androgen receptor mRNA levels were 75*, 34*, and 17%* of controls. Serum testosterone was 96, 64*, and 53*; FSH 101, 99, and 98; and LH 101, 84*, and 81%* of controls	Sun et al. (2011)
Wistar rats, males	0, 475, 950, 1425, or 1900 mg/kg $AlCl_3$ i.g. for 8 weeks	192, 384, 576, or 768 (10,746, 21,493, 32,239, or 42,986)	Misshaped seminiferous tubules, alteration of epithelial lining distribution, and vacuolar cytoplasm after the highest dose. The epididymis histological appearance was normal	Buraimoh et al. (2012b) Buraimoh et al. (2012a)
Wistar rats, 6 weeks, 120 g, males	10 mg/kg Al in gum acacia i.g. for 2 weeks	20 (280)	Testis MDA was 87, GSH 98, SOD 84, CAT 180, GR 73, and GPx 119% of controls	Chaitanya et al. (2012)
Humans, 600 treated for problems related to fertility, males	Soil contained a mean of 3.92% Al.		Increased soil Al correlated with decreased poor sperm quality*. The authors concluded that the anomalous Al concentration appears to have no correlation with male fertility disorder	Giaccio et al. (2012)
Wistar rats,150–200 g, males	0 or 100 mg/kg $AlCl_3$ orally for 3 days	40 (121)	Testes weight was 99% of controls. Testes MDA was 124*, SOD 65*, and CAT 44%* of controls. Sperm count was 51*, motility 50*, morphology 40*, and viability 39%* of controls. Serum testosterone was 54*, FSH 28*, and LH 39%* of controls. Degenerative necrosis with degeneration of spermatogenic cells lining the seminiferous tubules was seen	Ige and Akhigbe (2012)
Wistar rats, 207 g, males	0 or 0.5 mg/kg $AlCl_3$ orally for 35 days	*0.2* (7.1)	Testis and epididymis weights were 101 and 100% of controls. Sperm motility was 84*, count 90, abnormalities 176*, and live sperm 70%* of controls	Ighodaro et al. (2012)
Wistar rats, 6 weeks, 180–200 g, males	0 or 34 mg/kg $AlCl_3$ orally for 30, 45, or 60 days	14 (412, 618, or 824)	Weights of the testes were 84, 116, and 109; epididymis 83, 143, and 100; seminal vesicles 63, 115, and 121; and prostate gland 64, 115, and 118% of controls. Testes MDA was 111, 108, and 163%* of controls. Sperm motility was 32*, 33*, and 29*; live/dead ratio 18*, 31*, 27*; and abnormalities 304*, 212*, and 284%* of controls. Serum testosterone was 32*, 14*, and 33%* of controls.	Moselhy et al. (2012)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
			Increased testes small DNA fragments, peaking at 60 days. Spermatogenic cell degeneration with some exfoliated lumen. Seminiferous tubule thinning and disorganization. Severe degeneration of spermatogenic epithelium with necrosis. Sperm depletion in seminiferous tubule lumen. Marked desquamation and vacuolation of epididymal epithelial lining, diminished to lack of intraluminal sperm. Prostatic acini were smaller without intra-luminal secretions. The prostatic epithelium was hardly seen and very flat with intraluminal calcified materials	
Swiss mice, 15–20 g, males	25 mg/kg $AlCl_3$ once i.p.	5050	24 h later: Light microscopy showed spermatogenic and Sertoli cell cytoplasm vacuolar generation, mild detachment of germ cells, irregularly shaped and some atrophied seminiferous tubules, and Leydig cell hyperplasia. Electron microscopy showed Sertoli cell mitochondrial damage, inter-Sertoli cell tight junction destruction, spermatogonia and spermatocyte apoptosis, spermatid morphological abnormalities, and Leydig cell mitochondrial damage	Abdel-Moneim (2013)
Wistar rats, 200–250 g, males	0, 100, 200, or 400 mg/kg $AlCl_3$ in the drinking water for 6, 12 or 18 months	40, 81, or 162 (7373, 14,746, or 22,119 for 6 months; 14,746, 29,492, or 44,238 for 12 months; 29,492, 58,984 or 88,476 for 18 months)	Testes weight at 6, 12, and 18 months was 84, 101, and 112*; 89*, 94*, and 91*; and 72*, 79*, and 86%* of controls. At 6 months testes showed perturbation of spermatogenesis (200 and 400), intense necrosis (400), and adhesive junction alterations. At 12 months there were seminiferous tubule alterations (200), changes seen at 6 months with 400, and degradation of seminal epithelium (200 and 400). At 18 months the alterations seen at 12 months were seen after a lower Al dose	Hichem et al. (2013)
Wistar rats, 90 days, 190–210 g, males	0 or 50 mg/kg $AlCl_3$ orally for 45 days	20 (909)	Testes ALP activity was 64*, ACP 70*, LDH 74*, succinate dehydrogenase 69*, and MDA 135%* of controls	Tiroumavalavane et al. (2013)
Swiss mice, 25–30 g, ~75 days old, males	0 or 78.4 mg/kg Al orally for 7 days or 7.8 mg/kg Al as $Al_2(SO_4)_3{\cdot}16H_2O$ i.g. for 90 days	157 (1098) *16* (1404)	After 7 days Al exposure sperm count and motility were 26* and 33%* of control. Sperm abnormalities were 118% of controls. After 90 days Al exposure sperm count and motility were 70* and 79%* of control. Sperm abnormalities were 188% of controls. 90 days after completion of the 90-day Al exposure sperm count and motility were 90 and 85% of control. Sperm abnormalities were 139% of controls	Yadav et al. (2013)
Kunming or BALB/c mice, 20–24 g, males	0, 20, 40, and 60 mg/kg $AlCl_3$, i.p. once weekly for 3 weeks	577, 1154, or 1731 (1731, 3464, or 5194)	Testes total SOD was 77*, 68*, and 67*; GPx 71*, 46*, and 50*; H_2O_2 106, 121*, and 126*; and MDA 111*, 117*, and 114%* of controls. Testes Bax and Bcl-2 expression were 105, 127*, and 172*; and 89*, 84*, and 80%* of controls. There was a dose-dependent reduced number of seminiferous tubules with basement membrane decay or irregular shape, some with wide lumen and without spermatocytes and filled vacuoles. Most tubules were distorted with necrotic spermatocytes, reduced spermatogonia, secondary spermatocyte, and spermatid number. The middle dose increased apoptosis (DNA laddering)	Chen et al. (2014)
Swiss mice, 8 weeks, males	0, 50, 100, or 150 mg/kg aluminum acetate i.p. for 7 days	6600, 13,200, or 19,800 (46,200, 92,400, or 138,600)	Five weeks later testis weight was 100, 92, and 96; sperm count 94, 74*, and 73*; and abnormal sperm 203*, 291*, and 328%* of controls	D'Souza et al. (2014)
Wistar rats, 90 days, 190–200 g, males	0, 50, or 100 mg/kg $AlCl_3$ orally for 45 days	20 or 40 (909 or 1818)	Testis MDA was 126* and 147*; SOD 76* and 60*, CAT 77* and 58*, GST 95 and 83, GPx 75* and 63*, GR 96 and 70*, vitamin C 74* and 63*; and vitamin E 58* and 49%* of controls. Epididymis MDA was 138* and 150*, SOD 84 and 70*, CAT 83* and 66*, GST 94 and 88, GPx 75* and 57*, GR 94 and 65*, vitamin C 77* and 72*, and vitamin E 61* and 56%* of controls	Kalaiselvi et al. (2014)
Human semen			The authors state that patients with low sperm counts had a statistically higher semen Al concentration than others but also state that semen Al concentration was significantly lower in patients with low sperm counts (based on sperm number, progressive motility, vitality, and morphology)	Klein et al. (2014)
Wistar rats, 250 g, males	0 or 28 mg/kg $Al(NO_3)_3$ i.p. every other day for 7 injections	3556 every other day (24,892)	Testis weight was 100, MDA 219*, protein carbonyls 287*, GSH 158, and thiol groups 179%* of controls	Maghraoui et al. (2014)
Wistar rats, 90 days, 190–200 g, males	0, 50, or 100 mg/kg $AlCl_3$ orally for 48 days	20 or 40 (970 or 1939)	Testis weight was 95 and 85*, epididymis 97 and 89*, seminal vesicles 94 and 83*, and prostate 98 and 93%* of controls. Testis total protein was 93* and 88%* of controls. Testes ALP was 75* and 59*, 5′ nucleotidase 88* and 73*, gamma-glutamyltransferase 103 and 137*, and ATPase activity 89* and 80%* of controls. Epididymis total protein was 97 and 88%* of controls. Epididymis ALP was 81* and 68*, 5′ nucleotidase 96 and 73*, gamma-glutamyltransferase 107 and 118*, and ATPase activity 86* and 73%* of controls	Ramalingam et al. (2014)
Wistar rats, 5 weeks, 110–120 g, males	0, 64, 128, and 257 mg/kg $AlCl_3$ in the drinking water for 120 days	26, 52 or 104 (3103, 6205, or 12,459)	Testis weight was 94, 83*, and 75* and epididymis 95, 77*, and 62%* of controls. Testes zinc was 90, 77*, and 67*; copper 105, 130*, and 145*; and iron 87, 70*, and 59%* of controls. Testes ACP was 97, 93*, and 8*; succinate dehydrogenase 102, 90, and 85*; LDH 91, 89, and 82*; and LDH isoenzyme activity 85, 73*, and 60%* of controls. Sperm count was 87, 29*, and 12* and malformation rate 125*, 170*, and 209%* of controls	Zhu et al. (2014)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
Mice, 12 weeks, 20–30 g, male	0, 25, 50, and 100 mg/kg $AlCl_3$ orally for 30 days	*10*, 20, or 40 (303, 606, or 1212)	Testes weight was 95, 88, and 80*; epididymis 100, 81*, and 66*; and seminal vesicles 90, 79, and 57%* of controls. Testis MDA was 118, 124, and 169*; SOD 93, 88, and 56*; CAT 96, 79, and 46*; GPx 89, 69, and 49%*; and cholesterol 106, 113, and 127%* of controls. Sperm motility was 94, 88*, and 62*; viability 98, 85*, and 68*; count 100, 88, and 44*; and abnormalities 110, 187*, and 233%* of controls. Epididymal sialic acid was 56, 54, and 37%* of controls. Seminal vesicle fructose concentration was 97, 96, and 69%* of controls. Serum testosterone was 90, 94, and 61%* of controls. 100 mg/kg/day reduced mating ability, reducing fertile females to 20% of control and live blastocysts to 62% of control and increased pre- and post-implantation losses to 243* and 700%* of controls. Testis histology of the 25 mg/kg/day mice was normal. 50 mg/kg/day caused mild degenerative seminiferous changes (tunica propria thinning, germ cell loosening, and Leydig cell regressive changes). 100 mg/kg/day caused seminiferous tubule shrinkage and lumina devoid of spermatozoa or carbohydrate cell debris and Leydig cell atrophy. Seminal vesicle histology of the 25 mg/kg/day mice was normal. 50 mg/kg/day caused a slight increase of mucosal folding. 100 mg/kg/day caused increased mucosal folding and reduced lumen secretory material	Kumar and Singh (2015)
Wistar rats, 3–4 months, 190–210 g, males	0 or 34 mg/kg $AlCl_3{\cdot}6H_20$ i.g. for 10 weeks	*7.8* (547)	Testes weight was 75%* of controls. The number of Leydig cells/interstitial space was 24%* of controls. Testes zinc was 66%* of controls. Testes nitric oxide was 286*, GSH 38*, CAT 25*, GPx 35*, and SOD 25%* of controls. Testes CAT was 23*, GPx 18*, SOD 19*, and cAMP expression 28%* of controls. Expression of testes steroidogenic genes for 3-beta-hydroxysteroid dehydrogenase was 26*, 17 beta-hydroxysteroid dehydrogenase 24*, steroidogenic acute regulatory protein 15*, and cholesterol side-chain cleavage enzyme 25%* of controls. Testes testosterone was 44*, LDH 26*, and FSH 36%* of controls	Mohammad et al. (2015)
Albino rats, 160 g	0 or 50 mg/kg $Al_2(SO_4)_3$ i.g. for 45 days	16 (711)	Testis weight was 58%* of controls. Testis protein was 54*, lipids 120, cholesterol 56*, triglycerides 75, and phospholipids 53%* of controls. Serum testosterone was 42*, FSH 73*, LH 68*, and prolactin 150%* of controls. Seminiferous tubules showed shrinking, vacuolation, loss of spermatogenic cells, and increased focal Leydig cell proliferation. The tunica propria was separated from these structures, the seminiferous tubule lumen was very compact with cells, and there was some spermatogenic cell pyknosis and seminiferous tubule bleeding	Rawi and Al Nassr (2015)
Wistar rats 120–150 g, males	0 or 20 mg/kg $AlCl_3$ orally for 28 days	*8.1* (226)	Testis triglycerides were 129, cholesterol 48*, and phospholipid 99% of controls	Ugbaja et al. (2015)
Albino rats 140–160 g, males	0 or 30 mg/kg $AlCl_3$ orally for 8 weeks	12 (679)	Al caused seminiferous tubule basement membrane disturbance, disorganized germinal epithelium, interstitial vacuolation, and an 18%* decrease of diagonal diameter. Most spermatogenic cells were undifferentiated and decreased in number. There were decreased polysaccharides in the seminiferous tubule basement membrane, spermatogenic, and Leydig cells. There was decreased germ and Leydig cell proliferation, 68%* decrease in proliferating cell area, 37%* reduction of interstitial cell number, and 29%* reduction of epithelial wall thickness	Afeefy et al. (2016)
Wistar rats, 190–240 g, males	0 or 75 mg/kg $AlCl_3{\cdot}6H_2O$ orally for 30 days	17 (518)	Testis weight was 85*, SOD 48*, GPx 43*, and MDA 322%* of controls	Akay et al. (2016)
Wistar rats, 12 weeks, male (non-diabetic and diabetic)	250 ppm $AlCl_3$ in the drinking water for 30 days	15 (439)	Sperm count and epididymal spermatozoa motility were 82* and 92%* of controls. Serum testosterone and estradiol were 120* and 122%* of non-diabetic controls. Shrunken seminiferous tubules with germinal epithelium erosion	Akinola et al. (2016)
Rats, males	0 or 30 mg/kg $AlCl_3$ i.p. every other day for 8 weeks	6060 every other day (169,680)	Serum testosterone was 48*, FSH 65*, and LH 72%* of controls. Oligospermia, hypoplasia, exfoliated tubules progressed starting after 2 weeks. Increased space between tubules seen after 6 and abnormal Leydig cells after 8 weeks	Al Nahari and Al Eisa (2016) and Al-Eisa and Al-Nahari (2017)
Wistar rats 250–260 g	0 or 100 mg/kg $AlCl_3$ orally for 60 days	40 (2424)	Testes weight was 86*, epididymis 75*, seminal vesicles 88* and prostate 90%* of controls. Sperm count and motility were 80* and 60%* of controls. Sperm abnormalities (headless, banana head, bent neck, and bent tail) were 706*, live sperm 43*, and dead sperm 320%* of controls. Serum testosterone was 68%* of controls	Arumugam and Venugoapal (2016)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
Guinea pigs	0 or 100 mg/l $AlCl_3$ in the drinking water for 13 weeks	*6.1* (551)	Sperm count was 94, motility 97, and abnormal sperm 111% of controls. Testes steroidogenic acute regulatory protein and cytochrome P450 cholesterol side chain cleavage enzyme protein expression were 94 and 81%* of controls. Testes steroidogenic acute regulatory protein and cytochrome P450 cholesterol side chain cleavage enzyme mRNA were 83 and 79% of controls. Serum testosterone was 96% of controls. Seminiferous tubule morphology almost normal. Appearance of tiny cavities and decreased sperm bundle number	Dong et al. (2016)
Sprague Dawley rats, 200–250 g, males	0 or 18 mg/kg $AlCl_3$ orally for 30 days	*7.3* (218)	Sperm count was 49*, motility 67*, viability 66*, and abnormalities 174%* of controls. Testes germ cell layer irregularity, distorted seminiferous tubules, spermatogenic cell degeneration, necrotic debris in the tubules, multinucleated giant cell appearance, interstitial blood vessel congestion, interstitial edema, and abnormal luminal spermatozoa distribution were seen	Hadi and Jaffat (2016)
Albino rats, 60 days, 175 g, males	0 or 98 mg/kg $Al_2(SO_4)_3$ orally for 30 or 60 days	31 (929 or 1858)	Testes MDA after 30 and 60 days was 369* and 610*, and GSH 42* and 19%* of controls. Loss of Sertoli cell integrity. Interstitial cell size reduction with nuclear pyknosis. Marked distortion of seminiferous tubules with almost complete disintegration of connective tissue between them. After 30 days spermatogonia detached from seminiferous tubule basal lamina, germ cell desquamation, and interstitial blood vessel engorgement. After 60 days seminiferous tubule cell nuclear fragmentation, nuclear pyknosis, and germ cell cytoplasmic disintegration. Spermatogonia and spermatocyte cytoplasm vacuolization. Reduced sperm amount in seminiferous tubule lumen, many totally devoid of sperm	Jakkala and Ali (2016a) Jakkala and Ali (2016b)
Humans	Sperm exposed to 0, 0.125, 0.25, 0.5, 1 or 5 mM $AlCl_3$ for 2 h (motility) Sperm exposed to 0, 0.5, 1, 5, 10, 15, 20, 25 or 30 mM $AlCl_3$ for 2 h (lipid peroxidation)		Sperm motility was 100, 97, 93, 76*, and 17%* of controls. MDA was 100, 200*, 284*, 432*, 579*, 664*, 655*, and 648%* of controls	Jamalan et al. (2016)
Swiss mice, 25–35 g, males	0, 25, 50, and 100 mg/kg $AlCl_3$ orally for 30 days	*10*, 20, or 40 (303, 606, or 1212)	Blood testosterone was 68%* of controls Testes MDA was 124, 127, and 181*; SOD 90, 84, and 48*; CAT 86, 69, and 38*; GPx 64, 66, and 36*; ALP 111, 124, and 164*; and LDH 114, 203*, and 312%* of controls	Kumar and Singh (2016)
Wistar rats, 280–330 g, males and females	0, 200, 400, or 1000 ppb $Al_2(SO_4)_3{\cdot}18H_2O$ in the drinking water for 6 months to produce F_0 males, mated with females similarly exposed during gestation and lactation, then offspring exposed to 6 months (→ F_1 males), F_1 males mated with females similarly exposed during gestation and lactation, then offspring exposed to 6 months (→ F_2 males)	*0.005*, *0.009*, or *0.023* (11, 21, or 53)	Testes weight of F_0, F_1, and F_2 males was 93, 85*, and 80*; 85*, 83*, and 77*; and 82*, 76*, and 66%* of controls. Sperm count in F_0, F_1, and F_2 males was 96, 92, and 85*; 89*, 85*, and 72*; and 72*, 67*, and 59%* of controls. Immobile sperm in F_0, F_1, and F_2 males was 218*, 245*, and 345*; 128*, 193* and 175*; and 507*, 575*, and 588% of controls. Serum testosterone in F_0, F_1, and F_2 males was 87*, 73*, and 40*; 61*, 63*, and 33*; and 58*, 49*, and 27%* of controls. Testes had interstitial edema, seminiferous epithelial necrosis and exfoliation, basal membrane disintegration, and Leydig cell necrosis and disintegration. Sperm abnormalities included heads without tails, broken tails, and flexed heads	Muselin et al. (2016)
Albino rats, 150–200 g, males	0 or 100 mg/kg $AlCl_3$ i.g. for 4 weeks	40 (1131)	Testes had small shrunken seminiferous tubules with irregular basement membrane, necrotic germinal epithelial cells, and giant cell formation. Reduced spermatogenesis (single or double germ cell layers), necrotic and calcified tubules. Intertubular blood vessel congestion. Epididymal ducts had reduced density or no sperm and sloughed necrotic germinal cells in their lumina	Oda (2016)
Wistar rats, 250–300 g, males	0, 2 or 10 mg/kg $Al_2(SO_4)_3$ i.v. once or 0 or 3 mg/kg $Al_2(SO_4)_3$ i.p. for 7 days	316 or 1580 474 (3318)	Acute Al reduced intracavernosal pressure/mean arterial pressure (ICP/MAP) 39 and 71%. Subacute Al reduced ICP/MAP ∼ 30%, serum testosterone to 45%* of control and increased corpus cavernosum MDA, GSH, and Al to 128*, 119, and 354%* of control	Senbel et al. (2016)
Wistar rats, 150 − 200 g, males	0 or 4.3 mg/kg $AlCl_3$ i.p. for 21 days	869 (18,241)	Testes MDA was 148* and 147*, SOD 80* and 94*, CAT 80* and 77*, GST 70* and 77*, and GPx 78* and 80%* of controls in the two studies. Al produced shrunken seminiferous tubules; severe sperm cell aplasia; basement membrane thickening and rupture; and interstitial and peritubular tissue vacuolization and fibrosis	Arhoghro and Sule (2017a) Arhoghro and Sule (2017b)
Wistar rats, 240–260 g, males	0 or 10 mg/kg $AlCl_3$ i.p. for 28 days	2020 (56,560)	Testis weight was 80*, sperm count 48*, motility 52*, abnormalities 325*, and viability 45%* of controls. The seminiferous tubule germinal epithelial thickness was 65%*, tubule diameter 87*, tubule lumen 128*, and spermatogonia nuclear diameter 100% of controls. Plasma testosterone was 35*, FSH 116, LH 32*, and SOD 39%* of controls	Cheraghi et al. (2017)
Sprague Dawley rats, adult, males	0, 75, 150, or 300 mg/kg $AlCl_3$ presumably orally for 59 days	20, 61, or 121 (1788, 3575, or 7151)	Sperm count was 100, 92, and 44*; sperm motility 96, 88*, and 62*; normal sperm 97, 87*, and 75*; and abnormal sperm	Falana et al. (2017)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
			115, 135*, and 170%* of controls. Serum testosterone was 98, 95*, and 73%* of controls. Testes histology was normal for the 75 and 150 mg/kg-treated rats. 300 mg/kg resulted in severe testicular damage, abnormal seminiferous tubules, incomplete maturation of germinal cell layers, absence of luminal sperm and Leydig cell hyperplasia	
Rats, 6–7 weeks, 90–120 g, males	0 or 30 mg/kg of $AlCl_3$ i.p. for 35 days followed by 0 Al for 60 days	6060 first 35 days (212,100)	On day 61 testes weight was 73, epididymis 54, seminal vesicle 2, and ventral prostate 24% of controls. Testes protein was 75, MDA 177, SOD 11, CAT 50, cholesterol 140, and gamma-glutamyltransferase 44% of controls. Epididymal protein was 63, MDA 149, SOD 14, CAT 30, and gamma-glutamyltransferase 9% of controls. Sperm count was 31, motility 40, and viability 22% of controls. Libido test mounts and intromissions on day 55 were 35 and 13% of controls. Testes showed spermatogenesis impairment and disorganized seminiferous tubule germinal epithelium with spermatozoa-free lumen, degeneration, and necrosis. There was interstitial tissue reduction. The epididymal tubule lumen contained immature nucleated spermatocytic cells. Partial recovery was seen after Al termination. Spermatogenesis seemed to be taking place in the seminiferous tubules. Some spermatozoa were seen in epididymal lumen	Francine et al. (2017)
Albino rats, 180 g, males	0 or 100 mg/kg of $AlCl_3$ i.g. for 8 weeks	40 (2262)	Serum testosterone was 51%* of controls. Testes exhibited completely atrophied seminiferous tubules, with germinal epithelial necrosis and sloughing. Interstitial edema and congestion were seen. There was multinucleated giant cell aggregation. Ductal germinal epithelial vacuolization and sloughing was seen and the absence of sperm. The lumen of some tubules had acidophilic foamy material admixed with exfoliated necrotic germ cells. Epididymal tissues showed alteration of most ductules that appeared devoid of mature spermatozoa	Khafaga (2017)
Wistar rats, 3 months, 362 g, males	0, 1.5, or 8.3 mg/kg Al as $AlCl_3{\cdot}6H_2O$ in the drinking water for 60 days 0 or 100 mg/kg Al i.g. daily for 42 days	*3* or 17 in the 60-day study (180 or 996) 200 in the 42-day study (8400)	60-day study testes were 118 and 122, epididymis 108 and 106, full seminal vesicle 100 and 100, vesicular secretion 100 and 122, vas deferens 87 and 102%, and ventral prostate 89 and 95% of controls. MDA in the testes was 141* and 162*, epididymis 142 and 224*, and prostate 136 and 156%* of controls. Reactive oxygen and nitrogen species in the testes were 138 and 160*, epididymis 137* and 141*, and prostate 133* and 131%* of controls. Antioxidant capacity in the testes was 73* and 83, epididymis 120 and 66*, and prostate 69* and 117% of controls. 60-day study normal sperm were 96* and 90*, abnormal sperm 171 and 248, testis sperm number 73* and 65*, daily production 73* and 65*, sperm that were motile with progressive movement 85 and 53*, sperm that were motile without progressive movement 122 and 167*, immotile 161 and 197*, epididymis sperm number 95 and 93, epididymis transit time 128* and 162*, cauda sperm number 78 and 84, and cauda transit time 107 and 132% of controls. For the 8.3 mg/kg subject's testis activated macrophages were 265%*, seminiferous epithelial thickness 76%*, empty seminiferous tubule number 273%*, and empty epididymis efferent ducts 100% of controls. 42-day study testes weights were 100, epididymis 93, ventral prostate 84*, full seminal vesicle 108, vesicular secretion 129, and vas deferens 89% of controls. Testes MDA was 177*, epididymis 170*, and prostate 138% of controls. Testes antioxidant capacity was 126*, epididymis 97, and prostate 69%* of controls. 42-day study normal sperm were 89*, abnormal sperm 219, testis sperm number 78*, daily production 78*, sperm that were motile with progressive movement 33*, sperm that were motile without progressive movement 173*, immotile 258*, epididymis sperm number 94, epididymis transit time 118, cauda sperm number 84, and cauda transit time 107% of controls. Testes reactive oxygen and nitrogen species were 181*, epididymis 141*, and prostate 124%* of controls. Testis activated macrophages were 114% of controls Testis seminiferous epithelial thickness was 74%* of controls. Empty seminiferous tubule number was 126% of controls. Empty epididymis efferent ducts were 80% of controls	Martinez et al. (2017)
Bank voles, 4 weeks, males and females	0, 1.5, or 100 mg Al/kg/day as $AlCl_3{\cdot}6H_2O$ in the drinking water for 12 weeks	*3* or 200 (252 or 16,800)	Testis and accessory gland weights were 102 and 104; and 103 and 117% of controls. Sperm count was 61* and 48*; sperm motility 91* and 75*; swollen sperm 91 and 70*; viable sperm 85* and 64*; sperm cell head abnormalities 132 and 195*; and spermatogenic index (a measure of seminiferous epithelium activity, spermatogenesis) 96 and 77%* of controls	Miska-Schramm et al. (2017)
Albino rats, 180–200 g, males	0 or 10 mg/kg $AlCl_3$ i.g. daily for 3 months	*4* (364)	Testes MDA was 147*, GSH 52*, CAT 64*, and SOD 63%* of controls. Serum testosterone was 30%* of controls.	Mohamed and El-Moneim (2017)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
			Testis showed marked necrosis and degeneration of seminiferous tubule spermatogonia lining cells, incomplete spermatogenesis, and intraluminal spermatid giant cells	
Wistar rats, 100–196 g, males	0 or 0.5 mg/kg $AlCl_3$ i.g. daily for 3 weeks	*0.2* (4.2)	Serum testosterone was 78, FSH 43, and LH 33% of controls	Olawuyi et al. (2017)
Wistar rats, 160 g, males	0 or 20 mg/kg $AlCl_3$ orally daily for 6 weeks	*8* (339)	Testis caspase-3 and proliferating cell nuclear antigen (a measure of cell replication) expression were 278 and 22% of controls. Seminiferous tubule diameter and thickness were 58 and 48% of controls. Serum testosterone and LH were 18 and 33% of controls. Testes blood vessels were enlarged and congested, tubule germ layers were detached from the basal lamina, intertubular spaces had blood hemorrhages, germ layers had vacuoles, and there was a severe reduction of spermatogenic cells with appearance of giant cells	Sakr et al. (2017)
Wistar rats, 160 g, males	40 mg/kg $AlCl_3$ in the drinking water for 21 days	16 (339)	Testis total protein was 63*, MDA 148*, GSH 59*, CAT 43*, and SOD 27%* of controls	Adedosu et al. (2018)
Mice, 3 months, 30–35 g, males	0 or 55.45 mg/kg $AlCl_3$ i.p. daily for 60 days	11,200 (78,406, 168,014, 336,027, or 672,054 after 7, 15, 30, or 60 injections)	After 7, 15, 30, or 60 injections sperm count was 72*, 75*, 25*, and 13*; live sperm 95, 92*, 78*, and 60*; and abnormal sperm 91, 161*, 206*, and 261%* of controls. After 30 injections sperm abnormalities included amorphous head, bent at the cephalocaudal junction, bent with projecting filaments, microcephaly with tail defects and defective head with tail duplication. Testes were enlarged after 60 injections. Testis showed fibrin deposition; seminiferous tubule vacuolization with hyalinization; Leydig cell proliferation; tunica albuginea fibrous thickening; lack of spermatocytes in some seminiferous tubule lumens; spermatogenic cell sloughing in seminiferous tubule lumens; seminiferous tubule necrosis, interstitial fibrosis, distension, and giant cell formation; mononuclear cell infiltration; Epididymis showed destruction of ductal epididymal epithelia, mild interstitial fibrosis, mononuclear cell infiltration, spermatid loss and spermatid clumping in some tubules, and epithelial caput destruction. Prostate stromal tissue showed fibromuscular proliferation with mononuclear cells aggregation and epithelial hyperplasia	Mohammed et al. (2018)
Wistar rats, 70 days, 264–368 g, males	0, 0.000067, 0.000335, 10, and 40 mg/kg Al as $AlCl_3$ i.g. daily for 112 days	*0.000134*, *0.00067*, 20, or 80 (0.015, 0.075, 2240, or 8960)	Testis total weight was 92*, 88*, 87*, and 86*; tunica albuginea 118, 94, 82, and 61; and parenchyma 89*, 88*, 88*, and 88%* of controls. Leydig cell nuclear diameter was 87*, 85*, 80*, and 83*; nuclear percentage 105, 110, 126, and 128; and cytoplasm percentage 117, 135, 131, and 204%* of controls. Number of Leydig cells/testis was 124, 168, 168, and 160% of controls. Epididymis weight was 84*, 74*, 78*, and 77%* of controls. Epididymal caput epithelial height was 94, 98, 98, and 111*; tubular diameter 108, 96, 101, and 96; luminal diameter 111, 94, 103, and 92; lumen with sperm 93, 83*, 96, and 84*; and percent epithelium 105*, 118*, 102, and 119%* of controls. Normal sperm morphology was 104, 97, 100, and 96; sperm motility 88, 90, 93, and 84*; and sperm with tail defects 58, 110, 102, and 127% of controls. Sperm with intact plasma and acrosomal (secretory vesicle of sperm head with enzymes that digest the oocyte's investments) membranes were 63, 47*, 12* and 9%* of controls. Serum testosterone was 31*, 31*, 56*, and 54%* of controls Testis volumetric proportion; tubular and intertubular volume; tubular morphometry; and seminiferous tubule diameter, luminal diameter, and length were not different from controls. Epididymal lamina propria volumetric proportions, lumen without sperm, blood vessels, connective tissue, and smooth muscle were not different from controls	Mouro et al. (2018)
Wistar rats, 3 weeks, 70–95 g, males	0, 64, 128, or 256 mg/kg $AlCl_3$ in the drinking water for 120 days	25, 52, or 103 (3103, 6205, or 12,411)	Testes Na^+-K^+-ATPase activity was 94, 90 and 74*; Mg^{2+}-ATPase 100, 72*, and 66*; and Ca^{2+}-ATPase 96 84, and 78%* of controls. Testes follicle stimulating hormone receptor and luteinizing hormone receptor expression were 89, 73*, and 64*; and 86, 74* and 68%* of controls. Testes from the 64 mg/kg group stroma were slightly expanded, with decreased spermatogenic cells and sperm count. Testes sperm in the 128 mg/kg group were in the lumen and sperm count was significantly decreased. Testes from the 256 mg/kg group showed congestion, blood, edema, and were withered. Testicular stroma from the 256 mg/kg group were significantly expanded, the seminiferous tubules narrow, with decreased sperm count. Testes showed cell disintegration, incomplete cell membranes, foal-like structures, mitochondrial swelling, and irregular nuclear envelope	Sun et al. (2018)
Sprague Dawley rats, ~ 8 weeks, males	0 or 0.4–0.55 mg Al as Al hydroxy-phosphate sulfate (in Merck's	77–106 (2658–4616)		Wise et al. (2018)

(*continued*)

Table 6. Continued.

Al-treated subjects	Al exposure	Approximate systemic Al exposure as μg/kg/day and (total μg/kg)[a]	Study results*	Reference
	aluminum adjuvant) i.m. on study days 1, 22, 43, and 64 Terminated 3 or 21 days later		There was no effect on testis or prostate weight, or testis, epididymis, seminal vesicle, prostate, or prostate histomorphology	
Gerbils, 3–4 months old, females	0 or 20.2 mg Al/kg/day as $AlCl_3$ orally GD 17–24	40.4 [323]	Offspring body weight; anogenital distance; and prostate epithelial buds, mesenchyme, and smooth muscle were 87*, 98, 122*, 80*, and 131%* of controls. Androgen receptor and proliferating cell nuclear antigen in the prostate epithelial buds, mesenchyme, and smooth muscle were 82*, 73*, and 77; and 484*, 174*, and 267%* of control. The results suggest Al acts as an antiandrogenic endocrine disruptor	Gomes et al. (2019)
Wistar rats, 100–196 g, males	0 or 0.5 mg/kg $AlCl_3$ i.g. daily for 3 weeks	*0.2* (4.2)	The visual field percentage of seminiferous tubules was 89*, Leydig cells 122, and non-Leydig cells 190% of controls. The volume of seminiferous tubules was 89*, Leydig cells 115, and non-Leydig cells 185% of controls. Seminiferous duct diameter was 116, luminal diameter 106, epithelial height 24*, and interstitial space diameter 992%* of controls. Spermatogonia were 30, primary spermatocytes 60, secondary spermatocytes 31, round spermatids 62, elongated spermatids 14, spermatozoa 6, and Sertoli cells 33% of controls	Olawuyi et al. (2019)
Wistar rats, 180–200 g, males	0, 64, 128, or 257 mg/kg $AlCl_3{\cdot}6H_2O$ in the drinking water for 16 weeks	15, 30 or 59 (1653, 3307, or 6613)	Progressively motile, dead, and abnormal sperm were 70*, 51*, and 26*; 155*, 282*, and 434*; and 131*, 163*, and 220%* of controls. Mitochondrial membrane potential and membrane permeability transition pore were 82*, 69*, and 51*; and 181*, 238*, and 423%* of controls. Al exposure increase sperm mitochondrial swelling	Yuan et al. (2019)
Kunming mice, 4 weeks, 18–23 g, males	0 or 10 mg/kg Al (form not reported) i.g. for 4 weeks	20 (560)	Testis weight was 96% of controls. Testis Na was 151*, K 77*, Ca 154*, and Mg content 83%* of controls. Testis MDA was 195*, H_2O_2 135*, CAT 49*, SOD 70*, and total antioxidant capacity 45%* of controls. Testes NO content was 134*; activity of iNOS was 105, tNOS 177*, and cNOS 270*; and mRNA expression of nNOS 151*, iNOS 435*, and cNOS 180%* of controls. Testes Na^+-K^+-ATPase activity was 82*, Mg^{2+}-ATPase 68*, Ca^{2+}-ATPase 55*, and Ca^{2+}-Mg^{2+}-ATPase 68%* of controls. Seminiferous tubules were disorderly with loose arrangement and damage. Mature sperm count was decreased with enlarged and loose cells and swollen sperm heads	Cao et al. (2020)
Wistar rats, 8–10 weeks old, 220–250 g, males	0 or 34 mg/kg $AlCl_3$ orally for 10 weeks	14 (962)	Testis MDA, GSH, GPX, CAT, Nrf-2, HO-1, and caspase 3 and Bcl2 expression were 125*, 65*, 83, 77*, 47*, 68*, 1750* and 470%* of controls. Johnsen testicular biopsy score was 41%* of controls. Sperm motility, concentration, dead/live ratio, and abnormal sperm were 58*, 53*, 220*, and 209%* of controls. Tubular germ cells were largely separated from the basement membrane, the tubulus membrane was thickened, tubules were closer to each other, interstitial space was narrowed, there was significant cell loss or tubule disorganization, increased space between Sertoli cells, increased spermatogonia, degenerated germinal cells, spermatogonial nuclei shrinkage, halted or decreased spermatogenesis, and interstitial edema and vascular congestion	Güvenç et al. (2020)
Albino mice, 3–4 months, 23–35 g, males	0 or 50 mg/kg $AlCl_3$ presumably orally for 45 days	20.2 (303, 606, and 909 after) 15, 30, and 45 days)	Testis weight and as a percentage of body weight after 15, 30, and 45 days were 100, 99, and 90*; and 80, 85, and 81%* of controls. Epididymis and vas deferens weight and as a percentage of body weight after 15, 30, and 45 days was 91, 87, and 73; and 73, 73, and 70% of controls. Seminal vesicle weight and as a percentage of body weight after 15, 30, and 45 days was 72, 72, and 68*; and 57, 63, and 85% of controls. Sperm count after 15, 30, and 45 days was 98, 90, and 55%* of controls. Sperm mobility after 15, 30, and 45 days was 80, 78, and 64% of controls. Serum testosterone, FSH, and LH after 15, 30, and 45 days were 189*, 46, and 36*; 80, 79, and 62*; and 13, 3, and 0.3%* of controls. After 15 days shrunken interstitial cells and damaged basement membrane were seen; after 30 days irregularly shaped seminiferous tubules; and after 45 days vacuolation, damaged spermatocytes, and irregularly shaped seminiferous tubules	Sajjad et al. (2020)

The approximate systemic Al exposure from the additional Al was calculated as described in the text. Daily exposures that do not add more Al than expected from the diet are in italics.

[a]See the footnote in Table 3.

*Results that are statistically significantly different from controls.

exposure-dependent increase in placental Al concentration. The considerably higher placental Al levels in mice and rats compared to humans may be due to the higher Al content of rodent than human diet (see the Animal diet Al content and daily food and water consumption section). Exposure of human placental brush-border membranes and microsomes to 0.05–10 mM Al salts increased MDA in a concentration-dependent manner (Anand and Kanwar 2001), suggesting Al-increased lipid peroxidation could have detrimental effects on the placenta. No association was seen between placental Al concentration and orofacial clefts (Pi et al. 2019).

The fetus inhales and swallows amniotic fluid. In mice exposed to topical $AlCl_3$ solution for 20 days, estimated to provide negligible systemic Al exposure (see Table 8), amniotic fluid was 35 compared to 29 μg/L in controls (Anane et al. 1997). Human samples obtained at 16–19 weeks of gestation averaged 93 μg/L (Hall et al. 1983), 111 μg/L at 16–26 weeks and 160 μg/L at 21–26 weeks (Sulibarska et al. 2016), 19 μg/L at 12–20 weeks (Jalali and Koski 2018), and at birth 78 (Takács et al. 1992) and 144 μg/L (Markiewicz et al. 2017). Amniotic fluid Al was higher for male than female fetuses, 179 versus 107 μg/L, respectively (Sulibarska et al. 2016). Amniotic fluid Al concentration did not significantly correlate with fetal heart rate, umbilical artery pulsatility index, biparietal diameter, head or abdominal circumference, femur length, or estimated fetal weight (Sulibarska et al. 2016). There was no relationship between Al concentration and ultrasound measures (estimated weight, bi-parietal diameter, head circumference, abdominal circumference, and femur length) at 16–20 or 32–36 weeks (Jalali and Koski 2018). Amniotic fluid Al in women whose fetus was found to have congenital neural tube defects averaged 440 μg/L, significantly higher than women with healthy fetuses (256 μg/L) (Ovayolu et al. 2019).

Infant meconium of low socio-economic mothers from 19 sites in Karachi, Pakistan, averaged 130 ppm Al (Aziz et al. 2017). The authors found a significant correlation among maternal blood, cord blood, and meconium Al concentration at 13 of the 19 sites.

Only two reports were found of Al concentration in female reproductive organs. Ovary Al concentration in Wistar rats that consumed 0, 200, 400, or 1000 ppb $Al_2(SO_4)_3$ in the drinking water for 3 months before mating was 38, 95*, 101*, and 77* μg/g after offspring weaning. The corresponding uterus and fallopian tube Al concentrations were 7.0, 8.9*, 8.2*, and 8.7* μg/g. Ovary Al concentration in similarly exposed F1 offspring was 40, 99*, 102*, and 104* μg/g after weaning. Uterus and fallopian tube Al concentration was 7.8, 9.2*, 9.4*, and 10.2* μg/g (Trif et al. 2010). Some of these values are much higher than reported for the placenta and non-reproductive organs of pregnant rodents (perhaps they are expressed as dry weight, although this cannot be determined from the report). Ovary Al concentration in Wistar rats that consumed 0, 64, 128, or 257 mg/kg $AlCl_3$ in the drinking water for 120 days was 0.16, 0.54*, 1.14*, and 1.18* μg/g. Since the authors do not report if these are based on wet or dry weights, these data only provide a basis for within-study comparisons (Wang et al. 2012). Both reports show increased female reproductive organ Al concentration as a result of increased Al exposure, associated with structural changes in the ovaries and uterus, and decreased female hormones and increased testosterone in the blood (Table 3).[3]

There are many reports of Al quantification in mouse and rat testes, four in rabbits, and one in humans. Details are summarized in Table 10. Aluminum deposits in human Leydig cells and seminiferous tubules were visualized using laser microprobe mass analysis (Reusche et al. 1994). Many of the reports found an Al-exposure-dependent increase in testes Al concentration. For the studies that determined testes Al concentration shortly after completion of exposure in the absence of citric acid, there is a strong correlation between total systemic Al exposure and the dietary plus added Al contribution (e.g. Pearson correlation $r(30) = 0.67$, $p = 0.000027$ for the $\log_{10}$ mouse and rat total Al exposure versus $\log_{10}$ testes Al concentration as a fold of control). An increase in seminal fluid Al concentration was found in humans exposed to occupational environments that might increase Al exposure (Hovatta et al. 1998; Dawson et al. 2000), along with an inverse relationship between sperm quality and Al concentration (Dawson et al. 1998; Klein et al. 2014). These results suggest seminal fluid Al concentration may be a sensitive indicator of Al-induced male reproductive toxicity and that Al-induced decreased male fertility may be fairly common.

The two studies that reported both fetal and placental Al concentrations found higher levels in the placenta than in the fetus and a greater increase in the placenta after additional Al exposure (Cranmer et al. 1986; Colomina et al. 1994). The logs of the fetal and placental Al concentrations as a multiple of the Al concentration in animals that did not receive additional Al (Tables 8 and 9) are normally distributed. The linear regression best fit slope of the placental Al concentrations is greater than the slope of the fetal Al concentrations, further indicating greater Al distribution into the placenta than fetus. Similarly, a study that quantified Al in the placental body and membrane and umbilical cord found less Al in the cord (0.56 and 0.53 versus 0.27, respectively) (Kruger et al. 2010). A normally distributed transform of the testes Al concentration as a multiple of the Al concentration in animals that did not receive additional Al (Table 10) was not identified. The slopes of the logs of the placental and testes Al concentrations are significantly different from zero. The slope of the log of the testes Al concentration is greater than the placental Al concentration, suggesting greater Al distribution into testes. Comparison of the Al-exposure-dependent increased testes Al concentration (up to >100-fold, Table 10) compared to Al-exposure-dependent increased placental Al concentration (up to 10-fold, Table 9) further suggests greater Al distribution into testes than placenta.

Initial adverse outcomes pathways for Al-induced reproductive toxicity

An adverse outcome pathway (AOP) is a conceptual construct creating a link between a molecular initiating event (MIE) produced by exposure to a substance and an adverse outcome (AO). It captures key biochemical and physiological

Table 7. Studies conducted in males categorized according to study report of significant findings and approximate systemic Al exposure.

	Daily approximate systemic Al exposure (μg/kg)	Total approximate systemic Al exposure (μg/kg)
A. GLP compliant studies conducted following an OECD test guideline showing no statistically significant toxicity		
Beekhuijzen (2007)	20, 98, or 494	554, 2744, or 13,832
Hirata-Koizumi et al. (2011b), F0 generation	*2.7 or 13*	*247 or 1179*
Hirata-Koizumi et al. (2011b), F1 generation	*3.4 or 16*	*308, 1444*
Hirata-Koizumi et al. (2011a), F0 generation	*0.9 or 8*	*78 or 695*
Hirata-Koizumi et al. (2011a), F1 generation	*1.0 or 10*	*95 or 867*
B. No significant effects from exposures similar to A. above		
McCollum et al. (1928)	90	∼ 1890
Dixon et al. (1979)	1.5, 15, or 149	135, 1350, or 13,410
Katz et al. (1984)	10, 27, or 88	1830, 4917, or 16,040
Hicks et al. (1987)	67, 141, 288, or 302	1876, 3948, 8064, or 8456
Pettersen et al. (1990)	8, 20, 54, or 150	1456, 3640, 9828, or 27,300
Roy et al. (1991) $Al_2(SO_4)_3{\cdot}18H_2O$	34 or 58	*721 or 1208*
Roy et al. (1991) $KAl(SO_4)_2{\cdot}12H_2O$	57	*1204*
Wise et al. (2010)	34	745
Chaitanya et al. (2012)	20	280
Hichem et al. (2013)	40	*7373*
Kumar and Singh (2015)	*10*	*303*
Kumar and Singh (2016)	*10*	*303*
Falana et al. (2017)	*20*	*1788*
Wise et al. (2018)	77–106	2658–4616
C. GLP compliant studies conducted following an OECD Test Guideline showing statistically significant toxicity		
Hirata-Koizumi et al. (2011b), F0 generation	59	5406
Hirata-Koizumi et al. (2011b), F1 generation	73	6671
Hirata-Koizumi et al. (2011a), F0 generation	70	6328
Hirata-Koizumi et al. (2011a), F1 generation	85	7718
D. Studies with some significant results from exposures similar to A. above		
Kamboj and Kar (1964)	30	907
Krasovskiĭ et al. 1979)	5	1350
Pettersen et al. (1990)	150	27,300
Roy et al. (1991) $Al_2(SO_4)_3{\cdot}18H_2O$	86	1803
Roy et al. (1991) $KAl(SO_4)_2{\cdot}12H_2O$	87	1831
Bataineh et al. (1998)	33	2800
Yousef (2004)	34	3808
El-Demerdash (2004)	*7*	206
Mayyas et al. (2005)	104, 125, or 145	8755, 10,507, or 12,258
Yousef et al. (2005)	34	3808
Trif et al. (2007)	0.009, 0.018, or 0.045	0.4, 1.7, 3.3 or 8.4
Al-Hashem (2009)	0.12	3.4
Entissar et al. (2009)	16 or 32	485 to 1940
Yousef and Salama (2009)	14	962
Hala et al. (2010)	8	566
Thirunavukkarasu et al. (2010)	40	3636
Abu-Taweel et al. (2011)	121 or 242	2424 or 4848
Mahran et al. (2011)	14	962
Sun H et al. (2011)	26, 52, or 104	3103, 6205, or 12,459
Ige and Akhigbe (2012)	40	121
Ighodaro et al. (2012)	0.2	7.1
Moselhy et al. (2012)	14	412, 618, or 824
Hichem et al. (2013)	40, 81, or 162	14,746 to 88,476
Tiroumavalavane et al. (2013)	20	909
Yadav et al. (2013)	16 or 157	1098 or 1404
Kalaiselvi et al. (2014)	20 or 40	909 or 1818
Ramalingam et al. (2014)	20 or 40	970 or 1939
Zhu et al. (2014)	26, 52 or 104	3103, 6205, or 12,459
Kumar and Singh (2015)	*20* or 40	*606 or* 1212
Mohammad et al. (2015)	7.8	547
Rawi and Al Nassr (2015)	16	711
Ugbaja et al. (2015)	8.1	226
Afeefy et al. (2016)	12	679
Akay et al. (2016)	17	518
Akinola et al. (2016)	15	439
Dong et al. (2016)	6.1	551
Hadi and Jaffat (2016)	7.3	218
Jakkala and Ali (2016a)	31	929 or 1858
Arumugam and Venugoapal (2016)	40	2424
Kumar and Singh (2016)	*20* or 40	*606 or* 1212
Muselin et al. (2016)	0.005, 0.009, or 0.023	11, 21, or 53
Oda (2016)	40	1131
Falana et al. (2017)	61 or 121	*3575 or 7151*
Khafaga (2017)	40	2262
Martinez et al. (2017)	*3, 17,* or 200	180, 996, or 8400
Miska-Schramm et al. (2017)	*3* or 200	252 or 16,800

(*continued*)

Table 7. Continued.

	Daily approximate systemic Al exposure (μg/kg)	Total approximate systemic Al exposure (μg/kg)
Mohamed and Abd El-Moneim (2017)	4	364
Sakr et al. (2017)	8	339
Adedosu et al. (2018)	16	339
Mouro et al. (2018)	0.000134, 0.00067, 20, or 80	0.015, 0.075, 2240, or 8960
Sun et al. (2018)	25, 52, or 103	3103, 6205, or 12,411
Gomes et al. (2019)	40	323
Olawuyi et al. (2019)	0.2	4.2
Yuan et al. (2019)	15, 30 or 59	1653, 3307, or 6613
Cao et al. (2020)	20	560
Güvenç et al. (2020)	14	962
Sajjad et al. (2020)	20.2	909
E. Study found some statistically significant results from higher exposure		
Melograna and Yokel (1984)	3400	68,000
Oneda et al. (1994)	114, 285, 570, or 1140	69,312, 173,280, 346,560, or 693,120
Llobet et al. (1995)	3600, 7200, or 14,400	72,000, 144,000, or 288,000
Guo et al. (2001)	13,000 or 35,000	182,000 or 490,000
Guo et al. (2002)	13,000 or 35,000	182,000 or 490,000
Guo et al. (2005a)	35,000	420,000
Guo et al. (2005b)	1470 or 2730	20,580 or 38,220
Guo et al. (2006)	1470 or 7350	20,580 or 102,900
Reza and Palan (2006)	10,100	202,000
Khattab (2007)	3030 or 6060	53,025 or 105,050
Kutlubay et al. (2007)	339	4790
Guo et al. (2009)	1414 or 7070	19,796 or 98,980
Cui et al. (2009)	7214, 10,821, or 14,428	72,140, 108,210, or 144,280
Buraimoh et al. (2012b)	768	42,986
Abdel-Moneim (2013)	5050	5050
Chen et al. (2014)	577, 1154, or 1731	1731, 3464, or 5194
D'Souza et al. (2014)	6600, 13,200, or 19,800	46,200, 92,400, or 138,600
Maghraoui et al. (2014)	1778	24,892
Al Nahari and Al Eisa (2016) Al-Eisa and Al-Nahari (2017)	3030	169,680
Senbel et al. (2016)	316, 474, or 1580	3318
Arhoghro and Sule (2017a, 2017b)	869	18,241
Cheraghi et al. (2017)	2020	56,560
Francine et al. (2017)	6060	212,100
Mohammed et al. (2018)	11,200	78,406, 168,014, 336,027, or 672,054

Italicized entries are reports that include results at lower exposures that did not result in significant findings and higher exposures that did result in significant findings.

events (KE) and key event relationships (KER) that link the MIE to the AO. The OECD and US EPA actively support AOP development. The OECD maintains a wiki-based interface for developing AOP descriptions that issues formal descriptions of well-defined AOPs (https://aopkb.oecd.org). The OECD site, SciFinder and Google searches, and the review of the reports summarized in this review failed to identify an AOP for Al for any endpoint. Unlike organic molecules whose primary activities often result from interaction with specific receptors, such as enzymes, the biological and toxicological effects of an element are usually not limited to a single mechanism of action. Al-induced reproductive dysfunction is likely to be mediated by more than one MIE, as has been suggested (Pandey and Jain 2013). The frequency, consistency, and direction of reported changes following Al exposure summarized in Table 6 show decreased SOD and CAT and increased MDA in the testes, and decreased testosterone in the blood, as discussed in section Assessment of Al reproductive toxicity in male animals. These results were incorporated into an initial proposed AOP for Al-induced male reproductive toxicity (Figure 1). The role of oxidative stress in Al-induced male reproductive impairment is supported by the reversal of Al-induced increased oxidative stress reported by many studies cited in Table 6, reflected in the report titles. In the spirit of AOP development, researchers are encouraged to challenge, and more importantly, scientifically address, the proposed AOP.

Conclusions

The inherent Al content of the diet, and very much less the drinking water, represent appreciable contributors to total Al exposure, as noted in 1932 (Mackenzie 1932). The lack of documentation of dietary Al content in most studies creates some uncertainty about total Al exposure, complicating extrapolation of results from animal studies to the human. Aluminum can produce reproductive toxicity in female and male rodents. Studies that were GLP compliant and followed an OECD Test Guideline in females, as well as numerous other studies that utilized comparable Al exposures, reported no significant effects following daily Al exposures that delivered up to 25-fold the typical equivalent human daily Al consumption. In contrast, numerous studies utilizing similar Al exposure showed some significant effects, although more often the studied endpoints were non-significant. Generally,

Table 8. Al concentration in fetuses of mothers exposed to additional Al.

	Additional maternal Al exposure			
Maternal diet Al concentration (mg/kg)	Al species and route	Approximate added total systemic Al exposure (μg/kg)	Fetal Al concentration (μg/g) [as multiple of no added Al][b]	Reference
Mouse				
	Purina 5010 rodent feed	400 from the diet from GD 7 to 16 assuming it contained 100 mg Al/kg	0.59 (dry weight, whole fetus)	Cranmer et al. (1986)
	$AlCl_3$ i.p.	202,000	2.0[b] (dry weight, whole fetus) [3.4]	
		303,000	1.3[b] (dry weight, whole fetus) [2.2]	
	$AlCl_3$ i.g.	808	1.1[b] (dry weight, whole fetus) [1.9]	
		1212	0.85[b] (dry weight, whole fetus) [1.4]	
	Panlab	400 from the diet from GD 6 to 15 assuming it contained 100 mg Al/kg	< 0.05 (wet weight, whole fetus) < 0.41 dry weight	Colomina et al. (1992)
	$Al(OH)_3$ i.g.	1150	0.18 (wet weight, whole fetus) 1.5 (dry weight) [3.5]	
	Al lactate i.g.	1150	17 (wet weight, whole fetus) 142 (dry weight) [344]	
	Panlab	400 from the diet from GD 6 to 15 assuming it contained 100 mg Al/kg	0.66 (wet weight, whole fetus) 5.5 (dry weight)	Colomina et al. (1994)
	$Al(OH)_3$ i.g.	2076	0.88 (wet weight, whole fetus) 7.3 (dry weight) [1.3]	
	UAR4 chow	800 from the diet over 20 days assuming it contained 100 mg Al/kg	0.040[a] brain 0.040 kidney 0.031 liver 0.029 lung Assume wet weight	Anane et al. (1997)
	$AlCl_3$ topically	0.0090	0.042[b] brain [1.05] 0.042[b] kidney [1.05] 0.036[b] liver [1.16] 0.029 lung [1.0]	
Rat				
	Lab Blox	119 from the diet GDs 6, 9, 12, 15, and 18	0.68 (dry weight, whole fetus)	McCormack et al. (1979)
119	$AlCl_3$ in the diet	160	0.74 (dry weight, whole fetus) [1.09]	
		319	1.37 (dry weight, whole fetus) [2.0]	
	Extra Labo food pellets	380 from the diet from GD 1 to 19 assuming it contained 100 mg Al/kg	0.023 (wet weight, whole fetus) 0.19 (dry weight)	Muller et al. (1993)
380 from the diet from GD 1 to 19 assuming it contained 100 mg Al/kg	Al lactate in the diet	15,200	0.066 (wet weight, whole fetus) 0.55 (dry weight) [2.9]	
	N° GPF81 de la société INAAM	100 from the diet from GD 9 to 13 assuming it contained 100 mg Al/kg	1.00 μg/ml Plasma 0.25 Liver 0.3 Kidneys 0.20 Intestine (dry weight)	Mestaghanmi et al. (2003)
	$AlCl_3$ i.p.	206,122	0.98 μg/ml Plasma [0.98] 0.23 Liver [0.92] 0.47 Kidneys [1.6] 0.19 Intestine [0.95] (dry weight)	
		412,245	0.97 μg/ml Plasma [0.97] 0.82[b] Liver [3.3] 0.92[b] Kidneys [3.1] 0.90[b] Intestine [4.5] (dry weight)	
		824,490	1.06 μg/ml Plasma [1.06] 1.5[b] Liver [6]	

(*continued*)

Table 8. Continued.

Maternal diet Al concentration (mg/kg)	Additional maternal Al exposure: Al species and route	Additional maternal Al exposure: Approximate added total systemic Al exposure (μg/kg)	Fetal Al concentration (μg/g) [as multiple of no added Al][b]	Reference
			1.8[b] Kidneys [6] 1.4[b] Intestine [7] (dry weight)	
	$^{26}AlCl_3$ s.c.	48	0.21% of dose whole fetus	Yumoto et al. (2000)
	$^{26}AlCl_3$ s.c.	48	0.23% of dose whole fetus 0.00038% of dose in the brain 0.0038% of dose in the liver	Yumoto et al. (2001)
	$^{26}AlCl_3$ s.c.	3.4	0.0001% of dose/gm brain 0.0002% of dose in the brain 0.0005% of dose/gm kidney 0.0008% of dose/gm liver 0.0006% of dose in the liver 0.001% of dose/gm blood 0.013% of dose/gm bone	Yumoto et al. (2010)
Rabbit				
1215	Purina rabbit chow	2430 from the diet GD 2–6, 9–13, 16–20, and 23–27	0.6 brain (hippocampus) 39 bone 2.1 heart 1.1 kidney 1.7 liver 1.0 lung 4.9 muscle 7.5 spleen (dry weight)	Yokel (1985)
	Al lactate s.c.	2268	1.1[b] brain (hippocampus) [1.8] 60 bone [1.5] 1.4 heart [0.67] 2.4[b] kidney [2.2] 0.6 liver [0.35] 1.9 lung [1.9] 4.2 muscle [0.86] 17 spleen [2.3] (dry weight)	
		9072	1.4[b] brain (hippocampus) [2.3] 92[b] bone [2.4] 2.1 heart [1] 4.2[b] kidney [3.8] 1.7 liver [1] 1.6 lung [1.6] 7.9[b] muscle [1.6] 13 spleen [1.7] (dry weight)	
		36,288	3.6[b] brain (hippocampus) [6] 169[b] bone [4.3] 6.8[b] heart [3.2] 20[b] kidney [18] 16[b] liver [9.4] 4.7[b] lung [4.7] 15[b] muscle [3.1] 37 spleen [4.9] (dry weight)	

The maternal diet Al concentration is from the cited report or based on the assumption that the diet contained 100 mg Al/kg, as described in the text. For studies reporting the fetal Al concentration on a wet weight basis, the concentration on a dry weight basis was calculated using fetal-age-dependent dry/wet weight ratios (Davis 1989; Gardner et al. 1999).

[a]Not known if reported as wet or dry weight.

[b]Results that are statistically significantly different from controls.

Table 9. Al concentration in placentas.

	Additional maternal Al exposure			
Maternal diet Al concentration (mg/kg)	Al species and route	Approximate added total systemic Al exposure (μg/kg)	Placental concentration (μg/g) [as multiple of no added Al][a]	Reference
Mouse				
	Purina 5010 rodent feed	400 from the diet from GD 7 to 16 assuming it contained 100 mg Al/kg	2.7 (dry weight)	Cranmer et al. (1986)
	$AlCl_3$ i.p.	202,000	27.6[a] (dry weight) [10]	
		303,000	17.8[a] (dry weight) [6.6]	
	$AlCl_3$ i.g.	808	5.9[a] (dry weight) [2.2]	
		1212	3.1 (dry weight) [1.1]	
60	Panlab	240 from the diet GD 6–15	2.35 (wet weight) 14 (dry weight)	Colomina et al. (1994)
	$Al(OH)_3$ i.g.	2076	4.49[a] (wet weight) 28 (dry weight) [1.9]	
	$Al(OH)_3$ with ascorbic acid i.g.	2076	4.43[a] (wet weight) 28 (dry weight) [1.9]	
Rat				
60	Panlab	120 from the diet GD 6–15	1.92 (wet weight) 12 (dry weight)	Gomez et al. (1990)
	$Al(OH)_3$ i.g.	1329	2.51 (wet weight) 16 (dry weight) [1.3]	
		2657	1.60 (wet weight) 10 (dry weight) [0.83]	
		5315	1.71 (wet weight) 11 (dry weight) [0.89]	
60	Panlab	120 from the diet GD 6–15	3.19 (wet weight) 20 (dry weight)	Gomez et al. (1991)
	$Al(OH)_3$ i.g.	2660	3.02 (wet weight) 19 (dry weight) [0.95]	
	Al citrate i.g.	5320	9.24[a] (wet weight) 58 (dry weight) [2.9]	
	$Al(OH)_3$ with citric acid i.g.	5320	5.08 (wet weight) 32 (dry weight) [1.6]	
	$^{26}AlCl_3$ s.c. injection	48	0.2% of dose	Yumoto et al. (2000)
	$^{26}AlCl_3$ s.c. injection	48	0.29% of dose	Yumoto et al. (2001)
Guinea pig				
47	Purina Guinea Pig Chow 5025		0.1, 0.09, and 0.13 on GD 30 and 45 and PND 0	Golub et al. (1996)
Human				
			1.51 (dry weight)	Ward et al. (1987)
			0.56 (dry weight, placental body)	Kruger et al. (2010)
			0.53 (dry weight, placental membrane)	
			0.88 (dry weight)	Pi et al. (2019)

The maternal diet Al concentration is from the cited report or based on the assumption that the diet contained 100 mg Al/kg, as described in the text. When reported, it enabled the approximate total systemic exposure, calculated as described in the text, and for studies citied in Tables 3 and 4. For studies reporting the placental Al concentration on a wet weight basis, the concentration on a dry weight basis was calculated using a placenta dry/wet weight ratio of 0.16, based on (Husain et al. 2001).

[a]Results that are statistically significantly different from controls.

the additional daily Al systemic exposure of studies that reported statistically significant results in females was greater than 100-fold above the typical human daily Al consumption equivalent. Three studies that were GLP compliant and followed an OECD Test Guideline studied both females and males, delivering similar or lower Al exposures to the males. In contrast to the lack of significant toxicity in females, significant toxicity was seen after the highest exposure in males in two of the studies. Many other studies found significant effects after exposures comparable to the highest exposure in males in two of the studies, suggesting male rodents are more susceptible to Al-induced reproductive toxicity than females. Increased Al intake increases fetus, placenta, and testes Al concentration, to a greater extent in the placenta than fetus, and perhaps to a greater extent in the testes than placenta. One human study showing reduction in normal and mobile sperm and positive correlations between high spermatozoa Al concentration and decreased sperm motility and

Table 10. Al concentration in male reproductive organs and fluids.

	Additional Al exposure			
Diet Al concentration (mg/kg)	Al species and route	Approximate added total systemic Al exposure (μg/kg)	Al concentration (μg/g) [as multiple of no added Al][a]	Reference
Testes mouse				
	Panlab	800 from the diet over 20 days assuming it contained 100 mg Al/kg	0.10 (wet weight)	Llobet et al. (1995)
	$Al(NO_3)_3·9H_2O$ i.p.	72,000	0.92[a] (wet weight) [9.2]	
		144,000	1.19[a] (wet weight) [12]	
		288,000	1.47[a] (wet weight) [15]	
370	Purina 5001 rodent chow	1776 over 12 days	5.1[c]	Guo et al. (2001)
	$AlCl_3$ i.p.	156,000	77[a] 1 day after injections [15]	
		208,000	141[a] 1 day after injections [28]	
370	Purina 5001 rodent chow	2368 over 16 days	5.7	
	$AlCl_3$ i.p.	420,000	32[a] 15 days after injections [5.6]	
		560,000	59[a] 15 days after injections [10]	
370	Purina 5001 rodent chow	2072 over 14 days	5[c]	Guo et al. (2002)
	$AlCl_3$ i.p.	98,000	62[a] [12]	
		490,000	120 [24]	
370	Assume Purina 5001 rodent chow	1776 over 12 days	5[c]	Guo et al. (2005a)
	$AlCl_3$ i.p.	420,000	133[a] [27]	
370	Purina 5001 rodent chow	2072 over 14 days	5[c] 3 weeks later	Guo et al. (2005b)
	$AlCl_3$ s.c.	20,580	22[a] 3 weeks later [4.4]	
		38,220	35[a] 3 weeks later [7]	
	Purina 5001 rodent chow	2072 over 14 days	5 5 weeks later	
	$AlCl_3$ s.c.	20,580	20[a] 5 weeks later [4]	
		38,220	28[a] 5 weeks later [5.6]	
	Purina 5001 rodent chow	2072 over 14 days	5 11 weeks later	
	$AlCl_3$ s.c.	20,580	8[a] 11 weeks later [1.6]	
		38,220	11[a] 11 weeks later [2.2]	
370	Purina 5001 rodent chow	2072 over 14 days	7.7[c]	Guo et al. (2006)
	$AlCl_3$ s.c.	20,580	40[a] [5.2]	
		102,900	130[a] [17]	
370	Purina 5001 rodent chow	2072 over 14 days	5.1[c]	Guo et al. (2009)
	$AlCl_3$ i.p.	98,000	37[a] [7.2]	
		490,000	120[a] [24]	
		1200 from the diet over 30 days assuming it contained 100 mg Al/kg	0.55 (wet weight)	Kumar and Singh (2016)
	$AlCl_3$ i.g.	303	0.90 (wet weight) [1.6]	
		606	1.1 (wet weight) [2]	
		1212	2.4[a] (wet weight) [4.4]	
Testes rat				
170	Larsen diet	952 from the diet for 28 days	1.7 (wet weight)	Ondreička et al. (1966)
	Al sulfate in the diet	15876 from the diet for 28 days	[2.8]	
27.9	AIN-76 diet	11 daily	0.61 (wet weight)	Que Hee and Boyle (1988)
		560 from the diet over 28 days assuming it contained 100 mg Al/kg	1 (dry weight)	Julka et al. (1996)
		300,000 as one injection	198[a] (dry weight) [198]	
		280,000 as 28 injections	126[a] (dry weight) [126]	
	Panlab	3690 from the diet over 6.5 months assuming it contained 100 mg Al/kg	< 0.001 (wet weight) 3-weeks old	Gomez et al. (1997)
	$Al(NO_3)_3·9H_2O$ with citric acid i.g.	39600	0.41[a] (wet weight) 3-weeks old [410]	
		79200	0.58[a] (wet weight) 3-weeks old [580]	
	Panlab	3690 from the diet over 6.5 months assuming it contained 100 mg Al/kg	0.99 (wet weight) 8-months old	
	$Al(NO_3)_3·9H_2O$ with citric acid i.g.	39600	0.82[a] (wet weight) 8-months old [0.83]	
		79200	0.85[a] (wet weight) 8-months old [0.86]	
	Panlab	3690 from the diet over 6.5 months assuming it contained 100 mg Al/kg	0.42 (wet weight) 16-months old	
	$Al(NO_3)_3·9H_2O$ with citric acid i.g.	39600	0.51 16-months old [1.2]	
		79200	4.2[a] 16-months old [10]	
		3650 from the diet over 6 months assuming it contained 100 mg Al/kg	0.015[b,c]	Hichem et al. (2013)
	$AlCl_3$ i.g.	7373 over 6 months	0.016 [1.1]	
		14,746 over 6 months	0.021 [1.4]	

(*continued*)

Table 10. Continued.

	Additional Al exposure			
Diet Al concentration (mg/kg)	Al species and route	Approximate added total systemic Al exposure (μg/kg)	Al concentration (μg/g) [as multiple of no added Al][a]	Reference
		22,119 over 6 months	0.026[a] [1.7]	
		7300 from the diet over 12 months assuming it contained 100 mg Al/kg	0.011 [0.73]	
	$AlCl_3$ i.g.	14,746 over 12 months	0.018[a] [1.2]	
		29,492 over 12 months	0.029[a] [1.9]	
		44,238 over 12 months	0.031[a] [2.1]	
		10,950 from the diet over 18 months assuming it contained 100 mg Al/kg	0.028	
	$AlCl_3$ i.g.	29,492 over 18 months	0.043[a] [1.5]	
		58,984 over 18 months	0.085[a] [3.0]	
		88,476 over 18 months	0.03 [1.1]	
		2400 from the diet over 120 days assuming it contained 100 mg Al/kg	6.6	Zhu et al. (2014)
	$AlCl_3$ i.g.	3103	8.8 [1.3]	
		6205	13.5[a] [2.0]	
		12,459	19.5[a] [3.0]	
		1400 from the diet over 10 weeks assuming it contained 100 mg Al/kg	13.7 (wet weight)	Mohammad et al. (2015)
	$AlCl_3 \cdot 6H_2O$ i.g.	547	37.9 (wet weight) [2.8]	
		900 from the diet over 45 days assuming it contained 100 mg Al/kg	0.18[d] (wet weight)	Rawi and Al Nassr (2015)
	$Al_2(SO_4)_3$ i.g.	711	1.2[a] (wet weight) [6.7]	
		600 from the diet over 30 days assuming it contained 100 mg Al/kg	2.9[e] (wet weight)	Akay et al. (2016)
	$AlCl_3 \cdot 6H_2O$ i.g.	518	6.1[e] (wet weight) [2.1]	
		1200 from the diet over 60 days assuming it contained 100 mg Al/kg	1.79 (dry weight)	Martinez et al. (2017)
	$AlCl_3 \cdot 6H_2O$ i.g.	996	3.35[a] (dry weight) [1.9]	
Testes rabbit				
	Purina rabbit chow	2440 from the diet over 20 days	0.3 (dry weight)	Melograna and Yokel (1984)
	Al chloride s.c.	68,000	19[a] (dry weight) [63]	
	Wayne rabbit food	15 from the diet over 28 days	0.12 (wet weight)	Du Val
	Al chloride s.c.	14,818	1.8[a] (wet weight) [15]	et al. (1986)
	Purina rabbit chow	122 daily	3.9 (dry weight)	Yokel and
	Al lactate i.v. once	5400	No significant change	McNamara (1989)
	Al lactate 20 i.v. injections	54,000	39	Yokel et al. (1996)
	Al citrate 20 i.v. injections	54,000	4.0	
Testes human				
			4.2 [c]	Yamamoto et al. (1959)
Prostate human				
			3.6 [c]	Yamamoto et al. (1959)
Epididymis mouse				
370	Purina 5001 rodent chow	2072 from the diet over 14 days	12 [c]	Guo et al. (2006)
	$AlCl_3$ i.p.	20,580	25 [2.1]	
		102,900	52[a] [4.3]	
Epididymis rat				
		1200 from the diet over 60 days assuming it contained 100 mg Al/kg	6.4 (dry weight)	Martinez et al. (2017)
	$AlCl_3 \cdot 6H_2O$ i.g.	996	6.1 (dry weight) [0.95]	
Epididymis human				
			5.0[c]	Yamamoto et al. (1959)
Seminal vesicle human				
			2.5[c]	Yamamoto et al. (1959)
Seminal fluid human				
			3.3[c]	Yamamoto et al. (1959)
	Apparently healthy 21- to 35-year olds		18 μg/L > 50% sperm viability	Dawson
			59 μg/L 25–50% sperm viability	et al. (1998)

(*continued*)

Table 10. Continued.

Diet Al concentration (mg/kg)	Additional Al exposure: Al species and route	Additional Al exposure: Approximate added total systemic Al exposure (μg/kg)	Al concentration (μg/g) [as multiple of no added Al][a]	Reference
			101 μg/L < 25% sperm viability	
			0.87 sperm donor candidates	Hovatta et al. (1998)
			0.54 refinery and polyolefin factory employees	
			460 μg/L medical center (control) work environment	Dawson et al. (2000)
			2200 μg/L metal ore smelter work environment	
			1530 μg/L petroleum refinery work environment	
			270 μg/L chemical plant work environment	
			299 μg/L normal semen	Klein et al. (2014)
			385 μg/L semen with pathology	
Spermatozoa human				
			2.52 sperm donor candidates	Hovatta et al. (1998)
			0.93[a] refinery and polyolefin factory employees	

A dry/wet weight ratio for rat testis of 0.78 was used (Takhtfooladi et al. 2015).
[a]Results that are statistically significantly different from controls.
[b]Unknown units.
[c]Not known if reported as wet or (dry weight).
[d]Reported as mg/g; assumed to be μg/g.
[e]Reported as ng/g; assumed to be μg/g.

normal morphology suggest the rodent studies are predictive of human outcomes.

Recommendations

Studies to further define the potential for Al to produce reproductive toxicity in animals should include the following design parameters. Female exposure should be long-term, at least starting from sexual maturity and preferably from weaning. Male exposure duration should be at least as long as the time course of spermatogenesis. Studies should utilize a diet containing a known Al concentration that is comparable to that consumed by humans. An exposure route of known Al bioavailability, probably oral to be relevant to the human, should be used. An Al species that is human relevant should be used. An example might be a diet to which FDA-approved food additives have been added at known concentrations. Given the most sensitive endpoint to Al-induced toxicity in the pregnant female rodent was resorption; in the fetus, death; and in males, sperm number, sperm SOD, and abnormal sperm, these endpoints should be included in the study. Studies verifying the contribution of oxidative stress, and/or other molecular initiating events, and the key event relationships, mediating Al-induced reproductive toxicity are needed to advance understanding of the AOP proposed here.

Due to concerns about potential Al toxicity, controlled-exposure human studies, particularly including high exposure, create ethical concerns (Molloy et al. 2007). However, there are humans exposed to higher Al intake than most people who could serve as epidemiological study subjects. Aluminum welding results in release of airborne Al, higher exposure, and persistent elevated Al body burden (Elinder et al. 1991). Dietary studies have identified some foods high in Al, particularly those containing Al as a food additive, such as baked goods including Chinese fried bread and salted jellyfish, that could identify highly exposed subjects worth studying. Large volume, prolonged, consumption of Al-containing antacids/phosphate binders presents another study opportunity. For reasons noted above, those with prolonged, high, Al exposure are of greatest potential value in future studies.

Notes

1. Benett et al. (1975), Dixon et al. (1979), McCormack et al. (1979), Katz et al. (1984), Wide (1984), Cranmer et al. (1986), Hicks et al. (1987), Bernuzzi et al. (1989), Muller et al. (1990), Roy et al. (1991), Misawa and Shigeta (1992), Muller et al. (1993), Agarwal et al. (1996), Gonda et al. (1996), Gonda and Lehotzky (1996), Gonda et al. (1997), Albina et al. (1999), Guo et al. (2005b, 2006287), Beekhuijzen (2007), Wise et al. (2008), Guo et al. (2009), Hala et al. (2010), Wise et al. (2010), Segal et al. (2011), Abu-Taweel et al. (2012), Ighodaro et al. (2012), Yadav et al. (2013), D'Souza et al. (2014), Kalaiselvi et al. (2014), Ramalingam et al. (2014), Akinola et al. (2016), Falana et al. (2017), Miska-Schramm et al. (2017), Inohana et al. (2018), Mouro et al. (2018), and Gomes et al. (2019).
2. For the calculation of the approximate systemic Al exposure from rabbit diet consumption of 5% of body weight daily was assumed http://agritech.tnau.ac.in/animal_husbandry/animhus_rabbit%20feeding.html, https://www.purinamills.com/rabbit-food/products/detail/purina-fibre3-rabbit-feed. Daily water intake for guinea pigs was assumed to be 0.15 l/kg. When necessary to estimate Sprague Dawley rat body weight, Taconic Biosciences I. (2020)_. Sprague Dawley® Outbred. was used.
3. Asterisks indicate data obtained from the abstract. The full report was not obtained.

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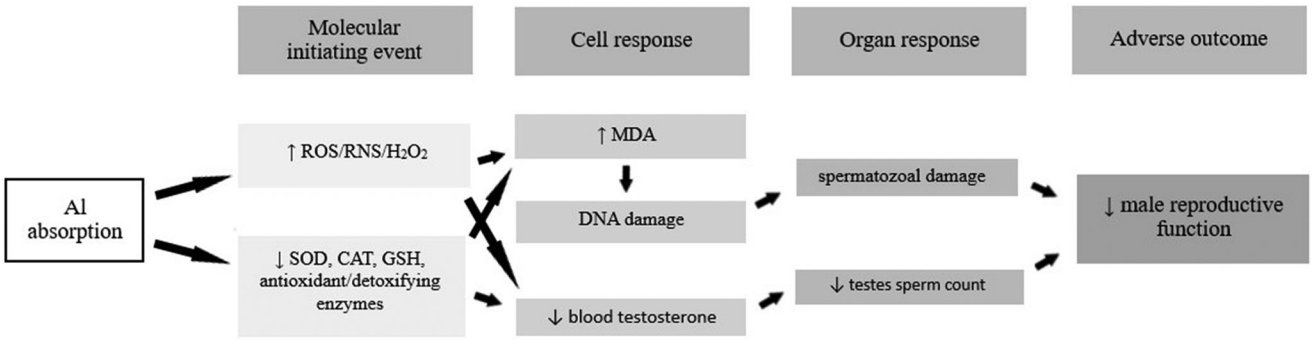

Figure 1. Adverse outcomes pathways for Al-induced reproductive toxicity in males.

Krewski, McLaughlin Centre for Population Health Risk Assessment, University of Ottawa. Your corrections, questions, and suggestions improved this review. Thank you!

Declaration of interest

The author is serving as a consultant for the Division of Vaccine Injury Compensation, Health Resources and Services Administration regarding aluminum and primary ovarian insufficiency.

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