Aluminium, Dusts containing aluminium as metal, aluminium oxide and aluminium hydroxide[1)]

Aluminium metal	7429-90-50
Aluminium oxide	1344-28-1
Aluminium hydroxide	21645-51-2
MAK value (1997)	**4 mg/m³ I (inhalable fraction) 1.5 mg/m³ R (respirable fraction)**
Peak limitation (1997)	**see Sections Vf) and Vg) of the *List of MAK and BAT Values***
Absorption through the skin	**–**
Sensitization	**–**
Carcinogenicity	**–**
Prenatal toxicity (2006)	**Pregnancy Risk Group D**
Germ cell mutagenicity	**–**
BAT value (1989)	**200 µg aluminium/l urine /(revised in 2009 to 60 µg Aluminium/g Creatinine** documentation BAT Aluminium, Addendum, 2009**,** in German)

Since the documentation from 1986 (appeared in German) (documentation "Aluminium" 1991), numerous studies about dusts containing aluminium, aluminium oxide and aluminium hydroxide have been published which make a new assessment necessary.

1) Except for ultrafine particles and aluminium oxide fibres (monocrystalline and polycrystalline). Co-exposures to ozone or quartz should be assessed additionally in a number of work areas such as aluminium welding or the production of corundum.

The MAK-Collection Part I, MAK Value Documentations 2013
DFG, Deutsche Forschungsgemeinschaft

Exposure

Exposure of the general population

Because of its strong affinity to oxygen, aluminium is usually covered by an oxide layer. In the pH range between 4.5 and 8.5 this protective layer is to a great extent insoluble. Therefore, at workplaces there is no primary contact with metallic aluminium.

The aluminium concentration in the environmental air is 0.05 to 0.5 µg/m³ in areas with no emission, 0.5 to 4 µg/m³ in urban areas, and 4 to 15 µg/m³ near an aluminium emission source (Wilhelm 1994).

Aluminium is found at various concentrations in a multiplicity of foods. In Germany, foods of plant origin have a higher aluminium content than animal foods (on average 5.4 mg aluminium/kg wet weight compared with about 1.7 mg aluminium/kg). Aluminium can accumulate in spices and tea leaves (Wilhelm 1994). As a result of the preparation and storage of foods and drinks containing acids or salts in containers made with aluminium, some of the aluminium can enter the food depending on the length of contact (Lindner 1990, Schmidt and Grunow 1991).The concentration of aluminium in surface, ground and drinking water depends, among other things, on geological factors and on the pH of the water, and increases with pH of less than 5 (Greger 1992). The German Drinking Water Ordinance (Trinkwasserverordnung) at present stipulates a threshold value for the aluminium content in drinking water of 200 µg/l. However, the aluminium content of acidic well water is above this value in many regions of Germany. Values of up to 20 000 µg/l have been found (Wilhelm 1994). Aluminium salts are used to clean drinking water. When used correctly, there is no significant increase in the aluminium content of the water.

Many pharmaceuticals contain aluminium or aluminium compounds; antacids containing aluminium hydroxide have the highest aluminium content.

Exposition at the workplace

Exposure to dusts containing aluminium, aluminium oxides or hydroxides is to be expected in the metal industry (during welding, grinding and polishing in aluminium powder production or processing), in foundries (during smelting, casting, cleaning, blasting) and in plants processing or treating the corresponding materials (during blasting work on metals or corundum or while coating surfaces).

Since the 1970s, the German Social Accident Insurance- the DGUV (Berufsgenossenschaften), have been recording exposure data in various work areas. Evaluation of the data available in the MEGA[2)] documentation of the BGIA[3)] shows that

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2) Messdaten zur Exposition gegenüber Gefahrstoffen am Arbeitsplatz (in English: "Measurement data relating to workplace exposure to hazardous substances")

3) Berufsgenossenschaftliche Institut für Arbeitsschutz (Institute for Occupational Safety and Health of the German Social Accident Insurance (DGUV) (IFA)

Table 1 The dust concentration and amount of aluminium contained in it in the metal industry and in foundries

Time period	Number of determinations	Number of industrial plants	Dust fraction [mg/m³]		Aluminium [mg/m³]	
			50% value	90% value	50% value	90% value
R fraction						
1981–1991	151	54	0.60	2.37	0.01	0.13
1992–1999	449	170	0.47	2.76	0.03	0.45
I fraction						
1981–1986	11	6	3.57	14.96	0.09	2.45
1997–2000	22	13	1.50	8.84	0.08	2.08

R fraction = respirable dust, I fraction = inhalable dust

in the metal industry and foundries there are two time periods for exposure to dusts containing aluminium in the respirable (R) and inhalable (I) fractions (Table 1).

Before 1981 exposure data was not differentiated according to shift-related data or special or short-term measurement factors. Approximately 3% of the values determined were above 4 mg/m³ (guideline value). In relation to the average shift-value, this value would be expected to be lower (Table 1). Values above 4 mg/m³ occurred in the respirable (R) and inhalable (I) fractions and were not specific to any particular workplace.

A work area-related evaluation of the exposure to respirable dust in the metal industry and in foundries is shown in Table 2.

Table 2 Shift-related concentrations of respirable dust (R fraction) and the aluminium contained in it in the metal industry and in foundries

Work area	Number of determinations	Number of plants	R fraction [mg/m³]		Aluminium [mg/m³]	
			50% value	90% value	50% value	90% value
foundries	251	95	0.53	1.59	0.01	0.11
grinding	106	53	0.37	1.36	0.03	0.19
polishing	22	14	0.24	1.18	0.05	0.38
tungsten IGW	13	12	0.15	1.49	0.02	0.08
metal IGW	50	18	1.39	16.26	0.19	1.76
metal AGW	18	6	2.28	8.15	0.26	1.10

IGW = inert gas welding, AGW = active gas welding

The exposure data determined during inert gas and active gas metal welding are markedly above the exposure levels in the other work areas. During the inert gas welding of components containing aluminium, in addition to the welding fumes containing aluminium ozone is formed depending on the conditions of the process engineering (Spiegel-Ciobanu 1999). The formation of ozone is particularly increased by UV radiation and the highly reflective surface of the workpieces. In addition, the welding fume aerosols produced during inert gas welding of the aluminium alloys contain ultrafine particles with an individual particle diameter of less than 100 nm (Rödelsperger et al. 2000; Spiegel-Ciobanu 1999).

As regards the exposure situation, aluminium powder production is a special case. Here, depending on later use, leaf-shaped aluminium flakes and spherical aluminium granules are produced. The average particle diameters are requirement-based and are, according to the manufacturer's details, between 10 and 50 µm for aluminium flakes and between 6 and 150 µm for aluminium granules. The amount of aluminium contained in these dusts is on average 75% higher than that in other work areas.

Thirty-seven shift-related exposure analyses carried out by the respective (BG) institution in various areas of the aluminium powder industry (two plants, some before and some after technical improvements), revealed 50% and 90% values of 1.0 and 6.9 mg/m^3 for the respirable dust. No significant differences were found on assignment of the data to two work area groups (drop work/stamping/pounding mill/grate/sieve processing and decanting/transfer/weighing/packing). The highest exposure values for respirable dust, which were between around 4 and 8.6 mg/m^3, were determined because of ineffective exhaust systems or open air filling and refilling processes, and occurred in the stamping and pounding mills, sieving units and filling and refilling areas. Corresponding technical improvements reduced exposure to generally below 1 mg/m^3 (MEGA documentation of the BGIA 2006).

Analytical procedures

To monitor adherence to the proposed threshold values in air, the concentrations of the respirable and the inhalable fraction must be determined. The exposure can be determined either by stationary devices or dust sampling units worn by the individual. Details can be found in BGIA Work Folder No. 7490.

Should it be specifically required, the aluminium content in dusts can be determined after acid digestion, for example by atomic absorption spectrometry (AAS) and inductively-coupled plasma atomic emission spectroscopy (ICP-AES) or by mass spectroscopy (MS). There are procedural guidelines available from the American Occupational Safety and Health Administration, the American National Institute for Occupational Safety and Health and the Berufsgenossenschaften. With these frequently used analytical procedures, it is not possible to differentiate between aluminium and the various aluminium compounds. The analytical results

always refer to the total content of aluminium in the collected dust. However, this allows worst-case estimates to be made for specific compounds via stoichiometric conversions. The identification or differentiation of crystalline aluminium compounds can be performed qualitatively using X-ray diffraction. At present, there are no established analytical procedures with which the content of a specific aluminium compound can be determined quantitatively.

1 Toxic Effects and Mode of Action

Aluminium compounds are taken up orally and by inhalation. Dermal absorption is not known.

Aluminium compounds can accumulate in the lungs and impair lung clearance. The disease is known as aluminosis, and is characterized by diffuse interstitial fibrosis, which usually develops in the upper and central lobes of the lung. In its advanced stage, aluminosis is characterized by subpleural emphysema bleb and there is a danger of pneumothorax occurring.

After long-term exposure to aluminium, also impairment and disease of the central nervous system are observed.

Oral doses of 162 mg/kg body weight are acutely toxic in rats and mice.

Aluminium and its compounds have no irritative effects on the skin and eyes. Aluminium compounds are not sensitizing.

No fertility disorders occurred in male mice after oral administration of soluble aluminium salts. In male mice and rabbits, testicular weights were lower at doses which produced a decrease in body weights.

No developmental toxicity was observed after oral administration of aluminium hydroxide. Soluble aluminium salts, which have a markedly higher bioavailability, led to a reduction in foetal weights, delayed ossification, increased formation of cleft palates and dorsal hyperkyphosis at maternally toxic doses.

In prenatal and postnatal developmental toxicity studies with soluble aluminium salts, effects on the behaviour of the offspring were observed which usually occurred together with delayed body weight gains.

There is evidence of genotoxic effects of aluminium salts *in vitro*. An increase in the frequency of micronuclei, sister chromatid exchange and chromosomal aberrations was found. Aluminium salts can bind to isolated DNA.

In mice, aluminium sulfate increased the frequency of sister chromatid exchange (at 200 mg/kg body weight and above) and micronuclei (at 500 mg/kg body weight), and aluminium sulfate and potassium-aluminium sulfate were found to be clastogenic in rats at the cytotoxic doses of 530 and 764 mg/kg body weight. Aluminium is not carcinogenic in mice.

2 Mechanism of Action

Because of the low solubility of dusts containing aluminium, aluminium oxide and aluminium hydroxide, dust particles can accumulate in the lungs and lead to impairment of the clearance function. Dust particles can cause inflammatory processes in the surrounding tissue and can induce fibrosis (see also documentation for a "General Threshold Limit for Dust" 1999, a translation of the German from 1997).

No conclusive assessment can yet be made about the molecular mechanisms underlying the neurotoxic effects. *In vitro* investigations with neuronal cell cultures indicate that aluminium induces an increase in the intracellular calcium level and in reactive oxygen species (Mundy et al. 1997), and impairs the glutamate–nitric oxide–cyclic guanosine monophosphate (cGMP) pathway (Hermenegildo et al. 1999). *In vivo* investigations have confirmed these results.

The increased expression of neuronal nitric oxide synthetase caused by aluminium chloride was found in the sensomotor and cerebral cortex of female Fischer 344 rats (Kim 2003). In the brain, repeated aluminium treatment stimulated the formation of inducible nitric oxide synthase (iNOS). There was no interaction with iron (Bondy et al. 1998). Other investigations showed there to be an increase in lipid peroxidation in the brain after long-term exposure of young rats to aluminium L-glutamate. There were no changes in polyunsaturated fatty acids. In rats exposed to aluminium for 4 weeks, the biological effectiveness of the calcium-regulated proteins calmodulin and protein kinase C was affected (Julka and Gill 1996).

The aluminium-induced interaction with microtubuli-associated proteins is also important. Aluminium promoted tubulin polymerization via stabilization of the hyperphosphorylated T-protein and simultaneous aggregation of the neurofilaments (Yokel 2000).

The chromosome aberration types found in *in vitro* studies indicate both aneugenic effects and DNA damage (Migliori et al. 1999). According to data from isolated systems and lymphocyte cultures, there are mainly two mechanisms of action involved in aluminium-induced genotoxicity. These are, on the one hand, interaction with the phosphate groups of DNA and subsequent structural changes to the DNA and, on the other hand, interaction with the microtubules, resulting in aneugenic effects (Latha et al. 2002; Roy et al. 1991). Also precipitation and an increased nuclease resistance has been observed in chromatin isolated from rat liver and brain in the presence of aluminium chloride at pH 8 (Walker et al. 1989). The structural DNA changes can result in DNA strand breaks and chromosomal aberrations.

This interpretation is supported by the fact that aluminium has a marked influence on the functionality of the microtubules (see above). Also the neurotoxic effects are attributed to the effects on the microtubules (Kawahara et al. 2003). The increase in the number of micronuclei in the G0/G1 phase detected in lymphocytes cannot be attributed to interaction with microtubules. Suggested reasons for this are the increased formation of reactive oxygen species and the greater

permeability of lysosomal membranes and resulting release of DNases. The increase in the frequency of apoptosis occurring in parallel with these processes indicates that the development of micronuclei can be attributed also to toxic effects (Banasik et al. 2005).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution, elimination

Aluminium can be absorbed by inhalation and orally. There is no evidence of dermal absorption of aluminium (Alfrey 1997).

Absorption

Inhalation

In humans: Absorption by inhalation in the general population not occupationally exposed to aluminium is low. Depending on the individual exposure conditions, between 0.01 and 0.2 mg aluminium is inhaled per day (respiratory volume 20 m^3/day; aluminium concentration 0.5 to 10 µg/m^3 air), which generally corresponds to less than 5% of the total intake (Wilhelm 1994). In contrast, at the workplace, the level of exposure can be considerable and in some cases lead to a high body burden (Dehm et al. 1996; Elinder et al. 1991; Hänninen et al. 1994; Kraus et al. 1997, 1998; Letzel 1994; Letzel et al. 1996 a, b, 1999 a, b, 2006; Ljunggren et al. 1991; Röllin et al. 1991 a; Schlatter and Steinegger 1991; Sjögren et al. 1988, 1996 b). Improvements in industrial hygiene have reduced the amount of aluminium inhaled at many workplaces (Letzel et al. 1999 a, b).

According to calculations, about 1.9% of a quantity of aluminium initially deposited in the lungs was systemically available. This also agreed with the values for aluminium absorption of about 1.5% to 2% calculated for workers in the aluminium industry (Priest 2004).

After inhalation exposure of two volunteers to ^{26}Al aluminium oxide particles (aerodynamic diameter 1.2 µm), the absorbed 16 and 6 becquerels were reduced to 4 becquerels within a short period as the result of mechanical clearance (no other details). No aluminium was detected in the urine 900 days after exposure. Determination of the aluminium concentrations in lungs and urine revealed that the aluminium oxide particles deposited in the lungs were removed mainly by mechanical means (Priest 2004).

In animals: In groups of eight rabbits exposed to aluminium oxide dust (aluminium concentrations of 0.56 ± 0.17 mg/m^3) for five months (8 hours per day, 5 days per week) by inhalation, the serum aluminium concentration was increased

compared with that in animals not exposed (from about 0.2 µg/l to a maximum of 0.45 µg/l) (Röllin et al. 1991 b).

Ingestion

In humans: After two male volunteers were administered ^{26}Al-labelled aluminium compounds via a stomach tube, the aluminium concentrations in the urine, faeces and blood were determined for up to five days after administration. 0.5% of the administered dose was bioavailable after the administration of ^{26}Al aluminium citrate, 0.01% after administration of ^{26}Al aluminium hydroxide and 0.1% after ^{26}Al aluminium hydroxide in combination with citrate. In other investigations, bioavailability was 0.1% to 0.36% of the administered dose (Priest 2004). Depending on the prevailing peripheral conditions, less than 1 of the ingested aluminium contained in antacids was absorbed from the intestinal tract (Forth 1988).

In animals: After oral administration of ^{26}Al-labelled aluminium hydroxide, aluminium citrate, aluminium citrate plus sodium citrate or aluminium maltolate 0.1%, 0.7%, 5.1% and 0.1% of the administered dose was systemically available in rats. This was 0.8 % in the case of aluminium chloride (Priest 2004).

In rats 0.3% of the aluminium was absorbed from drinking water (Priest 2004), this is analogous to the data for humans.

Dermal absorption

Transdermal absorption of aluminium can occur after the use of a deodorant containing aluminium if the skin was damaged during shaving. In two volunteers, absorption of 0.012% was found after the application of aluminium chloride (Priest 2004).

Distribution

In humans: After absorption, aluminium is evenly distributed between the plasma and the cellular blood components, and binds preferably to low molecular species, to citrate, albumin or transferrin (Wilhelm 1994). In the plasma, 80% to 94% of the aluminium is bound to transferrin. The rest is found in the form of aluminium complexes with carboxylic acids, phosphate and amino acids (Priest 2004).

One hour after intravenous injection of ^{26}Al-labelled aluminium citrate, 99% of the administered dose was found in the plasma of one volunteer. Of this, 95 % was bound to proteins and 80% of this to transferrin, 10% to albumin and 5% to low molecular weight proteins. 880 days after the injection, 88% was still detectable in the plasma. The rest was associated with erythrocytes (Priest 2004).

Aluminium could be detected in practically all organs of the human organism (Hornstein 1988). A reference value for aluminium in the urine of < 15 µg/l was given by the Human Biomonitoring Commission (Bundesgesundheitsblatt 1998)

for persons not occupationally exposed. The values in whole blood and serum correlated well with each other. The reference value for serum aluminium was < 5 µg/l. As, however, contamination during sample taking and preparation cannot be excluded even when special care is taken, it can be assumed that the actual values may have been below the detection limit of atomic absorption spectrometry of < 1 µg/l (Bundesgesundheitsblatt 1998). In the population not occupationally exposed to aluminium, the total body burden to be expected in persons without impairment of the kidneys is in the range of about 35 to 40 mg per person (Alfrey 1989). Patients with chronic renal failure taking medication containing aluminium perorally or parenterally in doses of 1 to 3 g per day were found to have, in addition to increased aluminium concentrations in the blood, increased aluminium levels in the brain (Alfrey et al. 1976; Galassi et al. 1995; Roy et al. 1991) and in bone tissue (Drezner 1989). The aluminium concentrations determined by atomic absorption spectrometry were higher than those found in controls by a factor of 4 to 40 (Reusche et al. 1994). The findings indicate impairment in the permeability of the blood/brain barrier.

Inhaled aluminium is deposited, depending on size of the particles, first in the lungs and, from there, is continuously released into the organism. As it is released only slowly, accumulation in the lungs is possible. High concentrations (no other details) of aluminium and aluminium oxide were determined in the bronchoalveolar lavage fluid, lung tissue and lymph nodes of a metal polisher who had processed workpieces containing aluminium, and in whom lung fibrosis occurred five years after the end of exposure (De Vuyst et al. 1986). In one worker employed for many years as an aluminium welder, markedly increased aluminium concentrations were found in the lung tissue (608 to 2089 µg/g wet weight; normal range 2.6 to 7.7 µg/g wet weight) (Letzel 2006). Aluminium concentrations of 259 µg/l in the liquor (normal value < 10 µg/l) of patients with dementia who had been occupied in the aluminium powder industry for a long period (Sjögren et al. 1996 a) could not be confirmed after renewed investigation and were, in the authors' opinion, caused by contamination (Sjögren et al. 1999).

Whether there is a correlation between the aluminium concentrations in plasma and urine is a subject of some controversy (Kraus et al. 1997; Letzel 1994; Letzel et al. 1996 a; Schlatter and Steinegger 1991). In persons with high long-term exposure employed in the production of aluminium powder (Kraus et al. 1997; Letzel 1994; Letzel et al. 1996 a) and in some aluminium welders (Letzel et al. 2006; Rossbach et al. 2006), a linear correlation between the aluminium concentrations in urine and in plasma were, however, observed.

In the organism, aluminium was distributed as follows: skeleton (54%), muscles (14%), skin (13%), fatty tissue (5%), blood and vessels (4%), connective tissue (3%), liver (3%), gastrointestinal tract (2%) and central nervous system (1%) (Hornstein 1988; Priest 2004).

A high aluminium concentration in the liver, but not in the bones, of a stonemason was explained by the transport of macrophages via the lymphatic tract into

the liver. The aluminium concentration in the lungs was about 2000 mg/kg (Priest 2004).

In animals: In rabbits, in addition to a slight increase in the serum aluminium concentration (see above) compared with that in controls not exposed, increases in the aluminium concentrations in the lungs, brain, heart and bones were found after inhalation of aluminium oxide dust (aluminium concentrations of about 0.5 mg/m^3, 8 hours per day, 5 days per week for 5 months). The aluminium concentrations (mean value ± standard deviation given in µg aluminium per g dry weight) increased from 1.7 ± 1.3 µg/g to 270 ± 149 µg/g in the lungs and from 4.1 ± 2.9 µg/g to 10.1 ± 4.1 µg/g in the brain, and changed from 10.7 ± 2.2 µg/g to 7.5 ± 2.7 µg/g in the heart and from 18.2 ± 5.0 µg/g to 22.2 ± 4.1 µg/g in the bones (Röllin et al. 1991 b).

Elimination

In humans and animals: In humans and animals, the aluminium absorbed is eliminated mainly with the urine. The mechanism governing aluminium elimination is at present unclear (Exley et al. 1996). Approximately 98 % of the systemically available aluminium is eliminated with the urine (Priest 2004). Healthy persons not occupationally exposed to aluminium eliminate less than 15 µg/l urine (Bundesgesundheitsblatt 1998).

In workers employed in the production of aluminium powder, aluminium concentrations of > 1000 µg/l urine and of > 80 µg/l plasma were found after inhalation of the substance (Letzel 1994; Letzel et al. 1996 a). These values were far above the reference values for the general population: < 15 µg/l urine and < 10 µg/l plasma. In aluminium welders, urinary aluminium concentrations of 500 µg/l were found in some individuals (Letzel et al. 2006; Sjögren et al. 1988; Zhou 1996).

The elimination of aluminium via the gall bladder is possible in humans and animals, but only plays a minor role (Alfrey 1997; Exley et al. 1996; Greger and Sutherland 1997).

The data for the half-life of inhaled aluminium eliminated via the kidneys vary considerably. Depending on the exposure situation and the duration of exposure, half-lives were given ranging from several hours (Pierre et al. 1995; Sjögren and Ulfvarson 1985) to weeks and even years (Elinder et al. 1991; Letzel et al. 1999 b; Ljunggren et al. 1991; Sjögren et al. 1988). In addition to considerable individual differences, the storage of aluminium in different compartments of the organism with their different elimination behaviour may possibly play a decisive part in the renal excretion kinetics (Sjögren et al. 1988). The half-life for renal excretion of aluminium seems to depend not only on individual factors, but above all on cumulative pre-exposure (Letzel et al. 1999 b).

3.2 Metabolism

There are no data available for the effects of aluminium.

4 Effects in Humans

4.1 Single exposures

Ingestion

In Cornwall, England, about 20 tons of 8% aluminium sulfate was added by mistake to the drinking water. The acute symptoms of poisoning were ulceration of the lips and oral mucosa, nausea, vomiting, diarrhoea, headaches, tiredness and skin rashes. The acute symptoms receded relatively rapidly (Edwardson 1992). In addition to the increased aluminium concentration, also increased concentrations of copper, zinc and lead in the drinking water were discussed as further causes of the complaints. In a follow-up study with 55 exposed persons, marked central-nervous impairment, particularly in the symbol digit coding test and in recording the visually evoked potentials, was found three years after the event (Altmann et al. 1999). In two persons, around 7 months later the aluminium concentrations were determined in plasma (4.6 µg/l to 15.1 µg/l and < 2 µg/l to 5.4 µg/l; normal range < 10 µg/l) and in bone tissue (5.3 µg/g and 2.5 µg/g; normal range 1.5 to 13.3 µg/g). The administration of desferrioxamine doses of 20 µg/kg body weight reduced the aluminium concentration in the urine only in one person (Eastwood et al. 1990)

In the general population, no acute effects resulting from aluminium ingested with food were observed (WHO 1997). Even an intake of 100 mg/kg body weight had no harmful effects (Weber 1990; WHO 1997).

4.2 Repeated exposures

4.2.1 Inhalation

4.2.1.1

Effects on the lungs

In the production of aluminium powder, in aluminium foundries, in welding and also in mechanical processing, for example while grinding components containing aluminium, there is high inhalative aluminium contamination. Among the work-related respiratory and lung diseases caused by aluminium, mainly aluminosis (see below) is observed in aluminium powder production and elsewhere. Other lung diseases have been described after exposure to corundum, and welding fumes and grinding dusts containing aluminium.

Aluminosis

The clinical picture of aluminosis, also termed aluminium dust-induced lung disease, is characterized by diffuse interstitial lung fibrosis, primarily manifest in the

upper and middle lobes. In advanced stages, it is characterized by subpleural bullous emphysema with an increased risk of spontaneous pneumothorax.

Internationally the viewpoint prevails that aluminosis is extinct, thanks to improvements in industrial hygiene. However in Germany, particularly in the Franconian aluminium powder industry, an increase in this disease in recent years, sometimes with very severe cases, has been observed. Radiological diagnosis of aluminosis in its early stages, which had been difficult until recently, has now become possible thanks to high-resolution computed tomography (HRCT), which has a greater sensitivity and specificity than conventional X-rays (Kraus et al. 1997, 1998, 2000, 2006). Reports of individual cases (Dehm et al. 1996; Hartung et al. 1990; Kraus et al. 2000; Letzel 1994) and epidemiological investigations of aluminosis from the aluminium powder industry are available (Kraus et al. 1997, 1998, 2000; Letzel 1994). The cases of aluminosis occurring in aluminium powder production published since 1986 are summarized in Table 3. The information provided by Kraus et al. from 1997, 1998 and 2006 has been grouped together, as this refers to the same collectives or part of a total collective. Details of the concentrations of the dusts containing aluminium in the workplace air are not given in any of these studies.

In a cross-sectional study, the data of 32 workers exposed to aluminium from the aluminium powder industry, and 30 workers not exposed from the same factory were compared. In preliminary person-related dust analyses, a maximum total dust concentration of 33.6 mg/m^3 containing 62.2% aluminium was determined. In the exposed volunteers, the current internal exposure level of aluminium was found to be between 5.1 and 25.9 µg/l plasma and 5.0 and 336.6 µg/l urine. Depending on the exposure level, the exposed group revealed lower values for the forced expiratory volume in one second (FEV_1) and for the maximum expiratory flow of 75%, 50% and 25% compared to the controls. On the basis of bifactorial variance analysis, it was demonstrated that the statistically significant differences in the FEV_1 and maximum expiratory flow of 25% were influenced more by cigarette smoking than by the exposure to aluminium (Letzel 1994).

In another cross-sectional study, 62 workers from the aluminium powder industry with high-level exposure to aluminium were investigated. The median exposure duration was 123 months, the aluminium concentration in urine was between 7.9 and 821.2 µg/g creatinine (median: 104.3 µg/g creatinine), and in plasma between 2.5 and 84.4 µg/l (median: 12.5 µg/l). In 20 volunteers, the aluminium concentration in urine was higher than 200 µg/l. No air concentrations were given (see also Table 3). Chronic bronchitis was observed in 15 volunteers, four volunteers reported shortness of breath during exercise (Kraus et al. 2006). Aluminium-related lung changes were diagnosed in 15 volunteers using HRCT (see Figure 1).

Using the aluminium concentrations determined in the urine at the time of diagnosis, the collective was divided into two groups: persons exposed to high levels of aluminium (aluminium concentration in the urine > 200 µg/l or > 200 µg/g creatinine) and persons exposed to low levels (aluminium concentration in the urine ≤ 200 µg/l or ≤ 200 µg/g creatinine). In the high exposure group, there was an

Table 3 Case descriptions of aluminosis

Number	Age (years)	Exposure duration (years)	Aluminium powder	Aluminium concentration	References
3 patients	not specified	5–26	mainly greased	not specified	Hartung et al. 1990
1 patient	about 30[1a)]	about 5	not specified	urine = 109.9 (5–33.36) µg/l plasma = 8.7 (5.1–25.9) µg/l	Letzel 1994
1 patient	about 23[1a)]	about 2.5[2)]	not specified	urine = 187.5 µg/l [4)] plasma = 9.3 µg/l [4)]	Dehm et al. 1996
5 patients	24–51[1a)]	2–10[3)]	not specified	case 1[5)]: serum: 2 µg/l urine: 3 µg/l liquor: 259 µg/l case 2[5)]: serum: 3 µg/l urine: 10 µg/l liquor: < 1 µg/l	Sjögren et al. 1996 a
1 patient	40[1b)]	14[1c)]	mainly non-greased	urine: 407.4 µg/l plasma: 41.0 µg/l	Kraus et al. 2000
total collective: 62	39* (22–65)	about 10* (1–30)	greased and non-greased	urine: 7.9–821.2 µg/g creatinine plasma: 2.5–84.4 µg/l	Kraus et al. 1997, 1998, 2006
47 not patients	39* (22–64)	about 8.5* (1–30)	greased and non-greased	urine: 7.9–805.2 µg/g creatinine plasma: 2.5–84.4 µg/1	
15 patients	42* (31–55)*	about 13* (6.5–30)	greased and non-greased	urine: 17.3–821.2 µg/g creatinine plasma: 5.7–77.0 µg/l	

* median
[1a)] age on contracting disease, [1b)] age at diagnosis, [1c)] duration of exposure before diagnosis, [2)] intermittent exposure, [3)] exposure in the 1940s, [4)] investigation 2.5 years after end of exposure, [5)] investigation 40 years after end of exposure

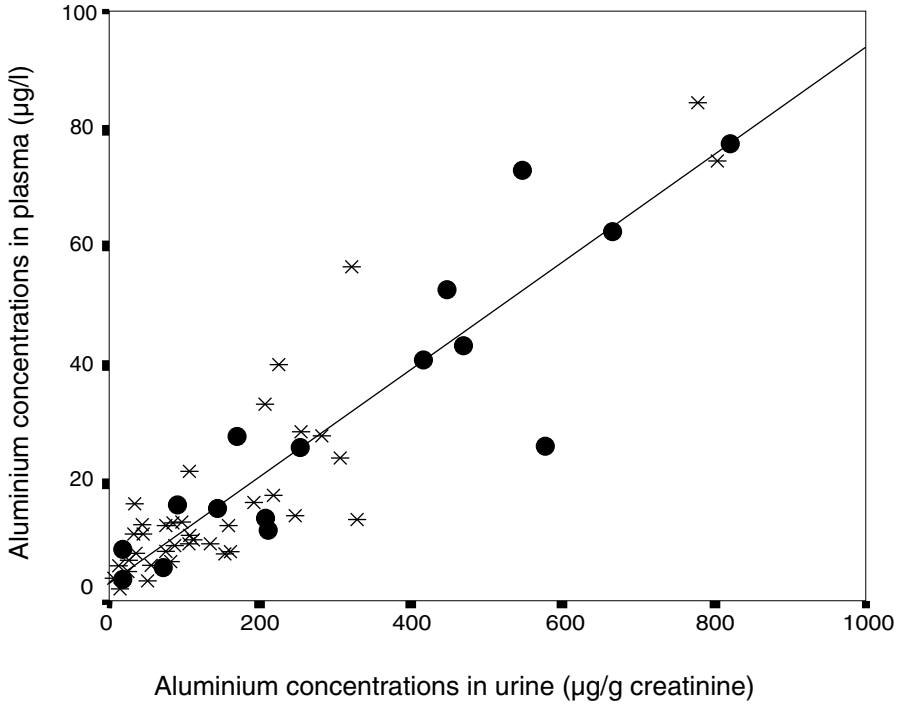

Figure 1 Aluminium concentrations in the urine and plasma of 62 workers from aluminium powder production (Kraus et al. 2006)* without diagnosed aluminosis, • with diagnosed aluminosis

increased odds ratio (OR) for aluminosis of 9.75 (95% confidence interval (CI) 2.6 to 36.3) in relation to the aluminium concentration per litre urine, and an OR of 6.6 (95% CI 1.8 to 23.3) in relation to the aluminium concentration per gram creatinine.

When interpreting the calculated risks, however, one must take into account that aluminosis is a chronic disease which takes years or decades to develop. In contrast, when calculating the odds ratios, the biomonitoring findings primarily reflect the current body burden determined at the time of diagnosis and, allow only indirect statements to be made about the exposure conditions existing in the past, by taking into account the possibility of aluminium deposits.

In 11 of 15 workers found by means of HRCT to have aluminosis, biological monitoring results were available from periods prior to diagnosis (from 1982 onwards). The maximum aluminium concentrations determined in the plasma of the persons concerned were distributed over a range of 9.8 µg/l to 183.0 µg/l (median 85.0 µg/l, mean value 84.6 µg/l). In the assessment of these initial findings obtained on a routine basis by occupational physicians, possible contamination in the pre-analytical phase cannot be excluded. Taking the occupational hygiene at the

particular workplaces and the available findings into account, it can be assumed that in persons with diagnosed aluminosis values exceeding the threshold value of 6 mg/m³ were reached at least some of the time.

In summary it can be said that the risk of contracting aluminosis depends on the level of cumulative exposure, the type of exposure and on individual factors. There seems to be a particularly high risk for persons working at stamping machines exposed to high concentrations of non-greased or barely greased, stamped aluminium powder. The data available at present, however, do not allow the evaluation of clear dose–effect relationships.

Corundum smelter's lung or Shaver's disease

It is generally believed toady that a distinction should be made between aluminosis and the form of lung disease contracted after exposure to corundum (corundum smelter's lung). Although the histological findings for corundum smelter's lung correspond to those of aluminosis, other changes are found such as those observed with silicosis (Kirchner 1968). In addition, lung tissue analyses showed increased concentrations of aluminium and free silicon dioxide (Morgan and Dinman 1989).

Nine cases of lung fibrosis were described in persons between 36 and 67 years. On average, they had been manufacturing grinding agents containing aluminium oxide (aluminium corundum) for 25 years. A lung biopsy was performed in the three worst cases. Microanalysis of the lung tissue revealed increased aluminium concentrations (9.5, 15.0 and 210.0 particles × 10^7/g dry lung tissue; reference value: 1.4 particles × 10^7/g dry lung tissue). The aluminium oxide concentrations in air given for these persons varied between 0.2 and 44.6 mg/m³. In view of these findings, exposure to aluminium oxide was considered to be the most probable cause of the fibrosis (Jederlinic et al. 1990).

In a cohort study with 106 workers between 23 and 64 years and a mean exposure duration of 15.2 years in three Brazilian factories in which bauxite and corundum was smelted and grinding agents manufactured, there were 14 workers with radiologically diagnosed lung changes. In some cases there was co-exposure to silicon dioxide. No relationship was found between the duration of exposure and the severity of the radiological findings. The publication gave no details of the levels of internal or external exposure to aluminium or silicon dioxide dust (De Capitani et al. 1992).

Diseases caused by welding fumes containing aluminium

In epidemiological studies, Nielsen et al. (1993) and Letzel et al. (2006) describe respiratory diseases occurring after exposure to welding fumes containing aluminium (see Table 4). There was no evidence of the occurrence of metal fume fever in aluminium welders (Morgan and Dinman 1989). In a cohort study, 25 aluminium welders (median duration of exposure 2.5 years, range 0.1 to 13 years) were compared with a control collective of 25 persons structurally equal as regards age and smoking habits who were not exposed to materials irritating to the airways

Table 4 Studies of exposure to welding fumes containing aluminium

Study collective	Age (years)	Duration of employment (years)	Exposure (total dust)	Biological monitoring (aluminium concentration in urine)	References
Cohort study					
25 aluminium welders	19–62	2.5* (0.1–13)	2.8 mg/m³** (0.7–19 mg/m³) ozone: < 0.01 ml/m³ ** (< 0.01–0.7 ml/m³) aluminium: 1.4 mg/m³* (0.2–6.1 mg/m³)	on Fridays: 0.29 mmol/mol creatinine* (0.08–1.1 mmol/mol creatinine) on Mondays: 0.16 mmol/mol creatinine* (0.07–0.16 mmol/mol creatinine)	Nielsen et al. 1993
25 controls	24–59	–	–	–	
Two longitudinal studies consisting of three cross-sectional studies					
101 (only 98 by the end of the study) aluminium welders in the car industry	35*1)	8.8*4) (4.8–10.9)	0.47 mg/m³** (0.1–6.17 mg/m³)1) 0.67 mg/m³** (0.2–1.5 mg/m³)** 0.55 mg/m³** (0.15–0.96 mg/m³)**	57.6 µg/l** (11.9–202.8 µg/l)**1) 52.4 µg/l** (2.4–192.5 µg/l)**2) 19.7 µg/l** (2.8–775.0 µg/l)**3)	Letzel et al. 2006
50 controls	35*1)	–	–	8.95 µg/l*** (2.8–40.20 µg/l)*** 7.30 µg/l*** (2.7–93.60 µg/l)*** 9.30 µg/l*** (0.5–95.42 µg/l)***	
31 aluminium welders in rail and special vehicle construction	40*1)	not specified	5.4 mg/m³** (0–31.5 mg/m³)**1) 5.4 mg/m³** (1.3–273.0 mg/m³)**2) 6.8 mg/m³** (1.9–29.7 mg/m³)**3)	124.50 µg/l** (28.7–653.4 µg/l)**1) 152.29 µg/l** (4.0–656.0 µg/l)**2) 117.90 µg/l** (24.7–590.2 µg/l)**3)	
27 controls	38*1)	–	–	1.32 µg/l*** (0.64–2.28)***1) 1.26 µg/l*** (0.24–2.79)***2) 1.46 µg/l*** (0.32–2.62)***3)	

*median value, **median value of the mean values of analyses before and after shift; ***median value of control collective, investigated once;
1) start of study, 2) 2 years after start of study, 3) 4 years after start of study, 4) end of study

and without known lung diseases. The aluminium welders were subdivided into two groups according to the duration of their employment in this particular job: welders exposed for a period of ≤ 2.5 years (n = 13) and of > 2.5 years (n = 12). The median aluminium concentration determined in the air at the workplace at the time of investigation was 1.4 mg/m³. In the Friday morning analyses, the median aluminium concentration in urine was 0.29 mmol/mol creatinine (35 µg/g creatinine; range 0.08 to 1.1 mmol/mol creatinine corresponding to 9.7 to 133.2 µg/g creatinine) in 19 aluminium welders. The welders with less than 2.5 years exposure had more symptoms in the lower respiratory tract than the long-term welders, which, according to the authors, indicates selection effects. In the long-term welders, however, there was evidence of significantly increased bronchial hyperreactivity (Nielsen et al. 1993).

In a longitudinal study comprising three cross-sectional studies over a period of about four years, a cohort of 101 aluminium welders (aged 23 to 51 years at the start of the study; total duration of aluminium welding at the start of the study: 7 to 118 months; 83% smokers and ex-smokers) was compared with a structurally equal control collective of 50 persons not exposed to welding fumes. The corresponding data and the aluminium concentrations at the workplace and in the urine of the workers and the controls is summarized in Table 4.

The aluminium concentrations in the workplace air of the two collectives did not differ significantly. In the first cross-sectional study, emphysemic changes of differing severity in 31.7% of the welders were the most conspicuous HRCT finding. Most (about 96%) of these persons were smokers and ex-smokers. In addition, HRCT revealed changes indicating aluminosis in one person. In the final examination (3rd cross-section) after five years, an increase in emphysemic lung changes of differing severity was found in 58.8% of the patients by means of HRCT. The authors attribute the radiological findings above all to cigarette smoking (Letzel et al. 2006). The special workplace factors, in particular the exposure to welding fumes containing aluminium or ozone could be regarded as additional influencing factors.

In another longitudinal study with observation periods of about four years, in which a cohort of 31 aluminium welders in rail and special vehicle construction was compared with a more or less structurally equal control collective of 27 persons (see Table 4), in eight persons changes were found by means of HRCT that were diagnosed as suspected aluminosis. This collective longitudinal comparison also revealed an increase in emphysemic changes in the exposed workers. Again in this study, particularly smokers and ex-smokers were affected by the lung changes. In three cross-sectional studies in the automobile industry, median values of between 0.47 and 0.67 mg/m³ and maximum values of up to 6.17 mg/m³ were determined for the inhalable dust fraction. In rail vehicle construction, median values of between 5.4 and 6.8 mg/m³ and maximum values of at least around 30 mg/m³ were found. A significant loss of participants in the longitudinal analysis made the evaluation of this study more difficult (Letzel et al. 2006).

After four years of intermittent exposure to welding fumes containing aluminium, a 32-year-old maintenance worker at a leather-making factory reacted with asthmatic complaints. Depending on the electrodes used for welding, the aluminium concentration was determined to be 0.165 or 0.813 mg/m³. In the investigations performed, an asthmatic reaction could be triggered after exposure to welding fumes containing aluminium but not, however, after exposure to the welding fumes produced when working with steel. The authors therefore concluded that the bronchial asthma was produced by welding fumes containing aluminium (Vandenplas et al. 1998).

To summarize, it can be said that in the case of aluminium welding effects occur as a result of the combination of welding fumes containing aluminium, ozone and ultrafine particles. Because of the exposure to a mixture of substances, the investigations available at present do not permit any conclusive assessment of the contribution of aluminium to the observed lung changes.

Potroom asthma

There are numerous reports of the occurrence of obstructive airway diseases in workers employed in the furnaces of aluminium smelting plants (Eklund et al. 1989; Hosovski et al. 1998; Kongerud and Soyseth 1991; Kongerud et al. 1990; Larsson et al. 1989; Samuelsen and Kongerud 1994; Sjahein et al. 2004; Soyseth and Kongerud 1992; Soyseth et al. 1994 a, b, 1997). This disease is also called potroom asthma. Exposure to aluminium or aluminium oxide could not, however, be demonstrated as being the sole cause of potroom asthma. It is the result of combined exposure, in which pathogenetically, in addition to the general exposure to dust, among other substances fluorides probably also play a toxicologically important role (Soyseth and Kongerud 1992).

Diseases from grinding dusts containing aluminium

After exposure to grinding or polishing dusts containing aluminium, fibrotic lung changes have been reported in individual cases (Akira 1995; De Vuyst et al. 1986). As no details are given of the precise exposure situation and particularly of the exposure concentration, and exposure to a mixture of substances must be taken into account, a conclusive evaluation of the health hazard from grinding or polishing dusts containing aluminium is not possible at present.

Treatment with McIntyre powder

No evidence of acute or chronic lung diseases was found after the use of powder containing aluminium as a prophylactic agent against silicosis. In Canada, between December 1943 and September 1979 miners were treated via inhalation with aluminium powder, so-called McIntyre powder, as prophylaxis against silicosis. McIntyre powder contained 15% elementary aluminium and 85% aluminium oxide (Rifat 1992; Rifat et al. 1990). The aluminium concentration administered was 35 mg/m³ and treatment lasted for 10 to 20 minutes per day (McLachlan 1992).

4.2.1.2 Effects on the central nervous system

All the neurological changes described in persons or groups exposed occupationally to aluminium affected the central nervous system. These investigations are summarized in Table 5.

There is no confirmed evidence of aluminium-induced diseases of the peripheral nervous system.

There are a number of individual case reports of central nervous changes after occupational exposure to aluminium (McLaughlin et al. 1962; Longstreth et al. 1985; Sjögren et al. 1996 a).

Aluminium powder production

A cross-sectional study included 32 workers involved in aluminium powder production. A collective of 30 employees not exposed to aluminium recruited within the company and matched for age, sex and duration of schooling was used as a control collective (Letzel 1994). After five years, a follow-up study was carried out (Letzel et al. 1999 a, 2000) in which 21 of the exposed workers and 15 of the persons not exposed participated. In both investigations, the aluminium concentrations (internally) in the exposed workers were markedly higher than those found in the controls. Significant group differences between the exposed workers and the non-exposed were not found on a group basis neither for the visually evoked potentials nor in the psychometric tests. There was no clear evidence of aluminium-induced neurological changes found after individual longitudinal comparison.

Welding fumes containing aluminium

In an investigation with 235 welders, symptoms were determined via questionnaire (Q16), 65 welders were exposed to aluminium and 217 to other metals. Compared with the other welders, aluminium welders with exposure times of 20 500 to 60 000 hours had a significantly increased risk of three or more positive responses in the questionnaire (OR 2.79; 95% CI 1.08 to 7.21) (Sjögren et al. 1990).

A number of neurophysiological tests were conducted in 17 male aluminium welders at a shipyard who had been carrying out metal inert gas welding work for a period of about four years. Although normal results were obtained in the psychometric tests, a negative association was found between the performed memory tests and the aluminium concentration in urine while a positive association was found between the extension of the reaction time and the serum aluminium concentration. In the electroencephalogram, the amount of delta and theta activity in the frontal region correlated positively and the amount of alpha activity negatively with the aluminium concentrations in serum. In the opinion of the authors, the results indicate that exposure to aluminium produces disturbances in short-term memory, learning and attention (Hänninen et al. 1994).

In another epidemiological study, 38 aluminium welders were compared with 39 welders who had reported that in their total working life they had welded high-

Table 5 Studies of the effects of occupational exposure to aluminium on the nervous system

Study collective	Age (years)	Duration of exposure (years[5])	Aluminium concentration	Findings in the nervous system	References
Aluminium powder					
Cross-sectional study					
32 workers	42.9* (26–60)	15.5* (2–41.3)	urine: 115.8 (5–336.6) µg/l* 103.0 (4.6–604.6) µg/g creatinine* plasma: 9.7 µg/l (5.1–25.9) µg/l*	no changes	Letzel 1994
30 controls	43.1* (26–60)		urine: 15.3 µg/l (2.6–73.8) µg/l* 12 (1.9–51.8) µg/g creatinine* plasma: 4.3 (1.6–7.1) µg/l*		
Case report					
5 patients with aluminosis	about 37* (24–51)[1)] about 4* (2–10)[2)]		–	one case of dementia, no further changes	Sjögren et al. 1996 a
Longitudinal study					
21 workers	41** (26–60)[4)]	11.8** (2–37.4)[4)]	urine: 98.8 (5.0–336.6 µg/l**[4)] 77.1 (4.6–321.4) µg/g creatinine**[4)] plasma: 8.5 (5.4–25.0) µg/l**[4)]	no changes	Letzel et al. 1999 a, 2000[a)]
15 controls	41** (30–57)[4)]		urine: 6.5 (2–25.4) µg/l**[4)] 4.5 (2.2–15.9) µg/g creatinine**[4)] plasma: 4.3 (1.9–12.9) µg/l**[4)]		

Table 5 (Continued)

Study collective	Age (years)	Duration of exposure (years[5])	Aluminium concentration	Findings in the nervous system	References
Welding fumes containing aluminium					
Questionnaire study (Q16)					
65 aluminium welders	40–49	14 100 hours**	–	aluminium welders with exposure times of 20 500–60000 hours: statistically significant ≥ three positive responses in the Q16	Sjögren et al. 1990
217 welders	30–39	7100 hours**	–		
Cross-sectional study					
17 aluminium welders no controls	37** (24–48)	about 4	urine: 75.6* (24.3–164.7) µg/l serum: 5.67* (0.81–17.28) µg/l	slight disturbances in short-term memory, learning and attention	Hänninen et al. 1994
Cross-sectional study					
38 aluminium welders	39.0* (26–56)	7065 hours** (1766–21 980)	urine: 22.0** (4–255) µg/l 24.0** (2.5–162) µg/g creatinine blood: 3.0** (DL-27) µg/l	performance deficits in some psychomotor tests, tiredness increased with exposure	Sjögren et al. 1996 b
39 controls	40.1* (23–59)		urine: 3.0** (DL-26) µg/l 4.7** (DL-24.9) µg/g creatinine blood: 1.0** (DL-11) µg/l		

Table 5 (Continued)

Study collective	Age (years)	Duration of exposure (years[5])	Aluminium concentration	Findings in the nervous system	References
Cross-sectional study					
51 workers: 24 with high exposure 27 with low exposure	41.33* 36.75*		urine: 269.46 µg/l* 60.75 µg/l*	adverse effects on cognitive performance	Akila et al. 1999
28 controls (steel welders)	37.62*		urine: 12.42 µg/l*		
Cross-sectional study					
20 aluminium welders	33* (21–52)	8.1* (2–21)	urine: 50.22* (18.9–129.6) µg/l air inside the breathing mask: 1.18* (0.57–3.77) mg/m³	better performance in psychometric tests, exposure time correlated with tremor decreased	Bast-Pettersen et al. 2000
20 controls	33.8* (22–53)		not specified		
Two longitudinal studies consisting of three cross-sectional studies					
101 aluminium welders from the car industry	35**3)	about 8.8 (4.8–10.9)**4)	no data for concentration, exposure to a mixture of steel, chrome and nickel	slight changes in reaction time between 1st and 2nd, but not in 3rd cross-sectional investigation	Buchta et al. 2003; Letzel et al. 2006
50 controls	35**3)				
46 aluminium welders from rail and special vehicle construction	40**3)				
37 controls	38**3)				

Table 5 (Continued)

Study collective	Age (years)	Duration of exposure (years[5])	Aluminium concentration	Findings in the nervous system	References
Aluminium smelting plant					
Case report					
3 potroom workers	38[1)], 40[1)] and 40[1)]	12, 15 and 16	–	neurological disturbances increased, possibly work-place-related	Longstreth et al. 1985
Case report					
25 persons from an aluminium smelting plant	47 (34–60)*	18.7 (12–23)*	–	equilibrium and memory disturbances increased, coordination and verbal IQ decreased	White et al. 1992
Cross-sectional study					
14 potroom workers	62.7*	19.2*	urine: 12.6 µg/l* serum: 3.6 µg/l*	significant subclinical tremor increased	Bast-Pettersen et al. 1994
8 casting workers	63.5*	19.6*	urine: 9.9 µg/l* serum: 4.1 µg/l*	significant for ≥ 3 positive responses in the Q16	Pettersen et al. 1992
16 controls	62.5*	19.6*	urine: 7.8 µg/l* serum: 2.9 µg/l*		
Cross-sectional study					
63 exposed workers (potroom)	54 (48–68)*	≥ 10	air: 0.5 mg/m³ (estimate)	from questionnaire: significantly more reports of disturbances in co-ordination, depression and fine motor response, no changes in psychometric tests	Sim et al. 1997
37 controls	54 (44–75)*	≥ 10	air: 0.08 mg/m³ (estimate)		

Table 5 (Continued)

Study collective	Age (years)	Duration of exposure (years[5])	Aluminium concentration	Findings in the nervous system	References
Cross-sectional study					
64 exposed workers	67.9*	not specified	air: 14.7* (7.46–39.26 µg/m³) serum: 14.1 µg/l*	differences in MMST, CDT and in P300 complexes about 11 years after exposure in former resmelting plant workers	Polizzi et al. 2002
32 controls	66.9*		serum: 8.2 µg/l*		
McIntyre powder treatment					
Retrospective cohort studies combined with a cross-sectional study					
631/261 exposed workers	not specified	0.5–9.9 (n = 105) 10–19.9 (n = 106) ≥ 10 (0.5–36) (n = 50)	not specified	no difference in neurological diagnoses; impairment of cognitive performance in cross-sectional study	Rifat 1992; Rifat et al. 1990
722/346 controls	not specified				
Summary of various kinds of exposure to aluminium					
Cross-sectional study					
15 workers from the aviation industry, 7 with exposure to McIntyre powder, 8 welders and metal workers	58*	17.6*	not specified	disturbances in memory, attentiveness, concentration, motor control, and tremor; evidence of Alzheimer's disease in 2 deceased persons	McLachlan 1992

Table 5 (Continued)

Study collective	Age (years)	Duration of exposure (years[5])	Aluminium concentration	Findings in the nervous system	References
Cross-sectional study					
119 exposed workers from potroom and foundry works	46.1 (24–63)**	> 5 years	urine: 4.0** (< 1–34) µg/l 4.2** (< l–23) µg/g creatinine blood: 1.0** (< 1–18) µg/l	no changes in psychometric and neurological tests	Iregren et al. 2001
=x(24)16 workers from aluminium powder production	34.7 (22–48)**	> 5 years	urine: 83** (12–282) µg/l 59** (12–139) µg/g creatinine blood: 9.0** (< 1–21) µg/l	no changes in psychometric and neurological tests	
38 aluminium welders	38.0 (25–56)**	not specified	urine: 22** (4–255) µg/l 24** (4.5–162) µg/g creatinine blood: 3.0** (< 1–27) µg/l	no changes in psychometric and neurological tests	
39 welders without exposure to aluminium	39.0 (23–59)**	not specified	urine: 3.0** (< 1–26) µg/l 4.7** (< 1–25) µg/g creatinine blood: 1.0** (< 1–11) µg/l	–	

a) longitudinal comparison of sub-collectives in the collective presented by Letzel (1994)
* mean value, ** median value,
1) age on contracting disease, 2) years before diagnosis, 3) start of study, 4) end of study,
5) unless indicated otherwise,DL = detection limit, MMST = mini mental state test, CDT = clock drawing test

alloy steels containing manganese, lead or aluminium for less than 25 hours. Among other things, the study included responses to five different questionnaires on neuropsychiatric symptoms, comprehensive psychometric tests with a total of 20 evaluated variables, electroencephalograms with auditory evoked potentials (P-300) and the determination of aluminium, lead and manganese in blood and urine. In the comprehensive listing of the complaints experienced (27 evaluation parameters), only the report of tiredness at the time of investigation was conspicuous in aluminium welders compared with the statements of the controls. Also, the aluminium welders displayed decreased motor function in some psychometric tests. No differences were found in the electroencephalogram and the P-300 complexes (Sjögren et al. 1996 b).

In a cross-sectional study, 51 aluminium welders were compared with 28 steel welders. The group of aluminium welders was subdivided into a collective with low exposure and one with high exposure according to the level of aluminium (internally). In the psychometric tests performed, no impairment in psychomotor performance was found in relation to the exposure determined from the aluminium concentration in urine. When complex tasks had to be carried out, a negative correlation was found between the aluminium concentration in urine and cognitive performance (Akila et al. 1999).

Twenty aluminium welders were compared with a control group matched for age, consisting of 20 assembly workers. On average, the aluminium welders reported more neuropsychiatric symptoms in the Q16 questionnaire than did the controls. In tests for tremor and reaction time, the results of the aluminium welders were better than those of the assembly workers. In the case of tremor (hand steadiness), however, a significant correlation was found between the duration of exposure and a decrease in test performance (Bast-Pettersen et al. 2000).

In two longitudinal studies carried out with 101 workers in automobile construction and 46 in rail and special vehicle construction, neurological symptoms (modified Q16 questionnaire) were recorded and different psychometric tests performed in addition to the lung investigations already described in Section 4.2.1. Although initial comparison of the 1st and 2nd cross-section revealed slight differences in reaction time between the aluminium welders and the control collective, these differences could not be confirmed in the 3rd cross-sectional study. Other evidence of changes in the central nervous system that may have been induced by aluminium were not observed in either study (Buchta et al. 2003; Letzel et al. 2006).

Primary aluminium production, aluminium smelting and aluminium casting plants

At an aluminium smelting plant 25 workerswere evaluated for neurological disturbances. The patients came from the same factory in which the cases of progressive neurological impairment had already been observed by Longstreth et al. (1985). These three cases were included in the study. To quantify the burden, an exposure index was established. In the anamnesis, 22 of the 25 persons examined described

frequent loss of balance, and 21 reported memory loss. In the neurological investigations, evidence of co-ordination disturbances was found in 21 persons. The psychometric tests revealed abnormalities in specific functional areas of the central nervous system, such as in the verbal intelligence quotients, memory disturbances and in a personality questionnaire. There was a significant correlation between the exposure index and the extent of co-ordination disturbances ($r = 0.42$; $p = 0.04$) (White et al. 1992).

22 workers exposed to aluminium in the Norwegian aluminium industry (furnace area, potroom: n = 14; foundry: n = 8) were compared with a control collective recruited within the same company comprising 16 employees not exposed to aluminium. Details of the cumulative exposure of each individual study participant could not be given. It was, however, stated that the mean annual total dust concentration in the potroom decreased continuously from 9.5 mg/m^3 in 1977 to 3.0 mg/m^3 in 1990, and that the foundry workers were exposed to a lesser extent. The foundry workers, with three and more positive responses in the Q16 questionnaire (OR 15.0; 95% CI 1.3 to 174.4), had a significantly increased risk compared with that of the control collective. Tremor was found to be significantly ($p = 0.03$) increased in workers from the potroom. No other significant differences were observed (Bast-Pettersen et al. 1994; Pettersen et al. 1992).

In a cross-sectional study, 63 current or former potroom workers of an aluminium smelting plant and 37 controls were examined for neurological changes. The exposed workers took up this particular job before 1970 and were employed in it for at least 10 years. Statistically significant differences were found between the two collectives for some neurological symptoms regarding co-ordination (OR = 10.6; 95% CI: 2.1 to ∞), depression (OR = 6.2; 95% CI: 1.2 to ∞) and fine motor ability (OR = 6.2; 95% CI: 1.2 to ∞). On the other hand, no significant differences between the two collectives were found for tremor and the other neurological and psychometric investigations performed. In the authors' opinion, no clear neurological effects for long-term workers in an aluminium smelting plant can be derived from these results (Sim et al. 1997).

In a cross-sectional study, 64 former workers at a re-melting plant exposed to aluminium dusts, among other substances, were compared with 32 matched controls not exposed. At the time of investigation, all persons in both collectives had on average retired more than 10 years previously. The median aluminium concentration in the air at the workplace was calculated from the available air analyses to be 14.7 µg/m^3 (7.46–39.3 µg/m^3). At the time of investigation, the median serum aluminium concentration was 14.1 µg/l in those exposed and 8.2 µg/l in the controls. Comparison of the two collectives showed there to be not only a significant difference in serum aluminium concentrations, but also significant differences in mean blood iron concentrations (exposed: 408.6 mg/l; controls: 277.3 mg/l). Comparison of the two groups also revealed significant differences in the psychometric tests and the auditory evoked potentials. The level of previous aluminium exposure had a significant influence on the results of the tests performed. There was a positive relationship between the serum aluminium concentration and the time

needed in the Mini Mental State Examination (MMSE) and Clock Drawing Test (CDT). There was a negative relationship to the scores obtained in the MMSE and CDT P-300 correlated positively with the serum aluminium concentration. The authors viewed the aluminium exposure as a possible cause of the preclinical differences found between the collectives (Polizzi et al. 2002).

Treatment with McIntyre powder

A retrospective cohort study involving 631 exposed persons and 722 controls with an additional cross-sectional study investigated a group of Canadian miners (261 exposed persons and 346 controls), some of whom had been prophylactically treated against silicosis with McIntyre powder (15% aluminium, 85% aluminium oxide) via inhalation. Exposure to McIntyre powder took place before every shift. No significant differences were found between the two collectives in regard to neurological disorders such as Parkinson's or Alzheimer's disease. In the psychometric tests, however, the exposed persons did not perform as well as the controls. The longer the duration of exposure to aluminium the poorer the test results. It must, however, be mentioned that the exposure status was estimated from at least one reported treatment with McIntyre powder. The results indicate, according to the authors, neurotoxic effects after long-term exposure to aluminium. The methodological problems do not allow these results to be included in the evaluation (Rifat 1992; Rifat et al. 1990).

Summary of different aluminium exposures

Thirty volunteers from different work areas with high exposure to aluminium dust were investigated with regard to their neurological condition: 15 workers from the aviation industry, 8 welders and 7 mine workers with exposure to McIntyre powder. The most conspicuous findings in the study collective were memory disturbances in 24 persons and tremor and motor control disturbances in 7 persons. Those with memory disturbances were subjected to various psychometric tests not defined in greater detail. Here, 27 persons had deficits in attentiveness, concentration and memory. Two persons died during the observation period. In the autopsy, changes typical of Alzheimer's disease with an unusually large number of Lewy bodies were found. The results were not assigned to any particular exposure situations or occupational fields in this publication (McLachlan 1992).

In a cross-sectional study, 119 workers from a potroom and aluminium foundry, 16 workers from aluminium powder production, 38 aluminium welders and 39 welders not exposed to aluminium, were investigated. The study programme included, among other things, biological monitoring, a questionnaire and various psychometric and neurological tests. The highest internal exposure levels (see also Table 4) were found in workers from aluminium powder production with median aluminium concentrations in urine of 83 µg/l (12 to 282) or 59 µg/g creatinine (12 to 139) and in plasma of 9.0 µg/l (< 1 to 21). On comparing the separate collectives,

no functional disturbances of the nervous system were found which could be attributed to occupational exposure to aluminium (Iregren et al. 2001).

In 2005, 8 of 22 studies of the effects on behaviour of occupational exposure to aluminium were selected for a meta-analysis. These studies were not homogeneous with regard to the consideration of exposure to a mixture of substances and alcohol consumption, the comparability of the controls and the education level of the exposed group. The meta-analysis provided evidence of impaired attention recorded via the digit symbol test. The mean aluminium concentrations in the workplace air were in the range of 4.6 to 11.5 mg/m^3. The mean exposure time was 15 to 19 years (Meyer-Baron 2005).

Aluminium exposure and Alzheimer's disease

A case-control study included 198 persons with diagnosed Alzheimer's disease. The control group was formed from 164 persons with other forms of dementia and 176 persons without dementia. Of the patients with Alzheimer's disease, 22 (11.1%) had been occupationally exposed to aluminium; in the control group 39 (11.5%) had been exposed. The differences in aluminium exposure between the two groups were not statistically significant (OR = 0.98; 95% CI 0.53 to 1.75). In the authors' opinion, there is no evidence of there being a relationship between previous occupational exposure to aluminium and the occurrence of Alzheimer's disease (Salib and Hillier 1996).In another case-control study, 89 patients suffering from Alzheimer's disease and a control group matched, among other things by age and sex, were compared with regard to their exposure to solvents and aluminium. A statistically significant relationship between Alzheimer's disease and occupational exposure to aluminium (OR = 1.46; 95% CI 0.62 to 3.42) or solvents (OR = 1.77; 95% CI 0.81 to 3.90) could not be demonstrated (Graves et al. 1998).

4.2.2 Ingestion

Many forms of medication, in particular antacids, contain aluminium. No aluminium-induced diseases have been described after the ingestion of medication containing aluminium in persons without impaired kidney function.

A number of years ago, aluminium was suspected of causing Alzheimer's disease or dementia of the Alzheimer type and amyotrophic lateral sclerosis. This suspicion has, however, not been confirmed (Doll 1993; Hof et al. 1991; Landsberg et al. 1992; Strong and Garruto 1991; Yasui et al. 1991).

4.2.3 Other administration routes

Considerable exposure to aluminium, with serum aluminium concentrations of above 200 µg/l occurred in dialysis patients after the use of dialysates contaminated with aluminium or phosphate binders containing aluminium. Encephalopathy developed in some patients (Ittel et al. 1992).

Morphologically, no gross pathological or histopathological changes were found in these patients. However, reduced acetylcholine, serotonin and noradrenalin levels and increased aluminium concentrations were determined in blood, serum and tissues, and especially in bones and the brain (Alfrey 1994; Hamdy 1990; Ittel et al. 1992; Wisniewski and Sturman 1989; Zumkley et al. 1988).

4.3 Local effects on skin and mucous membranes

There are no data available for the effects on the skin and mucous membranes.

4.4 Allergenic effects

Skin-sensitizing effects

Although the test chambers used in patch tests nearly always consist of aluminium, allergic reactions to contact with metallic aluminium have only very rarely been observed. The few observed cases were conspicuous in that in all, or nearly all, test areas, ring-shaped reactions occurred (Bajaj et al. 1997; Clemmensen and Knudsen 1980; O'Driscoll et al. 1991; Purello-D'Ambrosio et al. 2000; Strömer et al. 1992; Tosti et al. 1990), which were not always reproducible (Fischer and Rystedt 1982) and their clinical relevance could not always be determined (Dwyer and Kerr 1993; Helgesen and Austad 1997; Kotovirta et al. 1984; Meding et al. 1984; Strömer et al. 1992).

Contact with grinding materials containing aluminium oxide (Tosti et al. 1990) and with aluminium dust or fine aluminium shavings during aluminium processing (Hall 1944, Peters et al. 1998) has been described as a possible cause of sensitization at the workplace. Of 853 workers involved in the production of hard metal, 2 produced reactions in all test areas; in one of them, however, this was not reproducible and the other was regarded as an expression of sensitization to aluminium caused by using a deodorant containing aluminium chloride (Fischer and Rystedt 1982).

In a study with 127 workers from an aluminium smelting plant, reactions to aluminium in the prick test or in the patch test were more frequent than in 49 office workers (total 14.9% including one of five delayed reactions; control group: 2.0%), but without clinical relevance (Hosovski et al. 1998). As the test preparations were not specified in greater detail; the method of recording the results of the patch test did not meet present-day standards; and it was not definitely clear whether the delayed reactions occurred in the patch test or in the prick test, the results cannot be used for evaluation.

Irritative or allergic skin symptoms were found in 281 banana plantation workers, 54 of whom were employed in packing the bananas. Between 1988 and 1993,

8 reactions to 10% aluminium hydroxide in water were observed, 48 controls did not react. The authors reported that the packing workers were regularly exposed to aluminium hydroxide solutions, and therefore assumed these findings had clinical relevance. It was not stated how many of the workers were tested with aluminium hydroxide. Tests with lower concentrations were not carried out (Penagos 2002).

Most reports describe sensitization to aluminium especially in children and juveniles (Kaaber et al. 1992; Veien 1996; Veien et al. 1986), but also in adults (Cosnes et al. 1990) resulting from the subcutaneous injection of vaccines containing aluminium oxide (Böhler-Sommeregger and Lindemayr 1986; Cosnes et al. 1990; Cox et al. 1988; O'Driscoll et al. 1991; Skowron et al. 1997) or preparations for hyposensitization (Castelain et al. 1988; Clemmensen and Knudsen 1980; Lopez et al. 1994; Purello-D'Ambrosio et al. 2000). An immunological origin could not always be demonstrated in the patch test for the granulomatous skin reactions occurring with aluminium chloride (Nagore et al. 2001) or aluminium hydroxide (Vogelbruch et al. 2000). Non-immunological foreign body granulomas were Also observed (Linse et al. 1979).

In consecutive testing of 1922 patients with 2% aluminium chloride hexahydrate in water, four had 1+ or 2+ reactions, three had questionable and two irritative reactions. In none of the four patients could the reactions be reproduced upon renewed testing with different preparations of other aluminium compounds (Hemmer et al. 1996).

In individual cases it has been described that patch testing with aluminium salts (Clemmensen and Knudsen 1980) or ingested aluminium (Veien et al. 1993) produced flare-up reactions at the original site of the eczema.

In a maximization test, no sensitization was induced in any of the 20 volunteers. The induction treatment was carried out with 25% aluminium chloride and the challenge with 10% aluminium chloride, both in petrolatum and without pretreatment with sodium dodecylsulfate (Kligman 1966).

Airway sensitization

Despite the large number of cases of aluminosis following exposure to high levels of aluminium, there is little evidence of respiratory sensitization. Also the increased incidence of obstructive diseases of the airways ("potroom asthma"; Kongerud et al. 1992) in workers from aluminium smelting plants could not be attributed to an immunological origin, particularly as there was exposure to a mixture of substances (Desjardins et al. 1994).

A 32-year-old maintenance worker at a leather factory developed workplace-related asthmatic conditions after four years of intermittent exposure to welding fumes containing aluminium. On two occasions after exposure for two hours to welding fumes containing aluminium, obstructive reactions with a decrease in the FEV_1 of more than 50% occurred after around four hours. Depending on the electrodes used, the aluminium concentration determined was 165 or 813 $\mu g/m^3$.

Compared with the control value, non-specific bronchial hyperresponsiveness was increased after the second challenge ($PC_{20(histamine)}$ 0.01 mg/ml compared with 0.07 mg/ml). After exposure for one hour to the fumes occurring during steel welding, a drop in the FEV_1 of only 17% was found after seven hours. The authors came to the conclusion that in this case the bronchial asthma was induced by welding fumes containing aluminium (see also Section 4.2.1, Vandenplas et al. 1998).

A 46-year-old aluminium foundry worker developed a cough and tight chestedness after working for 19 years. Determination of the peak expiratory flow (PEF) performed every two hours for five weeks showed there to be a workplace-related effect, with a diurnal variation of less than 20%. There was moderate, non-specific reactivity ($PC_{20(histamine)}$ 133 mg/ml). A three-minute bronchial provocation test using a nebulized aluminium chloride solution of 10 mg/ml (pH 3.5) produced a dual reaction with a 34% drop in the FEV_1 delayed by about seven hours. Provocation with a potassium chloride solution of 10 mg/ml (pH 3.5) produced no effect. The result of a provocation test with an aluminium chloride solution of 1 mg/ml (pH 4.4) was not documented (Burge et al. 2000).

After working for about 3.5 years, a 38-year-old worker exposed to aluminium dust developed workplace-related respiratory symptoms which already occurred one hour after starting work, and increased during the evening and night. Prick tests with aluminium chloride concentrations of 1 and 10 mg/ml and an intradermal test with 10 mg/ml yielded negative results. After bronchial provocation with 10 mg aluminium powder (Spinhaler®: single-dose applicator with capsules), a drop in the FEV_1 of more than 20% occurred after 20 minutes. The FEV_1 was reduced by about 15% for up to about four hours after provocation. Provocation with a nebulized aluminium chloride solution of 10 mg/ml produced no clear reaction. The patient responded with an immediate reaction that was difficult to interpret and a maximum drop in the FEV_1 of about 20% after 20 minutes. There were no delayed reactions (Park et al. 1996).

Between 1975 and 1977, 19 workers from two plants producing aluminium fluoride or aluminium sulfate reported nocturnal wheezing and breathlessness with reversible airway obstruction . After bronchial provocation with dust from the factory, no immediate or delayed reactions to aluminium fluoride (two workers) and aluminium sulfate (one worker) were found. During provocation, the patients consecutively inhaled the dust in 2, 5, 10 and 20 breaths (7 to 17 mg/m^3; 25% of the dust with a particle size < 5 µm). During the subsequent 50 minutes, the specific airway conductivity was determined, and after that the persons were observed for the occurrence of possible obstructive airway symptoms (Simonsson et al. 1985).

Alveolitis developed in a 32-year-old chemist after eight years working in dusty air containing aluminium powder. T-cell helper lymphocytes were detected in the bronchoalveolar lavage fluid, and transbronchial biopsy revealed sarcoid-like, epithelioid granulomas. Immunological investigations did not indicate sarcoidosis, however. In the lymphocyte transformation test, peripheral blood lymphocytes could be stimulated by soluble aluminium salts. A somewhat weaker effect, that was not concentration-dependent, was observed in the patient with aluminium

chloride. The average value determined in 10 controls revealed no increase in lymphocyte proliferation (De Vuyst et al. 1987). No respiratory sensitization can be derived from these findings.

In an investigation with 127 aluminium smelting workers, 38.5% of the workers were found to have increased non-specific airway reactivity. However, bronchial provocation with aluminium (no other details) yielded positive results in only five of 127 workers (Hosovski et al. 1998). As there are no details of the test preparation and evaluation criteria, these findings cannot be used to assess respiratory sensitization.

Taking the widespread use of aluminium into account, which, among other things, is routinely used as inert material in patch testing with the so-called "Finn chambers", the few case reports of demonstrated sensitization to aluminium indicate it has low allergenic potency. Designation with "Sa" does not appear to be justified on the basis of the human data.

4.5 Reproductive toxicity

4.5.1 Fertility

In 27 Finnish men from a refinery and a polyolefin factory aged between 27 and 46 years and in 45 sperm bank donors aged between 20 and 45 years, sperm quality was investigated and the concentrations of aluminium, lead and cadmium in the spermatozoa and seminal fluid were compared. The mean aluminium concentration of 0.93 ± 3.37 mg/kg in the spermatozoa of the workers was significantly lower than that of the sperm donors (2.52 ± 4.14 mg/kg). In the seminal fluid, the aluminium concentrations were also lower in the workers (0.54 ± 0.61 mg/kg than in the sperm donors (0.87 ± 1.17 mg/kg). In a correlation analysis, it was found that high aluminium concentrations in the spermatozoa correlated with decreased sperm motility. In this study, the lead and cadmium concentrations were low and did not have any influence on semen quality. In the authors' opinion, the results indicate that aluminium is an environmental pollutant that influences semen quality (Hovatta et al. 1998).

4.5.2 Developmental toxicity

The outcome of pregnancy in 92 women from Cornwall, England, who during pregnancy were accidentally exposed to a high aluminium sulfate concentration in the drinking water, was compared with the outcome of 68 pregnancies prior to the accident and with that of 193 pregnancies in a neighbouring area with a different drinking water supply. No differences in perinatal deaths, birthweight, preterm delivery, or severe congenital malformations were found. Only the incidence of children with talipes (clubfoot) was significantly increased (5%; 5 cases in

88 births) compared with that in the controls (1%; one case in 65 births). The authors conclude that there is no evidence of severe problems at birth from this study. However, on account of the low number of cases, no conclusive statement is possible (Golding et al. 1991). Because of the low number of cases, no statement can be made as to whether the increased incidence of talipes is related to the increased aluminium exposure.

4.6 Genotoxicity

The lymphocytes of smokers and persons exposed to metals, pesticides or mycotoxins, and those of controls were investigated for DNA adduct formation. An increased number of aluminium–DNA adducts was found only in the group of smokers (Howard 2002). As a result of the exposure to a mixture of substances and interaction with other genotoxic substances, this study cannot be used to evaluate the genotoxic effects of aluminium.

4.7 Carcinogenicity

A number of studies report the occurrence of malignant diseases in persons employed in aluminium electrolysis or aluminium foundries (Peter and Schiele 1998; Romundstad et al. 2000; Ronneberg 1995; Ronneberg and Andersen 1995; Ronneberg et al. 1999; Selden et al. 1997; Spinelli et al. 1991). However, exposure to aluminium is not regarded as the cause of this, but air contaminants such as polycyclic aromatic hydrocarbons (PAH) (Morgan and Dinman 1989 Ronneberg et al. 1999). Information about the carcinogenicity of inorganic fibre dusts containing aluminium oxide can be found in Section III of the *List of MAK and BAT Values*.

5 Animal Experiments and in vitro Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no data available for the effects following inhalation.

5.1.2 Ingestion

After oral administration of various aluminium salts to rats and mice, the LD_{50} values corresponded to aluminium doses of between 162 and 980 mg/kg body weight.

5.1.3 Dermal absorption

There are no data available for this endpoint.

5.1.4 Intraperitoneal or intratracheal administration

After intraperitoneal injection of aluminium, LD_{50} values of between 25 and 133 mg/kg body weight were found (WHO 1997).

In rats, intratracheal instillation of aluminium oxide doses of 0.1 or 0.5 mg/kg body weight (median particle size 5.3 ± 2.3 µm) led to weak transient inflammatory changes and damage to the epithelial cells as determined in the bronchoalveol lavage fluid (BALF) using biochemical (lactate dehydrogenase, total protein, β-glucoronidase, N-acetylglucosaminidase) and cellular parameters. In the BALF, an increase in biochemical parameters was observed. Apart from the increase in the number of polymorphonuclear neutrophils at the highest dose of 0.5 mg/kg body weight, all other cell counts did not differ from those of the controls 63 days after the intratracheal instillation. No fibrosis was observed in the treated animals. Fibrosis occurred, however, after two months in all rats given silicon dioxide doses of 0.2, 1.0 or 5 mg/kg body weight via intratracheal instillation. The authors suspected that the effects seen were the result of a considerable overloading of the lungs with dust following the administration of aluminium (Lindenschmidt et al. 1990).

5.2 Subacute, subchronic and chronic toxicity

Toxicity to the lungs

Inhalation

In a number of inhalation studies, aluminium oxide or aluminium lactate were used as negative controls in fibrogenicity studies or as prophylactic agents to prevent or reduce quartz-induced lung fibrosis. Investigations in sheep showed that the biological activity of quartz coated with aluminium lactate was significantly reduced. Even a month after the exposure to quartz, inhalation of aluminium lactate significantly reduced the development of fibrosis (Begin et al. 1987). In animals with existing silicosis, however, this treatment had no effect (Begin et al. 1995). No side-effects occurred with the aluminium lactate doses administered (11 mg once a month for four months or up to 100 mg aluminium lactate weekly for two years).

In a five-month inhalation study, groups of 8 female rabbits were exposed to aluminium oxide concentrations of 0 or 0.56 mg/m^3 for eight hours a day on four days. The level of aluminium in the brain, lungs, liver, heart, kidneys and sternum of the animals was determined one day after the end of exposure. The highest

aluminium concentrations were found in the lungs (270 µg/g, control value 1.7 µg/g) and in the kidneys (4.9 µg/g, control value 3.0 µg/g). No further investigations were carried out (Röllin et al. 1991 b).

Several authors pointed out that aluminium is able to cross the blood–brain barrier in different hydrophilic or lipophilic forms, and that the aluminium level in the brain can be significantly increased after inhalation of aluminium oxide dust (Wilhelm 1994).

Intratracheal administration

After intratracheal instillation of 2.5 mg corundum (no other details) into the lungs, no differences between the exposed rats and the animals treated with physiological saline solution were observed with regard to inflammatory, proliferative or cytotoxic effects after 7, 21 or 90 days. No histopathological investigations were carried out (Nehls et al. 1997).

The fibrogenic properties of seven aluminium oxide samples were investigated following intratracheal administration (50 mg, 5 times 10 mg) in rats and intraperitoneal injection (5 mg) in mice. Five of the aluminium oxide samples (> 50% of the particles had a diameter < 11 µm) were air samples from workplaces in aluminium production, and two (all particles with a diameter < 11 µm and a surface area of 100 m^2/g) were not from aluminium production. One of these samples was chemically pure (Degussa), the other had been synthetized in a laboratory. A silicon dioxide sample was used as positive control for fibrosis formation. To determine the toxic potential of the samples, the lactate dehydrogenase activity and the number of alveolar macrophages and polymorphonuclear neutrophils in the BALF of the exposed rats were determined. In addition, the lungs and the peritoneal lymph nodes of the rats and the peritoneum of the mice were examined histopathologically. None of the five samples from aluminium production produced fibrogenic effects in the lungs or in the neighbouring lymph nodes of the rats or the peritoneum of the mice. However, slight inflammation was induced. The two other aluminium oxide samples induced inflammation and fibrotic lesions in the lungs of the exposed animals (Ess et al. 1993).

Neurotoxicity

Studies of the systemically toxic and especially of the neurotoxic effects are listed in Table 6. These were performed with oral administration or intraperitoneal injection of soluble aluminium salts. No studies with dusts containing aluminium, aluminium oxide or aluminium hydroxide are available.

Mouse

Ingestion

Aluminium lactate (aluminium doses of about 62 and 130 mg/kg body weight and day) (Golub et al. 1989, 1992 b) was administered with the diet to Swiss mice for six or 13 weeks. No significant effects on body weight gain or motor activity could be found after the administration of 62 mg/kg body weight and day for six weeks (Golub et al. 1989). Reduced motor activity was observed at 130 mg/kg body weight and day (Golub et al. 1989) and in addition, neuromotor impairments after 13 weeks (Golub et al. 1992 b).

On the other hand, administration of aluminium chloride with the diet (aluminium doses of about 200 mg/kg body weight and day) for five to seven weeks to Swiss mice reduced grip strength, but no uniform deviation regarding auditory startle response and fear reaction, thermal sensitivity and geotaxis could be found (Oteiza et al. 1993). Reduced conditioned avoidance reactions and body weight loss (no other details) were observed in CD mice only after administration of 1% aluminium chloride in the drinking water (aluminium doses of about 220 mg/kg body weight and day) over a period of eight weeks in an early postnatal phase, but not in a later developmental phase with exposure for four months (Yen-Koo 1992). After administration of 1 mg/kg body weight and day aluminium chloride to the drinking water of Swiss mice for 100 days, motor coordination was reduced in the Rotarod treadmill performance (Sahin et al. 1995). The study cannot be used in the present evaluation, however, as the dose was too low compared with the doses used in other studies: only one aluminium dose was used, and no details were given for body weight development.

In a study with 10-week-old mice, exposure for two weeks to 600 mg/kg body weight and day aluminium nitrate in the drinking water caused a reduction in body weights and reduced motor activity in the Rotarod treadmill. At the low dose of 300 mg/kg body weight and day, neurotoxic effects were observed only in connection with concurrent restraint stress (Colomina et al. 1999).

From the available studies in mice with oral administration of soluble aluminium salts, a no observed adverse effect level (NOAEL) for neurotoxic effects corresponding to an aluminium dose of 62 mg/kg body weight and day can be derived.

Intraperitoneal or subcutaneous administration

Parallel to the studies with ingestion of aluminium chloride, studies with intraperitoneal and subcutaneous injection were also performed in CD mice. Groups of ten mice aged four weeks were given intraperitoneal doses of aluminium of 0, 10, 30 or 100 mg/kg body weight and day or subcutaneous doses of 0, 3, 10 or 30 mg/kg body weight and day on two consecutive days. Intraperitoneal aluminium doses of 100 mg/kg body weight and day resulted in high mortality (70%). One month after exposure, reduced conditioned avoidance reactions were observed in all exposed groups compared with in controls (Yen-Koo 1992). The derivation of a fundamentally sound NOAEL is not possible from this investigation.

Table 6 Studies of the neurotoxic effects of aluminium salts in juvenile and adult animals

Species, strain, number of animals, age	Exposure	Findings	References
mouse, Swiss, groups of 25 ♀, 8–12 weeks old	**6 weeks**; 25 (controls), 500, 1000 mg **Al lactate**/kg diet, corresponding to 3 (controls), 62, 130 mg Al/kg body weight and day	**62 mg Al/kg body weight**: no significant impairment of motor activity; **130 mg Al/kg body weight**: body weight gains decreased, motor activity decreased	Golub et al. 1989
mouse, Swiss, groups of 10–12 ♀, 3–4 weeks old	**13 weeks**; 25 (controls), 1000 mg **Al lactate**/kg diet, corresponding to 6 (controls), 130 mg Al/kg body weight and day	**130 mg Al/kg body weight**: Al concentration in brain and liver increased, motor activity decreased, grip strength of rear limbs decreased, fear reaction after air jet to eyes decreased, auditory startle decreased	Golub et al. 1992 b
mouse, Swiss, groups of 10–12 ♀, 6 weeks old	5–7 weeks; 3 (controls), 1000 mg **$AlCl_3$**/kg diet, corresponding to 7 (controls), 200 mg Al/kg body weight and day	**200 mg Al/kg body weight**: body weight gains decreased, relative organ weights increased (spinal cord, heart, kidneys), Al concentration in the brain, spinal cord, liver, bones increased, grip strength of front/rear limbs decreased, fear reaction after air jet to eyes decreased, heat sensitivity, geotaxis and auditory startle not uniform	Oteiza et al. 1993
mouse, CD, groups of 5 ♂, 5 ♀, newborn pups or 1 month old	**8 weeks (newborn pups) or month 1 to 4**; 0, 1000 mg **$AlCl_3$**/l drinking water, corresponding to about 220 mg Al/kg body weight and day	**220 mg Al/kg body weight**: reduced avoidance reaction decreased (only after exposure of newborn pups for 8 weeks), body weight loss	Yen-Koo 1992
mouse Swiss, ♀, 20–23 g in weight, (no other details)	**100 days**; 0, 4 mg **$AlCl_3$**/l drinking water, corresponding to about 1 mg Al/kg body weight and day	**1 mg Al/kg body weight**: motor coordination decreased (Rotarod)	Sahin et al. 1995
mouse,CD, groups of 10 (no other details)	**90 days**; 0, 10 mg Al/animal and day in the drinking water, as **$AlCl_3$** or **Al lactate**, corresponding to 250 mg Al/kg body weight and day	**250 mg Al/kg body weight**: AChE activity in the brain increased	Zatta et al. 2002

Table 6 (Continued)

Species, strain, number of animals, age	Exposure	Findings	References
mouse CD, groups of 25 ♂, 8 weeks old	**14 days**; 0, 300, 600 mg Al/kg body weight and day, as **Al nitrate** in the drinking water	**300 mg Al/kg body weight and above**: Al concentration in brain increased, neurotoxic effects increased only in connection with restraint stress; **600 mg Al/kg body weight**: motor coordination decreased (Rotarod)	Colomina et al. 1999
mouse, CD, groups of 5 ♂, 5 ♀, 1 month old	**2 days**; 0, 10, 30, 100 mg Al/kg body weight and day; intraperitoneally as **$AlCl_3$**; or 0, 3, 10, 30 mg Al/kg body weight and day; subcutaneously as **$AlCl_3$**	**3 or 10 mg Al/kg body weight and above**: reduced avoidance reaction decreased; **100 mg Al/kg body weight**: mortality increased	Yen-Koo 1992
rat, Wistar, groups of 12 (no other details), 50 days old	**30 days**; 0, 260 mg **$AlCl_3$**/kg body weight and day, gavage, corresponding to 52 mg Al/kg body weight and day	**52 mg Al/kg body weight**: feed consumption decreased, body weight gains decresaed, motor activity and coordination decreased (Rotarod), AChE decreased	Rajasekaran2000
rat, Wistar, groups of 12 ♀, 240–270 g in weight, age not specified	**60 days**; 0, 50, 200 mg **$AlCl_3$**/kg body weight and day, gavage, corresponding to 0, 10, 40 mg Al/kg body weight and day	**10 mg Al/kg body weight and above**: body weight gains decreased, Al concentration in the brain (cortex) and serum increased; **40 mg Al/kg body weight**: relative adrenal gland weights increased, contradictory evoked potentials, no consistent abnormalities in open field test, on auditory startle, in electrocorticography and in sensory nerve conduction velocity	Baydar et al. 2003
rat, Sprague Dawley, groups of 6–7 adults or pups (PND 1–60)	**8 weeks or 60 days**; 0, 100 mg **$AlCl_3$**/kg body weight and day, gavage, corresponding to 0, 20 mg Al/kg body weight and day	**20 mg Al/kg body weight**: *adult animals*: lipid peroxidation in the brain increased (76%); *pups*: body weight gains decreased, brain weights decreased, lipid peroxidation in brain increased (178%)	Nehru and Anand 2005

Table 6 (Continued)

Species, strain, number of animals, age	Exposure	Findings	References
rat, Sprague Dawley, groups of 12 ♀, 6 weeks old	**90 days**; 0, 1600 mg **$AlCl_3$**/l drinking water, corresponding to 27 mg Al/kg body weight and day	**27 mg Al/kg body weight**: Al concentration in the brain (cortex) and serum increased, memory and learning performance decreased (avoidance test, Morris water maze)	Zheng and Liang 1998
rat, Lister-Hooded, 24 ♂ (exposed), 11 ♂ (controls), 21–25 days old	**7 months**; 0, 1000 mg **Al sulfate**/l drinking water, corresponding to about 0, 25 mg Al/kg body weight and day	**25 mg Al/kg body weight**: no effects in water maze test and for memory performance	Roloff et al.2002
rat, Wistar, groups of 8–9 dams (no other details)	**entire life (from birth)**; 0, 3000 mg **$AlCl_3$**/l drinking water, corresponding to 60 mg Al/kg body weight and day	**60 mg Al/kg body weight**: impairment of synaptic plasticity (excitatory postsynaptic potentials in the hippocampus)	Wang et al. 2002
rat, Wistar, groups of 8 ♂, 100–130 g in weight, age not specified	**4 weeks**; 0, 10 mg Al/kg body weight and day, intraperitoneal, as **Al lactate**	**10 mg Al/kg body weight**: Al concentration in hippocampus increased, acetylcholine, AChE and choline acetyltransferase activity in the brain decreased, choline uptake in brain decreased, passive and active avoidance task decreased	Julka et al. 1995
rat, Wistar, 19 ♂ (exposed), 10 ♂ (controls), 8 weeks old	**3 months**; 0, 0.7 mg Al/0.25 ml, intraperitoneal, 3× per week as **Al gluconate**, corresponding to 0, 2.7 mg Al/kg body weight and day	**2.7 mg Al/kg body weight**: Al concentration increased in serum (15-fold), brain (4-fold), liver (44-fold), no clearly interpretable tendency to slowed reaction in radial maze test	Struys-Ponsar et al. 1997

Table 6 (Continued)

Species, strain, number of animals, age	Exposure	Findings	References
rat, Wistar, 12 ♂ (exposed), 8 ♀ (controls), 173 ± 17 g in weight, age not specified	**6 months**; 0, 0.85 mg **Al gluconate**/kg body weight, intraperitoneal, 3× per week	**0.85 mg Al gluconate/kg body weight**: serum Al concentration increased (5-fold), flight reflex in Morris water maze decreased, emotionality increased in open field, activity decreased, fear conditioning decreased	Miu et al. 2003
rabbit,New Zealand White, groups of 5–12 ♀, 1 or 6 months or 3.4 years old	**4 weeks**; 0, 200 (only 3.4-year-old animals), 400 µmol **Al lactate**/kg body weight and injection, subcutaneous, corresponding to 0, 6, 11 mg Al/kg body weight and day	**about 11 mg Al/kg body weight**: conditioned eyeblink reflex: acquisition, retention, extinction disturbed only in 6-month-old rabbits, but not in animals 1 month or 3.4 years old	Yokel et al. 1994

AChE: acetylcholinesterase; PND: postnatal day

Rat

Ingestion

50-day-old Wistar rats were given gavage doses of aluminium chloride, corresponding to an aluminium dose of 52 mg/kg body weight and day, for 30 days. Aluminium chloride resulted in reduced feed consumption and reduced body weight gains. Motor activity and coordination in the Rotarod was reduced (Rajasekaran 2000). Adult Wistar rats were given gavage doses of aluminium chloride, corresponding to aluminium doses of approximately 10 or 40 mg/kg body weight and day, over a period of 60 days. The aluminium level in the brain and serum was increased in the exposed groups by 1.3 and 2.5 times, respectively, compared with that in the control group, and body weights were reduced in a dose-dependent manner. The results for sensorially and visually evoked potentials were contradictory. Inconsistent abnormalities were found in open field tests and in the auditory startle response, in electrocorticography and in the nerve conduction velocity (Baydar et al. 2003). Aluminium chloride doses of 20 mg/kg body weight and day given to adult Sprague Dawley rats for 8 weeks and to pups for 60 days induced

increased lipid peroxidation in the brain; this was particularly marked in the pups. Body weight gain and brain weights were additionally reduced in the pups (Nehru and Anand 2005). Aluminium chloride was administered to six-week-old Sprague Dawley rats with the drinking water for 90 days in concentrations corresponding to aluminium doses of about 27 mg/kg body weight and day. Body weight gain was not reduced compared with that in controls. In neuropsychological tests the performance of the exposed animals was impaired. The aluminium level in serum and cortex was increased approximately 2.4-fold (Zheng and Liang 1998). Deficits in synaptic plasticity in the hippocampus were found in Wistar rats given lifelong aluminium doses of 60 mg/kg body weight and day in the drinking water (Wang et al. 2002). In another study, male Lister hooded rats received aluminium lactate with the drinking water corresponding to an estimated aluminium dose of approximately 25 mg/kg body weight and day, for seven months. In the water maze test, no deficits in memory performance were observed in the exposed animals (Roloff et al. 2002). Because of the unclear dose level, this study cannot be used to derive a NOAEL.

From the studies with aluminium chloride a LOAEL for aluminium of 10 mg/kg body weight and day can be derived, but no NOAEL.

Intraperitoneal administration

Male Wistar rats were given intraperitoneal aluminium doses of 10 mg/kg body weight and day for four weeks. No significant effects on motor activity could be detected. Learning and memory performance were significantly impaired both in the active and in the passive avoidance task, which also included motor performance (Julka et al. 1995).

In two studies with Wistar rats, the aluminium concentrations in serum were increased after intraperitoneal injection three times a week of aluminium gluconate, prepared from a 1:1 mixture of aluminium chloride and sodium gluconate. After administration of aluminium doses of 2.7 mg/kg body weight and day for three months, no effects on recognition and orientation were found in the radial maze test. However, the exposed rats showed a tendency towards slower reactions which was not clearly interpretable (Struys-Ponsar et al. 1997, 2000). After administration of aluminium gluconate doses of about 0.85 mg/kg body weight and day for six months, the animals had higher emotionality and lower activity values in the open field test compared with those for the controls. Fear conditioning proceeded at a far slower pace, and the flight reflexes in the Morris water maze test were delayed (Miu et al. 2003). As this study could not be evaluated clearly on a dose-related basis, it cannot be used in the evaluation.

Rabbit

New Zealand White rabbits of different ages were exposed subcutaneously to aluminium lactate (corresponding to aluminium doses of approximately 6 and

11 mg/kg body weight and day) for 30 days. After doses of 11 mg/kg body weight and day, a significant disturbance in acquisition, retention and extinction of the conditioned blinking reflex was found only in adult rabbits. It was only slightly impaired in juvenile and old animals. The conclusion was drawn that the mature mammalian brain reacts with greater sensitivity to aluminium-related influences than the immature brain (Yokel et al. 1994).

Other forms of systemic toxicity

In a four-week study with rats, no effects were observed up to a dose of aluminium in the diet of 288 mg/kg body weight and day (in the form of aluminium sodium phosphate) or 302 mg/kg body weight and day (in the form of aluminium hydroxide) (WHO 1997).

Rats given different aluminium concentrations in the form of aluminium nitrate for 100 days with the drinking water, had significantly reduced body weights at aluminium doses of 260 mg/kg body weight and day, associated with lower feed consumption. The NOAEL was given as 52 mg/kg body weight and day (WHO 1997).

Aluminium doses of 0, 10, 24 or 77 mg/kg body weight and day were administered with the diet in the form of aluminium sodium phosphate to groups of four beagle dogs for six months. At the high dose of 77 mg/kg body weight and day, body weights, food consumption and testis weights were reduced in the males. Histopathological findings in the liver and kidneys were interpreted as secondary effects of the reduced food consumption (WHO 1997).

Groups of 6 male New Zealand White rabbits were given gavage doses of ascorbic acid of 40 mg/kg body weight and day, or doses of aluminium chloride of 34 mg/kg body weight and day (corresponding to aluminium doses of about 6.8 mg/kg body weight and day), or 34 mg aluminium chloride plus 40 mg ascorbic acid per kg body weight and day, for 16 weeks. The glucose, creatinine, total bilirubin and total cholesterol concentrations in the serum, and the packed cell volume (PCV) were increased. On the other hand, total serum lipids, the haemoglobin level, and the erythrocyte and leukocyte counts were decreased. The enzyme activity determined in the liver, testes, kidneys, brain and plasma revealed decreases in the activities of aspartate and alanine aminotransferase, alkaline and acid phosphatases (in the liver and testes), glutathione *S*-transferase and the SH groups (in plasma, the liver, testes and kidneys), phosphorylase (in the liver, testes and brain) and acetylcholinesterase (in plasma and the brain). In addition, increases in the concentrations of the thiobarbituric acid-reactive substances in plasma, the liver, testes and kidneys and in the activity of lactate dehydrogenase in plasma and the brain were found. Maximum lipid peroxidation was found in the brain. The addition of ascorbic acid generally produced a weakening of the toxic effects caused by aluminium (Yousef 2004).

5.3 Local effects on skin and mucous membranes

No data exists on this endpoint.

5.4 Allergenic effects

Skin-sensitizing effects

The granulomas formed in Hartley guinea pigs after single injections of aluminium hydroxide (corresponding to aluminium concentrations of 6.5, 0.65 and 0.065 mg/0.1 ml) and aluminium chlorohydrate (corresponding to aluminium concentrations of 5, 0.5 and 0.05 mg/0.1 ml) were regarded by the authors on the basis of the results of the histological investigation as being non-allergenic reactions (Turk and Parker 1977).

In a Landsteiner-Draize test, none of 25 guinea pigs were sensitized by intradermal injection of 100 ml 0.1% aluminium chloride in physiological saline solution administered ten times on alternate days or three times a week. Challenge was carried out by intradermal injection of 50 ml of the preparation used for induction ten days after the last induction treatment. Also a maximization test produced no sensitization in any of the 25 guinea pigs. Induction treatment was carried out intradermally with 2% aluminium chloride in Freund's complete adjuvant, or epicutaneously with 25% aluminium chloride in petrolatum, and challenge was performed epicutaneously with 2% aluminium chloride in petrolatum (Magnusson and Kligman 1969). Increased lymphocyte proliferation was not determined in groups of four CBA/Ca mice in the local lymph node assay with 5%, 10% or 25% aluminium chloride in petrolatum (Basketter et al. 1999).

Sensitizing effects on the airways

There are no data available for respiratory sensitization.

5.5 Reproductive toxicity

There are a large number of studies of reproductive toxicity available; these are summarized in Tables 7, 8, 9 and 10 according to toxic effects on fertility and prenatal, perinatal and postnatal development. Only those studies relevant to the evaluation are presented and discussed in the text.

5.5.1 Fertility

In vitro

The penetration ability of sperm cells from healthy volunteers was investigated *in vitro* after 10 to 60 minutes incubation with 10, 100 or 200 µM aluminium chloride. The penetration ability was significantly reduced after concentrations of 10 µM and above (Kaur 1988).

In vivo

Studies of the toxic effects of aluminium on male fertility are found in Table 7.

In male Sprague Dawley rats given aluminium chloride in the drinking water for 12 weeks in concentrations of 1000 mg/l (corresponding to aluminium doses of about 75 mg/kg body weight and day) significant changes were observed in sexual behaviour and aggression. Decreased relative and absolute testis weights and decreased absolute seminal vesicle weights were found together with a significant

Table 7 Animal studies of the effects of aluminium salts on male fertility

Species, strain, number of animals	Exposure	Findings	References
Oral administration			
rat, Sprague Dawley, groups of 10–13 ♂, ♀	**12 weeks (♂)**; 0, 1000 mg **$AlCl_3 \times 6\ H_2O$**/l drinking water, corresponding to 0, 75 mg Al/kg body weight and day	**75 mg Al/kg body weight and day**: body weight gains decreased, absolute testis weights decreased, absolute seminal vesicle weights decreased, changed sexual behaviour (copulatory efficiency decreased), aggression decreased, no effects on fertility (number of pregnant animals, number of implants, number of living foetuses or resorptions)	Bataineh et al. 1998
rat, Sprague Dawley, groups of 10 ♂	**10 weeks (♂)**; 0, 1000 mg Al/kg diet, corresponding to about 0, 75 mg Al/kg body weight and day; no other details	**75 mg Al/kg body weight and day**: Al concentration in pituitary (significantly) and testes (not significantly) increased, concentration of testosterone and luteinizing hormone in the plasma slightly decreased (not significantly)	Liu und Stemmer 1990

Table 7 (Continued)

Species, strain, number of animals	Exposure	Findings	References
rat, **guinea pig**, **rabbit**, (no other details)	**up to 30 days**; 6, 17, 50 mg Al/kg body weight and day (rat, guinea pig) or 3, 9, 27 mg Al/kg body weight and day (rabbit) orally (no other details) as **$AlCl_3$**	**27 or 50 mg Al/kg body weight and day**: moderate dystrophy of epithelial proteins, increased epithelial desquamation, pyknosis in the endothelium and hyperplasia of cell nuclei in the spermatozoa of all 3 species; inadequate documentation	Krasovskii et al. 1979
rat, (no other details)	**up to 12 weeks**; 0.0025, 0.25, 2.5 mg Al/kg body weight and day orally (no other details) as **$AlCl_3$**	**2.5 mg Al/kg body weight and day**: slowing of reflexes, changed motor activity, change in number and motility of spermatozoa, histological changes in testes; inadequate documentation	Krasovskii et al. 19791979
Intraperitoneal administration			
mouse, Swiss, groups of 18 ♂, groups of 16 ♀	**4 weeks (♂)**; 0, 50, 100, 200 mg **$Al(NO_3)_3 \times 9\ H_2O$**/kg body weight and day, intraperitoneally, corresponding to 0, 3.6, 7.2, 14.5 mg Al/kg body weight and day, 5 days/week	**3.6 mg Al/kg body weight and above**: body weight gains decreased, Al concentration in testes increased (0.1, 0.9, 1.2, 1.5 µg/g tissue corresponding to 0, 3.6, 7.2, 14.5 mg Al/kg body weight and day); **7.2 mg Al/kg body weight and above**: absolute testis weights decreased, sperm count decreased, necrosis of spermatozoa/spermatids, fertility decreased (number of pregnant females decreased); **14.5 mg/kg body weight:** absolute epididymis weight decreased, sperm count decreased	Llobet et al. 1995
mouse, BALBcAn NCR, groups of 15 ♂	**single dose 24 hours before mating (♂)**; 0, 1000 mg **AlO_3**/kg body weight, intraperitoneally, corresponding to 526 mg Al/kg body weight; dams and foetuses examined on GD 13	**526 mg Al/kg body weight**: no impairment in fertility (number of embryos GD 13); no histological investigations	Zelic et al. 1998

GD: gestation day

decrease in body weight gains. No effects on gestation were found compared to controls (Bataineh et al. 1998). The type of changes observed in sexual behaviour and aggression, and the reductions in the weights of the reproductive organs can be attributed to the simultaneous retardation in body weight gain.

Aluminium (no other details) doses of 1000 mg/kg feed (about 75 mg/kg body weight and day) given to Sprague Dawley rats for ten weeks produced significantly increased aluminium concentrations in the pituitary gland. The aluminium concentration in the testes was slightly, but not significantly, increased. The concentrations of testosterone and luteinizing hormone were slightly, but not significantly, reduced (Liu and Stemmer 1990).

In a fertility study, male Swiss mice were given intraperitoneal aluminium nitrate doses of 50, 100 or 200 mg/kg body weight and day for four weeks prior to mating. After aluminium nitrate doses of 100 mg/kg body weight and day (corresponding to aluminium doses of 7.2 mg/kg body weight and day) and above, decreases in absolute testis weights, necrosis of the spermatocytes or spermatids, a reduction in spermatid count and a lower number of pregnant animals were found. A decrease in body weight was, however, already observed at the low dose of 50 mg/kg body weight and day (corresponding to an aluminium dose of about 3.6 mg/kg body weight and day) (Llobet et al. 1995). In this study, the aluminium salt was injected intraperitoneally (into the abdominal cavity beside the gonads) thus, a direct toxic effect of the substance on the testes and epididymides cannot be excluded. The study is therefore not suitable for evaluating fertility.

Groups of 6 male New Zealand White rabbits were given gavage doses of ascorbic acid of 40 mg/kg body weight and day, or doses of aluminium chloride of 34 mg/kg body weight and day (corresponding to aluminium doses of about 6.8 mg/kg body weight and day) or doses of 34 mg aluminium chloride plus 40 mg ascorbic acid per kg body weight and day (see also Section 5.2) every other day for 16 weeks. The administration of aluminium chloride alone reduced food intake by about 20% compared with that of the controls and caused a marked loss in body weight; the final weights of the treated animals were about 300 g below the initial weights. The relative weights of the testes and epididymides were reduced and all sperm parameters were changed. The ejaculate volume, the sperm concentration, and sperm motility and function were impaired, the number of dead sperms was increased and the number of normal sperms reduced. In the seminal plasma, the glutathione *S*-transferase, aspartate aminotransferase, alanine aminotransferase and acid phosphatase activities were reduced and the concentration of thiobarbituric acid-reactive substances was increased. The addition of ascorbic acid generally produced a weakening of the toxic effects caused by aluminium (Yousef et al. 2005). The study therefore demonstrates that toxic doses of aluminium effect the testes, epididymides and sperms. In view of the marked toxicity, a secondary toxic effect must be assumed. As no non-toxic doses were investigated, it cannot be estimated whether and to what extent a possible specific effect of aluminium was involved.

Other studies of male fertility cannot be used for evaluation on account of methodological shortcomings, such as insufficient documentation (Krasovskii et al.

1979), or inadequate depth of investigation or the absence of histological investigations (Zelic et al. 1998).

5.5.2 Developmental toxicity

There are no studies available of developmental toxicity after inhalation exposure to dusts containing aluminium, aluminium oxide and aluminium hydroxide. There are, however, investigations with oral administration of aluminium hydroxide and with oral, intraperitoneal and subcutaneous administration of soluble aluminium salts in rats, mice or rabbits.

Poorly soluble aluminium hydroxide

Aluminium hydroxide is a poorly soluble aluminium compound with low bioavailability. Thus, after the administration of aluminium hydroxide (corresponding to aluminium doses of 70 or 140 mg/kg body weight and day) to pregnant rats (gestation days 1 to 20) and rats that were not pregnant (20 days), aluminium concentrations changed in some cases in certain organs; these changes were, however, neither consistent nor dose-dependent, (Bellés et al. 2001).

In studies of the toxic effects of aluminium on prenatal development, neither maternal toxic effects nor developmental toxicity could be found during gestation after Swiss mice were given oral doses of aluminium hydroxide of up to 300 mg/kg body weight (corresponding to aluminium doses of about 100 mg/kg body weight and day) (Colomina et al. 1992, 1994; Domingo et al. 1989), and Wistar rats were given doses of up to about 770 mg/kg body weight and day (corresponding to aluminium doses of about 266 mg/kg body weight and day) (Gomez et al. 1990, 1991). Reduced food intake was observed only in Swiss mice at the highest aluminium dose of 100 mg/kg body weight and day (Colomina et al. 1994). A study with a preparation containing aluminium hydroxide (Anderson et al. 1985) cannot be used in the evaluation as there are no details of the dose given (Table 8). The NOAEL for the toxic effects on prenatal development of aluminium hydroxide after oral administration corresponds to aluminium doses of 100 mg/kg body weight and day in mice and 266 mg/kg body weight and day in rats, the highest doses used in each case. Table 8 gives a summary of the animal studies on the developmental toxicity of aluminium hydroxide.

Studies with soluble aluminium salts

In vitro

Sprague Dawley rat embryos were explanted 9.5 days after mating and incubated for 48 hours *in vitro* with aluminium sulfate in concentrations corresponding to

Table 8 Animal studies of the toxic effects on prenatal development of aluminium hydroxide

Species, strain, number of animals	Exposure	Findings	References
mouse, Swiss, groups of 10–13 dams	**GD 6–15** 0, 166 mg $Al(OH)_3$/kg body weight and day, gavage, corresponding to 0, 57.5 mg Al/kg body weight and day; investigation on GD 18	**57.5 mg Al/kg body weight**: *dams*: no effects, Al concentration in the bones increased; *foetuses*: no effects	Colomina et al. 1992
mouse, Swiss, groups of 18–20 dams	**GD 6–15** 0, 66.5, 133, 266 mg $Al(OH)_3$/kg body weight and day, gavage, corresponding to 0, 23, 46, 92 mg Al/kg body weight and day; investigation on GD 18	**up to 92 mg Al/kg body weight**: *dams, foetuses*: no effects	Domingo et al. 1989
mouse, Swiss, ♀ (no other details)	**GD 6–15** 0, 300 mg $Al(OH)_3$/kg body weight and day, gavage, corresponding to 0, 103.8 mg Al/kg body weight and day; investigation on GD 18	**103 mg Al/kg body weight**: *dams*: Al concentration in kidneys, brain and placenta increased, not increased in the bones, food consumption slightly decreased, body weight gains unchanged; *foetuses*: Al concentration not increased, no effects	Colomina et al. 1994
rat, Wistar, groups of 15–19 dams	**GD 6–15** 0, 192, 384, 768 mg $Al(OH)_3$/kg body weight and day, gavage, corresponding to 0, 67, 133, 266 mg Al/kg body weight and day; investigation on GD 20	**up to 266 mg Al/kg body weight**: *dams, foetuses*: Al concentration not increased, no effects	Gomez et al. 1990, 1991
rat, Holtzman, 6 (exposed) or 10 (controls) dams	**GD 2–21** 1:4 mixture of MaaloxTC [probably 100 mg $Al(OH)_3$/ml] in the drinking water, corresponding to about 138 mg Al/kg body weight and day; offspring investigated up to PND 70	**about 138 mg Al/kg body weight**: *dams*: abortions increased; *offspring*: stillbirths increased, body weight gains decreased (dose imprecise, as calculation based on assumption)	Anderson et al. 1985

GD: gestation day; PND: postnatal day

aluminium concentrations of 0.6 to 9 mg/l. Embryonic development was delayed at 1.2 mg/l and above. At 3 mg/l and above, embryonic growth and morphogenesis were significantly inhibited, and an increase in neural tube defects was found (Zhang et al. 2002).

In a another study, groups of 10 to 12 fertilized egg cells were incubated after their first division for 72 hours in concentrations of 3 to 200 µM aluminium citrate. The frequency of blastocyte formation and proliferation was unchanged by aluminium citrate compared with the frequencies in the controls (Hanna et al. 1997). Either a single dose of 6 µM aluminium citrate on day 8 of incubation or a long-term dose of 1.5 µM aluminium citrate combined with 1.5 µM sodium citrate beginning on day 8 of incubation (no other details) were injected into chicken embryos (no other details). On day 16 of incubation, a significantly increased number of shorter tibias were observed and from day 9 of incubation a significantly increased number of malformations of the femur and tibia. In addition, the relationship of tibia length to body weight was significantly reduced. A significant increase was observed in the amount of aluminium deposited in the tibia (Firling et al. 1994).

The injection of 3, 6, 12, 15 or 18 mg aluminium chloride in 100 ml distilled water on incubation days 0, 1, 2 and 3 (investigated on incubation day 9), produced no significant changes in 18 chicken embryos (Gilani and Chatzinoff 1981).

In vivo

Prenatal developmental toxicity

Animal studies of the toxic effects of soluble aluminium salts on prenatal development are found in Table 9.

In mice, maternal toxicity and foetotoxicity, such as reduced foetus weights, delayed ossification, increased incidences of cleft palates and dorsal hyperkyphosis, were found after single gavage doses on only one gestation day of aluminium nitrate (corresponding to aluminium doses of 72 or 95 mg /kg body weight and day; Albina et al. 2000), or repeated doses on days 6 to 15 of gestation of aluminium lactate (corresponding to aluminium doses of 57.5 mg/kg body weight and day; Colomina et al. 1992), or repeated doses on days 7 to 16 of gestation of aluminium chloride (corresponding to aluminium doses of 40 or 60 mg/kg body weight and day; Cranmer et al. 1986). A NOAEL for the toxic effects on prenatal development in mice cannot be derived from the available studies. The lowest effective dose of aluminium was 40 mg/kg body weight and day.

No maternal or developmental toxicity could be found in Sprague Dawley rats given gavage doses of aluminium citrate (corresponding to aluminium doses of 133 mg/kg body weight and day) on days 6 to 15 of gestation (Gomez et al. 1991). On the other hand, maternal and developmental toxicity, such as reduced foetus weights and delayed ossification, were observed after the administration of aluminium nitrate on days 6 to 14 of gestation even at the lowest dose (corresponding to aluminium doses of 13 mg/kg body weight and day); these effects were dose-

Table 9 Animal studies of the toxic effects of soluble aluminium salts on prenatal development

Species, strain, number of animals	Exposure	Findings	References
Oral administration			
mouse, CD1, groups of 10–11 ♀	**single doses on GD 8, 9, 10, 11 or 12**; 0, 995 mg **$Al(NO_3)_3 \times 9 H_2O$**/kg body weight, gavage, corresponding to 0, 72 mg Al/kg body weight and day; investigation on GD 18	**72 mg Al/kg body weight**: dams: body weight gains decreased, food consumption decreased (GD 12), uterus weights decreased, absolute liver weights decreased, relative liver weights decreased (GD 11), absolute kidney weights decreased (GD 9, 12); foetuses: body weights decreased, disturbed ossification increased (GD 8, 9 11, 12), delayed ossification (GD 8–12)	Albina et al. 2000
mouse, CD1, groups of 11–15 ♀	**single dose on GD 12**; 0, 1327 mg **$Al(NO_3)_3 \times 9 H_2O$**/kg body weight, gavage, corresponding to 0, 95 mg Al/kg body weight and day; investigation on GD 18	**95 mg Al/kg body weight**: dams: food consumption decreased, body weight gains decreased, absolute liver weights decreased, abortions increased, number of litters decreased; foetuses: body weight/litter decreased, delayed ossification increased (902 mg sodium nitrate/kg body weight also produced an increase in delayed ossification in the foetuses)	Albina et al. 2000
mouse, Swiss, groups of 10–13 ♀	**GD 6–15**; 0, 627 mg **Al lactate**/kg body weight and day, gavage, corresponding to 0, 57.5 mg Al/kg body weight and day; investigation on GD 18	**57.5 mg Al/kg body weight**: *dams*: food consumption decreased, body weight gains decreased; foetuses: body weights decreased, cleft palates increased, dorsal hyperkyphosis, delayed ossification	Colomina et al. 1992
mouse, BALB/c, groups of 6 ♀	**GD 7–16**; 0, 200, 300 mg **$AlCl_3$**/kg body weight and day, gavage, corresponding to 0, 40, 60 mg Al/kg body weight and day; investigation on GD 18	**40 mg Al/kg body weight and above**: dams: Al concentration in placenta increased (2.2-fold), body weights not determined; *foetuses*: Al concentration increased (1.8-fold), body weights decreased, resorptions increased (study to determine Al concentration in maternal liver, placenta and foetus)	Cranmer et al. 1986

Table 9 (Continued)

Species, strain, number of animals	Exposure	Findings	References
rat, Sprague Dawley, groups of 15–19 ♀	**GD 6–15**; 0, 1064 mg **Al citrate**/kg body weight and day, gavage, corresponding to 0, 133 mg Al/kg body weight and day; investigation on GD 20	**133 mg Al/kg body weight**: dams: no effects, Al concentration in liver, bones and placenta increased; foetuses: no relevant effects [absence of xiphoid process and sternum in 31 foetuses in 9 litters (control 20 foetuses in 9 litters)]	Gomez et al. 1991
rat, Sprague Dawley, groups of 7–10 ♀	**GD 6–14**; 0, 180, 360, 720 mg **$Al(NO_3)_3 \times 9\ H_2O$**/kg body weight and day, gavage, corresponding to 0, 13, 26, 52 mg Al/kg body weight and day; investigation on GD 20	**13 mg Al/kg body weight and above**: dams: body weight gains decreased; foetuses: increase in atrophied foetuses, body weights decreased, changes in ribs decreased, delayed ossification (skull) increased **26 mg Al/kg body weight and above**: dams: placenta weights decreased; *foetuses*: delayed ossification (sternum); **52 mg Al/kg body weight**: foetuses: haematomas (abdomen, thorax)	Paternain et al. 1988
rat, Wistar, groups of 5–6 ♀	**GD 0–16**; 0, 345 mg **$AlCl_3$**/kg body weight and day, gavage, corresponding to 0, 70 mg Al/kg body weight and day; investigation on GD 17	**70 mg Al/kg body weight**: dams: Al concentration in blood, brain, placenta increased, body weight gains decreased, resorptions increased, GSH, GR, GST, GPx, SOD and AChE in the brain decreased, catalase, lipid peroxidation increased; foetuses: Al concentration increased, body weights decreased, delayed ossification, GSH, and GST in brain decreased, catalase and lipid peroxidation increased	Sharma and Mishra 2006

Table 9 (Continued)

Species, strain, number of animals	Exposure	Findings	References
Intraperitoneal, intravenous or subcutaneous administration			
mouse, Swiss, groups of 11 ♀	**GD 6–15**; 0, 37.5, 75 mg **$AlCl_3$**/kg body weight and day, intraperitoneal, corresponding to 0, 7.5, 15 mg Al/kg body weight and day; investigation on GD 18	**7.5 mg Al/kg body weight**: foetuses: body weights decreasd; **15 mg Al/kg body weight**: dams: no effects; foetuses: body weights decreased, no skeletal changes	Colomina et al. 1998
mouse, BALB/c, groups of 1–4 ♀	**GD 7–16**; 0, 100, 150, 200 mg **$AlCl_3$**/kg body weight and day, intraperitoneal, corresponding to 0, 20, 30, 40 mg Al/kg body weight and day; investigation on GD 18	**20 mg Al/kg body weight and above**: dams: Al concentration increased in liver (58-fold), placenta (10-fold), body weight not specified; foetuses: Al concentration increased (3-fold), body weights decreased, resorptions increased **40 mg Al/kg body weight**: dams: mortality increased (2/2)	Cranmer et al. 1986
rat, Holtzman, groups of 5–10 ♀	**GD 9–13 or 14–18**; 0, 75, 100, 200 mg **$AlCl_3$**/kg body weight, intraperitoneal, corresponding to 0, 15, 20, 40 mg Al/kg body weight and day; GD of investigation not stated	**15 mg Al/kg body weight**: dams: resorptions increased (only GD 9–13), foetuses: body weight no malformations; **20 mg Al/kg body weight**: dams: liver damage; foetuses: body weight unchanged, resorptions increased (only GD 14–18), malformations; **40 mg Al/kg body weight**: dams: mortality increased; foetuses: body weights decreased, absorptions increased (only GD 9–13), no malformations	Bennett et al. 1975
mouse, NMRI, groups of 6–12 ♀ (exposed), 20 ♀ (controls)	**GD 3 (0, 50, 100 mM)**, **GD 8 (0, 50 mM)**; 0, 50, 100 mM **$AlCl_3 \times 6\ H_2O$** (in 0.1 ml), intravenous, corresponding to 0, 48, 97 mg Al/kg body weight and day; investigation on GD 17	dams: no details, **48 mg Al/kg body weight (GD 8)**: foetuses: haemorrhages, delayed ossification; **97 mg Al/kg body weight**: foetuses: haemorrhages (abdomen)	Wide 1984

Table 9 (Continued)

Species, strain, number of animals	Exposure	Findings	References
rat, Wistar, groups of 3 ♀	**GD 16**; 705 pg ^{26}**Al** + 0.28 mg **$AlCl_3$**/ml, subcutaneous, corresponding to 0, 1.17 mg Al/kg body weight and day; investigation on GD 21	**1.17 mg Al/kg body weight**: dams: Al concentration in brain, liver, placenta increased; foetuses: Al concentration in brain, liver increased (only Al concentration in organs determined)	Yumoto et al. 2001

AChE: acetylcholinesterase; GD: gestation day; GPx: glutathione peroxidease; GR: glutathione reductase; GSH: glutathione; GST: glutathione *S*-transferase; SOD: superoxide dismutase

dependent (Paternain et al. 1988). Oral administration of aluminium doses of 70 mg/kg body weight and day (in the form of aluminium chloride) on days 0 to 16 of gestation led to maternal toxicity and delayed ossification, which was accompanied by an increased aluminium concentration and lipid peroxidation in the brain of the foetuses (Sharma and Mishra 2006). It is not possible to derive a NOAEL for the toxic effects on prenatal development in rats from the available studies. The lowest effective dose of aluminium was 13 mg/kg body weight and day.

Studies with intraperitoneal injection of aluminium chloride into mice (Colomina et al. 1998; Cranmer et al. 1986) and rats (Benett et al. 1974, 1975) were not used for evaluation on account of the non-physiological form of administration which can cause direct damage to the reproductive organs. One study with intravenous administration of aluminium chloride in mice (Wide 1984) is of little use on account of the bolus injection. In one study with subcutaneous injection of radioactively labelled aluminium chloride, increased aluminium concentrations were detected in maternal and foetal tissues in Wistar rats. No details of toxic effects were given (Yumoto et al. 2001).

Toxic effects on prenatal, perinatal and postnatal development

The results from animal studies of the toxic effects of soluble aluminium salts on prenatal, perinatal and postnatal development are shown in Table 10.

One research group carried out a number of studies with Swiss mice given prenatal and postnatal doses of aluminium lactate with the diet (Donald et al. 1989; Golub and Germann 2001; Golub et al. 1987, 1992 a, 1993, 1994, 1995, 2000). In some of the studies, doses as low as 500 mg/kg diet (corresponding to aluminium doses of 50 to 200 mg/kg body weight and day) produced effects in the dams such as reduced food intake and reduced body weight gains (Golub et al. 1987, 1992 a), whereas no maternally toxic effects were observed up to doses of 1000 mg/kg diet

Table 10 Animal studies of the toxic effects of aluminium salts on prenatal, perinatal and postnatal development

Species, strain, number of animals	Exposure	Findings	References
Oral administration			
mouse, Swiss, groups of 16–22 offspring	**GD 0–PND 21**; 100 (controls), 500, 1000 mg **Al lactate**/kg diet, corresponding to 17–54 (controls), 100–250, 170–350 mg Al/kg body weight and day (calculated from authors' data); investigation of offspring up to PND 20, investigation of dams up to a maximum of 4 months after giving birth	**100–250 mg Al/kg body weight and above**: dams: food intake and body weight gains decreased, ataxia (PND l2–15); offspring: body weight gains decreased (PND 10–20), crown-rump lengths decreased (PND 0, 20), neuromotor development decreased (PND 14–16, no change PND 8–13, 17–18); **170–350 mg Al/kg body weight**: dams: mortality (1 animal) after paralysis and dyspnoea; offspring: absolute and relative spleen weights decreased, absolute liver, kidney, heart, brain and thymus weights decreased, relative brain weights increased (PND 20)	Golub et al. 1987
mouse, Swiss, groups of 5 dams	**GD 0–PND 21**; 25 (controls), 500, 1000 mg **Al lactate**/kg diet, corresponding to 5–10 (controls), 100–210, 200–420 mg Al/kg body weight and day (authors' data); investigation of offspring up to PND 35	**100–210 mg Al/kg body weight and above**: offspring: behavioural changes (thermal sensitivity decreased, negative geotaxis decreased, foot splay); **200–420 mg Al/kg body weight** and above: dams: no effects	Donald et al. 1989
mouse, Swiss, groups of 6–12 offspring	**GD 0–PND 21**; 25 (controls), 1000 mg **Al lactate**/kg diet, corresponding to 5 (controls), 250 mg Al/kg body weight and day (authors' data); fostering study[1]; investigation of offspring postnatal (no other details)	**250 mg Al/kg body weight**: dams: body weight gains and feed intake decreased during lactation; offspring: litter size, birth weight and crown-rump length unchanged, body weight gains PND 21 decreased, grip strength forelimbs decreased, thermal sensi-	Golub et al. 1992 a

Table 10 (Continued)

Species, strain, number of animals	Exposure	Findings	References
		tivity decreased, grip strength hindlimbs increased, negative geotaxis decreased	
mouse, Swiss, groups of 3–11 offspring	**GD 0–PND 180**; 6 (controls), 1000 mg **Al lactate**/kg feed, corresponding to <1 (controls), 200–400 mg Al/kg body weight and day (estimated from Golub et al. 1994); investigation of offspring at the age of 6 months	**200–400 mg Al/kg body weight**: offspring: deficit in function of immune effector cells ($CD4^+$)	Golub et al. 1993
mouse, Swiss, groups of 6–7 offspring	**GD 0–PND 21 or 52**; 7 (controls), 1000 mg **Al lactate**/kg diet, corresponding to 1–3 (controls), 130 (offspring) or 200–420 (dams) mg Al/kg body weight and day (according to authors' data); investigation of offspring up to PND 55	**130–420 mg Al/kg body weight**: dams: no effects on body weight gain; offspring: auditory startle decreased, more rapid habituation	Golub et al. 1994
mouse, Swiss, groups of 6 offspring	**GD 1–PND 21, 50 or 170**; 7 (controls), 500, 1000 mg; **Al lactate**/kg diet, corresponding to 1–3 (controls), 100–210, 200–420 mg Al/kg body weight and day; investigation of offspring up to PND 170	**100–210 mg Al/kg body weight and above**: offspring: cage mate aggression after sexual maturity increased, operant learning behaviour increased, relearning decreased, grip strength of fore and hindlimbs decreased, fear reaction after air jet to eyes decreased; **200–420 mg Al/kg body weight**: dams: no effects on body weight gain; offspring: no effects on litter size, birth weights, body weight gains decreased PND 21	Golub et al. 1995
mouse, Swiss, groups of 6–18 offspring	**prenatal to end of life** ; 0.007, 1000 mg **Al lactate**/kg diet, corresponding to < 1, 100 mg Al/kg body weight and day (estimated from Golub and Germann 2001); investigation of offspring up to end of life	**100 mg Al/kg body weight**: offspring: body weight gains decreased, relative organ weights increased (spinal cord, heart, kidneys), Al concentration in brain decreased and spinal cord increased, grip strength of fore and	Golub et al. 2000

Table 10 (Continued)

Species, strain, number of animals	Exposure	Findings	References
		hindlimbs decreased, thermal sensitivity decreased, geotaxis decreased	
mouse, Swiss, groups of 15–20 offspring	**GD 0–PND 35**; 7 (controls), 100, 500, 1000 mg **Al lactate**/kg diet, corresponding to < 1 (controls), 10, 50, 100 mg Al/kg body weight and day (according to authors' data); investigation of offspring up to PND 150	**10 mg Al/kg body weight**: offspring: NOAEL; **50 mg Al/kg body weight and above**: offspring: no effects on litter size and birth weights, body weight gains decreased PND 21, learning in Morris water maze test decreased, 2 motor tests decreased; **100 mg Al/kg body weight**: dams: NOAEL; offspring: grip strength of hindlimbs decreased (covariation: body weight gains decreased)	Golub and Germann 2001
mouse, CBA and C57BL, groups of 12 offspring	**GD 10–17**; 0, 750, 1000, 1250 mg **Al sulfate**/l drinking water, corresponding to 0, 11, 15, 18 mg Al/kg body weight and day;investigation of offspring up to adulthood	**11 mg Al/kg body weight**: offspring: birth weights decreased (only CBA mouse); **15 mg Al/kg body weight**: offspring: birth weights decreased (CBA and C57BL mice); **18 mg Al/kg body weight**: dams: no effects (body weight); offspring: birth weights unchanged (CBA or C57BL mice), no uniform impairment in ultrasonic vocalization or radial maze test	Alleva et al. 1998
mouse, CBA, groups of 8–10 dams	**GD 10–17**; 0, 750 mg **Al sulfate**/l drinking water, corresponding to 11 mg Al/kg body weight and day; investigation on PND 15–308	**11 mg Al/kg body weight**: dams: not stated; offspring: no effect on body weights, changed choline acetyltransferase activity in the brain (inconsistent), no effects on grip strength, radial maze test, learning/memory	Clayton et al. 1992

Table 10 (Continued)

Species, strain, number of animals	Exposure	Findings	References
rat, Sprague Dawley, groups of 8–10 dams	**GD 14–PND 21**; 0, 180, 360, 720 mg **$Al(NO_3)_3 \times 9\ H_2O$**/kg body weight and day, gavage, corresponding to 0, 13, 26, 52 mg Al/kg body weight and day; investigation of offspring on PND 1, 4, 21	**13 mg Al/kg body weight and above**: offspring: body weights decreased (PND 21), relative kidney and brain weights increased; **26 mg Al/kg body weight and above**: offspring: relative heart weights increased (PND 21); **52 mg Al/kg body weight**: offspring: relative lung weights increased (PND 21), dead offspring/litter increased (PND 4)	Domingo et al. 1987 b
rat, Sprague Dawley, groups of 7–10 dams	**one-generation study: 60 days before mating (♂) or 14 days before mating up to PND 21 (♀)**; 0, 180, 360, 720 mg **$Al(NO_3)_3 \times 9\ H_2O$**/kg body weight and day, gavage, corresponding to 0, 13, 26, 52 mg Al/kg body weight and day; investigation of dams on GD 13 or PND 21; offspring on PND 1, 4, 21	**13 mg Al/kg body weight and above**: offspring: body weights decreased (PND 1); **26 mg Al/kg body weight and above**: offspring: body weights decreased, living offspring/litter decreased, dead offspring/litter increased (PND 21) **52 mg Al/kg body weight**: dams: corpora lutea decreased; offspring: no effects on resorptions, living or dead foetuses	Domingo et al. 1987 a
rat, Sprague Dawley, groups of 9–15 dams	**15 days before mating up to PND 21 (♀); offspring up to 2 years**; 0, 50, 100 mg Al/kg body weight and day, gavage, as **$Al(NO_3)_3) \times 9\ H_20$**; investigation of dams PND 21; offspring on PND 12–60, 1 year (adult), 2 years (old)	**50 mg Al/kg body weight and above**: dams: body weights decreased (GD 21); offspring: body weight gains decreased (PND 21, 2 years); **100 mg Al/kg body weight**: offspring: Al concentration in the brain not increased postnatally, significantly increased at 2 years, grip strength of forelimbs decreased (PND 11, 13), age at descent of	Colomina et al. 2005, Roig et al. 2006

Table 10 (Continued)

Species, strain, number of animals	Exposure	Findings	References
		testes increased, age at vaginal opening increased, no change in motor activity (1 or 2 years), learning in water maze test decreased (1 and 2 years)	
rat, THA, groups of 10–20 offspring	**GD 1–21**; 0, 90, 180, 360 mg **$AlCl_3$**/kg body weight and day, gavage, corresponding to 18, 36, 72 mg Al/kg body weight and day; investigation of offspring on PND 28	**36 mg Al/kg body weight**: offspring: no effects; **72 mg Al/kg body weight**: offspring: body weight gain unchanged, only changes in open field out of 15 tests	Misawa and Shigeta 1992
rat, THA, groups of 2–18 offspring	**GD 15**; 0, 900, 1800 mg **$AlCl_3$**/kg body weight and day, gavage, corresponding to 180, 360 mg Al/kg body weight and day; investigation of offspring on PND 28	**180 mg Al/kg body weight and above**: offspring: birth weights decresed, body weight gains decreased, pinna detachment decreased, auditory startle reaction decreased (♂); **360 mg Al/kg body weight**: offspring: opening of eyes delayed, open field decreased	Misawa and Shigeta 1993
rat, Wistar, groups of 5–6 ♀	**GD 0–PND 16**; 0, 345 mg **$AlCl_3$**/kg body weight and day, gavage, corresponding to 0, 70 mg Al/kg body weight and day; investigation of offspring on PND 17	**70 mg Al/kg body weight**: dams: GD 17: Al concentration in blood, brain, placenta increased, body weight gains decreased, resorptions increased, glutathione, glutathione reductase, glutathione *S*-transferase, glutathione peroxidease, superoxide dismutase and AChE in the brain decreased, catalase, lipid peroxidation increased; offspring: PND 17: Al concentration increased, glutathione, glutathione reductase and AChE in the brain decreased, glutathione *S*-transferase and substances reactive to thiobarbituric acid increased	Sharma and Mishra 2006

Table 10 (Continued)

Species, strain, number of animals	Exposure	Findings	References
rat, Wistar, groups of 10–12 offspring	**GD 1–21**; 0, 160, 200 mg Al/kg body weight and day, with the diet, as **$AlCl_3$**; investigation of offspring on PND 20	**160 mg Al/kg body weight and above:** offspring: body weight gains decreased, righting reflex decreased; **200 mg Al/kg body weight:** offspring: geotaxis decreased	Bernuzzi et al. 19861986
rat, Wistar, groups of 12 offspring/ litter	**GD 1–21**; 0, 100, 300, 400 mg Al/kg body weight and day, with the diet, as **$AlCl_3$**; investigation of offspring on PND 20	**100 mg Al/kg body weight:** dams, offspring: no effects; **300 mg Al/kg body weight and above:** dams: body weight gains decreased (only GD 18); offspring: postnatal mortality increased, righting reflex decreased, motor co-ordination decreased, grip strength decreased; **400 mg Al/kg body weight:** offspring: geotaxis decreased	Bernuzzi et al. 1989
rat, Wistar, groups of 10 offspring/ litter	**GD 1–21**; 0, 100, 300, 400 mg Al/kg body weight and day, with the diet, as **Al lactate**; investigation of offspring on PND 20	**100 mg Al/kg body weight and above**: offspring: grip strength decreased; **300 mg Al/kg body weight and above**: offspring: righting reflex decreased; **400 mg Al/kg body weight**: dams: body weight gains decreased (only GD 18); offspring: postnatal mortality increased, body weight gains decreased, motor activity decreased	Bernuzzi et al. 1989
rat, Wistar, groups of 6–9 dams	**GD 1–7; 1–14; 1–20**; 0, 400 mg Al/kg body weight and day, gavage, as **Al lactate**; investigation of offspring up to PND 65	**400 mg Al/kg body weight**: dams: Al concentration in the plasma increased (GD 1–20), body weight gains decreased; offspring: negative geotaxis decreased, motor co-ordination decreased, operant conditioning decreased	

Table 10 (Continued)

Species, strain, number of animals	Exposure	Findings	References
rat, Charles River CD, groups of 3 dams	**GD 5–15**; 0, 5, 25, 50, 250, 500, 1000 mg Al/kg body weight and day, gavage, as **Al lactate**; investigation of offspring (no other details)	**250 mg Al/kg body weight**: offspring: duration of oestrus cycle increased (only at this dose); **up to 1000 mg Al/kg body weight**: dams: not specified; offspring: no consistent or reproducible developmental toxicity (e.g.: birth weights, anogenital distance, gonadal weights, age of puberty in ♀)	Agarwal 19961996
Intraperitoneal or subcutaneous administration			
mouse, CBA, groups of 9–10 dams	**GD 10–13**; 0, 200 mg **Al sulfate**/kg body weight, intraperitoneal, corresponding to 16 mg Al/kg body weight and day; fostering study[1]; investigation of offspring on PND 21	**16 mg Al/kg body weight and above**: dams: body weight gains decreased (gestation); offspring: birth weights decreased, body weight gains decreased, grip strength of the forelimbs decreased, climbing behaviour decreased, ultrasonic vocalization decreased	Rankin and Manning 1993
mouse, CBA/T6, C57BL/6J, groups of 12 offspring	**GD 10–13**; 0, 200 mg **Al sulfate**/kg body weight, intraperitoneal, corresponding to 0, 16 mg Al/kg body weight and day; fostering study[1]; investigation of offspring up to adulthood	**16 mg Al/kg body weight**: dams: body weight gains decreased (only CBA); offspring: birth weights decreased, body weight gains decreased, ultrasonic vocalization decreased (CBA, C57 seldom), radial maze test decreased	Alleva et al. 1998
mouse, CBA, groups of 11–14 dams	**GD 10–13**; 0, 200 mg **Al sulfate**/kg body weight, intraperitoneal, corresponding to 16 mg Al/kg body weight and day; fostering study[1]; investigation of offspring on PND 15–308	**16 mg Al/kg body weight**: dams: not specified; offspring: birth weights decreased, body weight gains decreased, changed choline acetyltransferase activity in the brain (hippocampus, cortex), reflex maturation (including grip strength) decreased	Clayton et al. 1992
mouse, C57Bl/6J, groups of 14 dams	**GD 10–13**; 0, 200 mg **Al sulfate**/kg body weight, intraperitoneal, corresponding to 16 mg Al/kg body weight and day; fostering study[1]; investigation of offspring on PND 70	**16 mg Al/kg body weight**: dams: not specified; offspring (♂): radial maze test decreased, nerve growth factor (NGF) in brain increased	Santucci et al. 1994

Table 10 (Continued)

Species, strain, number of animals	Exposure	Findings	References
rat, SD, groups of 7–10 dams	**GD 7–15**; 0, 2.45, 4.9, 9.8 mg **Al lactate**/kg body weight, subcutaneous, corresponding to 0, 0.22, 0.44, 0.89 mg Al/kg body weight and day; investigation of offspring up to PND 93	**0.22 mg Al/kg body weight and above**: offspring: no effects on birth weight, body weight gains decreased (PND 21); **0.44 mg Al/kg body weight and above**: offspring: avoidance task, acquisition and extinction decreased; **up to 0.89 mg Al/kg body weight**: dams: no mortality or symptoms; offspring: explorative activity decreased (open field, PND 36, 93), passive and conditioned avoidance tasks decreased, no effects on motor co-ordination (Rotarod), fear reaction or taste aversion learning	Gonda and Lehotzky 1996 Gonda et al. 1996, 1997
rat, Wistar, groups of 3 dams	**PND 1–20**; 0, 470 pg ^{26}Al + 0.009 mg **$AAlCCl_3$**/0.2 /0.2 ml, subcutaneous, corresponding to 0, 0.75 mg Al/kg body weight and day; investigation of dams and offspring up to PND 20	**0.75 mg Al/kg body weight**: dams: Al concentration in maternal milk increased; offspring: Al concentration in bones, liver, kidneys, brain increased (determination of Al concentrations in dams and offspring only)	Yumoto et al. 2001
rabbit, New Zealand, groups of 6–23 dams	**GD 2–27 (20 injections)**; 0, 25, 100, 400 µmol **Al lactate**/kg body weight; subcutaneous, corresponding to 0, 0.7, 2.7, 11 mg Al/kg body weight and day; fostering study1; investigation of offspring on PND 2 and at the age of 13 weeks; investigation of dams up to 13 weeks after giving birth	**0.7 mg Al/kg body weight and above**: dams: NOAEL, Al concentration in liver and spleen increased; offspring: Al concentration in brain, kidneys increased (PND 2); **2.7 mg Al/kg body weight and above**: dams: body weight gains decreased, Al concentration in bones, heart and kidneys increased;	Yokel 1985

Table 10 (Continued)

Species, strain, number of animals	Exposure	Findings	References
		offspring: NOAEL, Al concentration in bones, muscles increased (PND 2); **11 mg Al/kg body weight**: offspring: milk intake decreased, mortality increased (58%), body weight gains decreased, Al concentration in heart, liver, lungs increased (PND 2), classical conditioning decreased (acquisition, retention)	
rabbit, New Zealand, groups of 5–12 dams	**GD 2-PND 1 or PND 1–30**; 0, 400 µmol **Al lactate**/kg body weight; subcutaneous, corresponding to 0, 11 mg Al/kg body weight and day; investigation of offspring at the age of 7 and 11 weeks	**11 mg Al/kg body weight**: offspring: no changes in conditioned eyeblink reflex (acquisition, retention, extinction)	Yokel et al. 1994

AChE: acetylcholinesterase; GD: gestation day; PND: postnatal day
[1] fostering study: exposure of offspring of one dose group during gestation or lactation only or during both gestation and lactation

(corresponding to 100 to > 400 mg/kg body weight and day) in other studies (Donald et al. 1989; Golub and Germann 2001; Golub et al. 1994, 1995). Developmental toxicity was found during the lactation phase in the form of delayed body weight gains after doses of 500 and 1000 mg/kg diet (corresponding to aluminium doses of 50 to 200 and 200 to > 400 mg/kg body weight and day). In some studies, impairments in neuromotor development, geotaxis or reflex behaviour were found (Donald et al. 1989; Golub et al. 1987, 1992 a). Also changes in complex learning performance were described in later investigations, although dose-effect relationships were not always observed (Golub et al. 1994, 1995, 2000). In a more recent investigation by this group, also the aluminium dose range below 100 mg/kg body weight and day (1, 10, 50 and 100 mg/kg body weight and day) was investigated in more detail. In particular, the body weight development of the pups was closely monitored, exposure during the peripubertal period was extended up to postnatal day 35, and motor and cognitive performance tests in which the animals were not motivated by feed were compared. Cognitive tests were performed in the female offspring after an exposure-free interval of about 2 months, and motor tests in the male offspring after an interval of 4 months. Tendencies towards impaired perfor-

mance were observed in the cognitive parameters (Morris water maze test) taking the delayed body weight gains in female mice after aluminium doses of 50 mg/kg body weight and day and above into account by covariance analysis. In the motor tests with the male offspring, the number of significant effects was reduced after a covariance analysis on significant effects in only one Rotarod test: that at the high aluminium dose of 100 mg/kg body weight and day. The NOAEL for toxic effects on perinatal or postnatal development was aluminium lactate doses of 100 mg/kg diet, corresponding to aluminium doses of 10 mg/kg body weight and day (Golub and Germann 2001).

No consistent changes in behavioural tests (grip strength, learning, memory, ultrasonic vocalization, radial maze test) were found in the offspring of CBA or C57BL mice given aluminium sulfate concentrations of 750 or up to 1250 mg/l drinking water (corresponding to aluminium doses of 11 to 18 mg/kg body weight and day) on gestation days 10 to 17. The reduced birth weights at some dose levels were contradictory and not dose-dependent. No maternal effects were found (Alleva et al. 1998; Clayton et al. 1992). From these studies, the NOAEL for the toxic effects of aluminium sulphate on perinatal and postnatal development corresponded to aluminium doses of 15 to 18 mg/kg body weight and day.

In Sprague Dawley rats exposed from gestation day 14 to postnatal day 21 of the offspring (Domingo et al. 1987 b) or throughout the lives of one generation (Domingo et al. 1987 a) body weights were reduced in the offspring on the first postnatal day after aluminium nitrate doses of 180 mg/kg body weight and day (corresponding to aluminium doses of 13 mg/kg body weight and day) and above (Domingo et al. 1987 a) or body weight gains were reduced up to postnatal day 21 and the relative kidney and brain weights were increased (Domingo et al. 1987 b). In the one-generation study (Domingo et al. 1987 a), a reduced number of corpora lutea was found in the dams of the high dose group (aluminium doses of 52 mg/kg body weight and day); however, the findings were not considered relevant as no changes were found regarding implants, early or late resorptions or living or dead foetuses. In another study, in which the dams were exposed for 15 days before mating and the offspring for up to 2 years, the administered aluminium doses of 50 and 100 mg/kg body weight and day were toxic for the dams and for the adult offspring; in the offspring reduced body weight gains, delayed maturation and impaired learning performance in the water maze test were observed (Colomina et al. 2005; Roig et al. 2006). The LOAEL for developmental toxicity was found to be aluminium nitrate doses of 180 mg/kg body weight and day, corresponding to aluminium doses of 13 mg/kg body weight and day. No NOAEL could be derived.

In THA rats, gavage doses of aluminium chloride of up to 360 mg/kg body weight and day (corresponding to aluminium doses of 72 mg/kg body weight and day) from gestation days 1 to 21 did not affect body weight gain or avoidance behaviour in the offspring. At this dose, significant changes in maturation were observed in 2 of 15 tests. The NOAEL obtained from this study corresponded to aluminium doses of 36 mg/kg body weight and day (Misawa and Shigeta 1992). Effects on birth weights,

increased body weights and conspicuous results in behavioural tests were observed after single doses of aluminium of 180 mg/kg body weight and day on day 15 of gestation (Misawa and Shigeta 1993). Prenatal and postnatal exposure resulted in increased aluminium concentrations and lipid peroxidation in the brain of the pups up to day 17 of lactation (Sharma and Mishra 2006). In investigations by another research group increased mortality in the offspring, reduced body weight gains and impaired neuromotor performance were also observed in some cases in Wistar rats at aluminium doses of 160 mg/kg body weight and day and above after administration of aluminium chloride with the diet from days 1 to 21 of gestation (Bernuzzi et al. 1986, 1989). A NOAEL corresponding to aluminium doses of 100 mg/kg body weight and day can be derived from the study by Bernuzzi et al. (1989).

In rats given aluminium lactate with the diet from days 1 to 21 of gestation, impairments were observed in grip strength at aluminium doses of 100 mg/kg body weight and day and above, and in the righting reflex at 300 mg/kg body weight and day and above; reduced motor activity was seen at 400 mg/kg body weight and day together with increased postnatal mortality and reduced body weight gains (Bernuzzi et al. 1989). In this study, 100 mg/kg body weight and day was considered to be the LOAEL. The aluminium concentration in plasma was increased and body weight gains reduced in rats given gavage doses of aluminium lactate (corresponding to aluminium doses of 400 mg/kg body weight and day) on gestation days 1 to 7 or 1 to 14 or 1 to 20. Reduced performance in tests for negative geotaxis, motor co-ordination and operant conditioning was found in the offspring (Muller et al. 1990). In one investigation, gavage doses of aluminium of 5 to 1000 mg/kg body weight and day were administered to Charles-River rats in the form of aluminium lactate on days 5 to 15 of gestation. Although significant deviations in birth weights, testis weights, the anogenital distance, the age at puberty and the duration of the oestrus cycle were occasionally found up to the high dose of 1000 mg/kg body weight and day, these were, however, either not dose-dependent or not consistently changed (Agarwal et al. 1996). No changes in the development and maturation of the offspring could therefore be determined from this study even at high doses. Changes in behaviour were not investigated.

Studies to determine neurotoxic effects during development with subcutaneous injection of aluminium salts are more suitable than the studies of the toxic effects on prenatal development with intraperitoneal injections, which can produce direct damage to the reproductive organs. It must be taken into account, however, that the injected aluminium salt is completely bioavailable in these studies, whereas only a certain amount is absorbed after oral administration and inhalation exposure. In a number of studies mice of different strains were given intraperitoneal aluminium sulphate doses of 200 mg/kg body weight and day (corresponding to aluminium doses of about 16 mg/kg body weight and day) on gestation days 10 to 13. In the dams this resulted in reduced body weight gains (Alleva et al. 1998; Rankin and Manning 1993) and in the offspring in reduced birthweights and delayed body weight gains (Alleva et al. 1998; Clayton et al. 1992; Rankin and Manning 1993). In addition, delayed ultrasonic vocalization responses and reduced

grasping performance of the forelimbs (Rankin and Manning 1993), reduced performance in the radial maze test (Alleva et al. 1998; Santucci et al. 1994), delayed reflex maturation and reduced motor activity (Clayton et al. 1992) were observed on postnatal day 21. All of these studies with mice with intraperitoneal administration of aluminium sulfate show there to be an influence on reflexes, neuromotor activity and behaviour in conjunction with an effect on body weights after aluminium doses in the range of about 16 mg/kg body weight and day.

After subcutaneous injection of aluminium lactate on days 7 to 15 of gestation no effects on birthweight were found in rats at the lowest dose (corresponding to an aluminium dose of about 0.22 mg/kg body weight and day) or above, but significantly delayed body weight gains, determined on postnatal day 21, were observed. Body weight development was not monitored further. Negative effects on avoidance learning (acquisition, extinction) were observed at aluminium doses of 0.44 mg/kg body weight and day and above, and on reaction ability and activity at 0.89 mg/kg body weight and day. There were no group differences in taste aversion learning (Gonda and Lehotzky 1996; Gonda et al. 1996) and no effects on social learning behaviour as regards conditioned avoidance responses (Gonda et al. 1997). In these studies, the LOAEL for postnatal toxicity in rats after subcutaneous injection of aluminium lactate during gestation corresponded to aluminium doses of about 0.22 mg/kg body weight and day.

In New Zealand White rabbits, the subcutaneous injection of aluminium lactate doses corresponding to aluminium doses of 0, 0.7, 2.7 or 11 mg/kg body weight and day on days 2 to 27 of gestation resulted in reduced body weight gains after doses of 2.7 mg/kg body weight and above, and increased mortality (58%), reduced body weight gains and poorer performance in the conditioned reflex test in the offspring after doses of 11 mg/kg body weight and day (Yokel 1985). The NOAEL in the rabbit offspring for the impairment in performance in the conditioned reflex test and the increased mortality after subcutaneous injection of aluminium lactate corresponded to aluminium doses of 2.7 mg/kg body weight and day, and the NOAEL for maternal toxicity to 0.7 mg/kg body weight and day.

Summary

There are no studies available of developmental toxicity after inhalation exposure to dusts containing aluminium, aluminium oxide and aluminium hydroxide. The NOAEL in mice for the toxic effects of aluminium hydroxide on prenatal development after oral administration corresponded to aluminium doses of 100 mg/kg body weight and day, and in rats to aluminium doses of 266 mg/kg body weight and day, the highest doses used. The bioavailability of these poorly soluble aluminium compounds therefore seems to be low.

On the other hand, the bioavailability of soluble aluminium salts is considerably better. In mice (Albina et al. 2000; Colomina et al. 1992) and rats (Paternain et al. 1988), the oral administration of soluble aluminium salts at maternally toxic doses

(mouse: aluminium doses of 57 to 95 mg/kg body weight and day; rat: aluminium doses of 13 to 52 mg/kg body weight and day) led to developmental toxicity, such as reduced foetal weights and delayed ossification, and additionally in mice to increased incidences of cleft palates and dorsal hyperkyphosis. In the mouse, cleft palates and other malformations are frequently observed also in the offspring of dams under stress without any substance being administered (Barlow et al. 1975). The disturbed ossification and variations occurring in the foetuses could therefore be secondary effects of maternal toxicity. Foetal weights were reduced even after aluminium doses as low as 7 mg/kg body weight and day (Colomina et al. 1998). Reduced foetal body weights can therefore be considered to be the most sensitive end point of prenatal developmental toxicity. In a developmental toxicity study with postnatal investigation of the offspring (Domingo et al. 1987 b) and a one-generation study (Domingo et al. 1987 a) the birthweights of the offspring were reduced after aluminium doses of 13 mg/kg body weight and day.

In prenatal and postnatal developmental toxicity studies with soluble aluminium salts effects on behaviour were observed, mostly together with a simultaneous reduction in body weight gains in the offspring. The NOAEL for the toxic effects of aluminium lactate on perinatal or postnatal development after oral administration in mice corresponded to aluminium doses of 10 mg/kg body weight and day (Golub and Germann 2001). In studies with mice with intraperitoneal injection of aluminium sulfate, developmental neurotoxicity and systemic effects were observed at aluminium doses of about 16 mg/kg body weight and day. After subcutaneous injection of aluminium lactate, a NOAEL corresponding to aluminium doses of 2.7 mg/kg body weight and day was obtained for developmental toxicity and developmental neurotoxicity in the rabbit; the NOAEL for maternal toxicity corresponded to aluminium doses of 0.7 mg/kg body weight and day.

The animal studies of neurotoxicity, however, have methodological shortcomings: inadequate correction of multiple tests and the inadequate experimental or statistical checking of potential confounders. The non-critical consideration of the number of reported significant test results thus produced an overestimation or misjudgement of the neurotoxicity of aluminium. Also insufficient knowledge of the relationship between delayed body weight development and neurotoxicologically relevant behavioural parameters was the cause of misjudgements. However, mechanistic studies indicate aluminium-related changes in the hippocampus (Clayton et al. 1992) that could be the cause of behavioural changes. Also, studies which experimentally monitor aluminium-related taste aversion and delayed body weight development or statistically account for the weight development factor in multivariate covariance analyses are lacking. The fact that some of the studies were performed using a low number of litters (7 to 10) must also be considered. A considerable theoretical shortcoming of all neurotoxicological studies is that the dose, duration and phase of exposure were hardly varied systematically. Studies including the low exposure ranges, which are of relevance for the workplace and environmental exposure of humans, are absent. There are also no studies which reflect exposure over a more extended life span and simulate possible deposit formation. In particular, no models

for long-term inhalation exposure in adult animals are available which could be used to determine workplace-relevant threshold values. It is at present not possible to answer the question whether the animal studies with behavioural effects reflect neurotoxic effects of aluminium or whether these are secondary effects produced by other toxic effects such as reduced body weight gains.

In addition, in the animal studies, the dose levels are imprecise, difficult to compare and often contradictory. The administration of aluminium salts with the diet cannot reflect the actual aluminium intake if no information is supplied about how food intake varies according to gestation phase, lactation phase, maturation phase or in connection with aversion to food or weight development, and how the food intake of exposed and control animals differs. The estimates for aluminium intake calculated here for study comparison are based on an interpretation of the quoted literature and only roughly reflect the actual intake.

The relevance of prenatally toxic and potentially neurotoxic effects in the evaluation of dusts containing aluminium, aluminium oxide and aluminium hydroxide after inhalation exposure is therefore not clear. Studies with subcutaneous injection allow the best estimates, as a known aluminium quantity is bioavailable without producing direct toxic effects on the reproductive organs, as found with intraperitoneal injection. Thus, subcutaneous injection of aluminium doses of 2.7 mg/kg body weight and day did not cause reduced birthweights in the offspring of rabbits (Yokel 1985) and 0.2 mg/kg body weight and day did not affect the birthweights in rats, although there were delayed body weight gains during lactation (Gonda and Lehotzky 1996; Gonda et al. 1996, 1997).

5.6 Genotoxicity

5.6.1 In vitro

After incubation of Novikoff ascites hepatoma cells with 0.05, 0.1, 0.2, 0.5, 1 or 5 mM aluminium chloride, the maximum number of DNA-protein crosslinks (matrix, chromatin, lamin and cytokeratin fractions) was found at 0.5 mM (Wedrychowski et al. 1986).

It was shown that 0.050 to 0.100 mM aluminium chloride led to the precipitation of isolated chromatin from liver and brain cells; the chromatin from cells of the cortical areas of the brain reacted the most readily. The reduced degradation of chromatin by nucleases as a result of 0.100 mM aluminium chloride was attributed to changes in chromatin structure (Walker et al. 1989).

In an investigation of the non-enzymatic glycation of the isolated histone H1 from rat liver, a repressor, selective glycation of lysin residues took place in the vicinity of the nucleotide binding site after the addition of 0.010 mM aluminium fluoride in the presence of 20 mM glucose and in the absence of nucleotides. This adduct formation seems to interfere with the nucleoside triphosphate hydrolysis of

H1 and with the nucleotide-controlled modulation of the H1-DNA bond, and consequently with the repressor function of H1 (Tarkka et al. 1993).

The addition of aluminium chloride to a calf thymus DNA solution led to the formation of DNA complexes. At an aluminium:DNA ratio of 0.5 and a pH of 5, absorption values (no other details) similar to those of single-strand DNA and serious ultrastructural changes were detected at 260 nm. The latter were manifest in the form of macromolecular aggregates, consisting of linear, filamentous and toroidal structures. This process was partially reversible after the addition of EDTA, sodium hydroxide or desferrioxamine mesylate. A number of thicker filamentous structures remained, however (Karlik et al. 1989).

In an investigation using nuclear magnetic resonance (NMR), circular dichroism (CD) and ultraviolet (UV) spectroscopy, a reversible change in DNA structure caused by the binding of aluminium ions from added aluminium nitrate or aluminium acetate was found. The NMR spectra changed after the addition of aluminium ions to calf thymus DNA fragments and the changed ^{31}P-NMR and ^{27}Al-NMR signals indicate in the authors' opinion the specific binding of aluminium ions with the oxygen of the phosphate group of the DNA while hydroxylated aluminium compounds bind with other DNA regions, for example DNA bases. The changes in CD spectra were reversible after the addition of EDTA, which is attributed to complexation of the aluminium by EDTA (Rao and Divakar 1993).

At pH 7.4, aluminium ions in the physiologically relevant concentration range of 33×10^{-6} to 333×10^{-6} mM induced irreversible superhelical DNA, whereby the proportion of unwinding DNA increased with higher aluminium ion concentrations. After simultaneous incubation of EDTA and aluminium ions, no uncoiling of superhelical DNA was observed (Rao et al. 1993).

In a more recent study, the influence of aluminium on (CCG)12 repeats (synthesized oligonucleotides) was investigated using circular dichroism spectroscopy and Z-DNA-specific antibodies. It was established that 0.010 mM aluminium produced a transition of the available B-DNA into the Z-DNA conformation form. The pH was 7.4. However, a highly soluble and pH-stable aluminium maltolate complex was used which is about 100 times more soluble than any other inorganic aluminium complex. The effective dose was 0.5×10^{-3} mM. The conformation change was irreversible even after administration of the chelator desferrioxamine (Latha et al. 2002).

The copying accuracy of DNA synthesis was unchanged between 0, 0.020 and 150 mM aluminium sulfate (Léonard and Gerber 1988).

At a pH of 4.5 to 5.5, the binding of aluminium ions to calf thymus DNA was demonstrated by potentiometric titration and atomic absorption spectroscopy (Dyrssen et al. 1987).

On heating the calf thymus DNA, no depurination of DNA was found in the tested concentration range of 0.01 to 0.1 mM aluminium chloride (Léonard and Gerber 1988).

In tests for the differential killing of DNA-repair proficient and deficient *Bacillus subtilis* strains H17 (Rec^+, arg^-try^-) and M45 (Rec, arg^-try^-) aluminium sulfate,

aluminium chloride, aluminium oxide and aluminium phosphate yielded negative results in the concentration range between 0.005 and 500 mM (Kada et al. 1980, Kanematsu et al. 1980, Nishioka 1975).

Aluminium fluoride concentrations of 1 to 5000 µg/plate in water were not found to be mutagenic in the *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and the *Escherichia coli* strain WP2uvrA in the presence and absence of S9 mix from the liver of male Sprague Dawley rats pretreated with polychlorinated biphenyls (Shimizu et al. 1985). In *Salmonella typhimurium* strain TA102 aluminium chloride ($AlCl_3 \times 6\ H_2O$) was not mutagenic in non-toxic concentrations of 10 to 1000 nM in water (Marzin and Phi 1985).

Investigations with *Salmonella typhimurium* strain TA98 yielded negative results with aluminium ion concentrations in the range of 0.3×10^{-3} and 3×10^{-3} mM (Ahn and Jeffery 1994).

In SOS chromotests, 0.001 to 3000 nM aluminium chloride and 1 to 3000 nM aluminium sulfate [$Al_2(SO_4)_3$] did not induce the expression of the sfiA gene in *Escherichia coli* PQ-37 ($uvrB^-$), which is expressed to an increased extent after DNA damage. Cytotoxicity occurred with both salts at 3000 nM (Olivier and Marzin 1987).

No toxic effects were found after incubation of the *Rhizobium* strains RDG-2002 or NZP-2037 for 18 hours with 50 μm aluminium potassium sulfate. After further, aluminium-free, incubation for 3 to 14 days, increased resistance to rifampicin was observed in the aluminium-treated RDG-2002 bacteria, which the authors attributed to a possible mutagenic effect of aluminium (Octive et al. 1991).

A $TK^{+/-}$ mutation test with L5178Y mouse lymphoma cells yielded negative results for aluminium chloride (Oberly and Piper 1980).

In another $TK^{+/-}$ mutation test with L5178Y mouse lymphoma cells, aluminium chloride concentrations of 0.570 to 0.625 mg/ml produced a non-concentration-dependent two-fold increase in mutation frequency with a non-linear reduction in the number of surviving cells. In the repeat test, aluminium chloride was not or only slightly mutagenic with non-linear toxic effects (Oberly et al. 1982).

Human lymphocytes from the blood of five healthy male and female donors per age group (0 to 10; 21 to 30; 41 to 50 years) were incubated with aluminium sulphate concentrations of 20 µg/ml medium for 72 hours. There was a statistically significant reduction in the mitosis index compared with that for the control group only in the lymphocytes of male donors in the age group of 41 to 50 years. The frequency of micronuclei and chromosome aberrations was significantly increased in the lymphocytes treated with aluminium sulfate compared with those in the control group (Roy et al. 1990). In another investigation, lymphocytes (blood) and fibroblasts (skin biopsies) of patients with sporadic (14) or hereditary (8) Alzheimer's disease and of 17 controls were incubated in the presence and absence of 1 mM aluminium sulfate [$Al_2(SO_4)_3$] and the micronucleus frequency was determined. The latter was significantly increased in the lymphocytes and fibroblasts of patients with sporadic and hereditary Alzheimer's disease. However, additional treatment of the cells *in vitro* with aluminium did not increase the micronucleus

frequency. In the lymphocytes and fibroblasts of the controls on the other hand, an increase in micronucleus frequency could be found after incubation with aluminium sulfate (Trippi et al. 2001).

The lymphocytes of two young healthy non-smoking donors (A and B) were isolated and treated in a medium with 0, 0.5, 1, 2 or 4 mM aluminium sulfate 24 hours after phytohaemoagglutinin stimulation. The cells were harvested after 72 hours. In addition, 50 lymphocytes from donor B containing micronuclei were analysed using the fluorescence *in situ* hybridization (FISH) method after incubation with 0, 1 or 2 mM aluminium sulfate. Fluorescein-5-isothiocyanate (FITC)-labelled micronuclei were evaluated as centromer-positive micronuclei and unlabelled micronuclei as centromer-negative micronuclei. As positive controls, mitomycin C was used for clastogenic effects, and griseofulvin for aneugenic effects. A significant increase in micronucleus frequency was found at 1 and 2 mM in the lymphocyte cultures of donor A. The micronucleus frequency was dose-dependently increased at 0.5 mM and above in cultures with lymphocytes from donor B, but this was not statistically significant. The FISH analysis revealed an increase in centromer-negative and centromer-positive micronuclei at both concentrations (1 and 2 mM) which indicates that aluminium acts both clastogenically and aneugenically. As the number of centromer-positive micronuclei was somewhat higher (68.6%) compared with the number of centromer-negative micronuclei, it was assumed that aluminium effectively interferes with the segregation of chromosomes (Migliore et al. 1999). In an abstract, it was reported that single strand breaks were induced at the lowest tested aluminium chloride concentration of 0.1×10^{-3} mM, whereby leukocytes in human blood reacted more sensitively than isolated lymphocytes (Valverde et al. 1996).

5.6.2 In vivo

Groups of 5 male Swiss mice were given single intraperitoneal injections of aluminium sulphate of 0, 100, 200 or 400 mg/kg body weight in 0.9% sodium chloride or, as positive control, mitomycin C doses of 2.5 mg/kg body weight immediately after subcutaneous implantation of 50 mg bromodeoxyuridine (Dhir et al. 1993). Twenty-two hours later, the animals were given a single colchicine dose of 4 mg/kg body weight. After a further two hours bone marrow cells were isolated and chromosome preparations were made and stained with fluorescence plus Giemsa stain. The bone marrow mitoses (60 metaphase cells per animal) showed sister chromatid exchange to be increased (trend test $p < 0.001$). The proliferation index was unchanged at all aluminium sulfate doses. The frequency of sister chromatid exchange was reduced after oral doses of water-soluble fruit extract from *Phyllanthus emblica* of 685 mg/kg body weight or of ascorbic acid doses of 16.6 mg/kg body weight for seven days before the intraperitoneal administration of aluminium sulphate; the fruit extract was found to be more effective for causing a reduction.

In a micronucleus test, groups of 6 male and 6 female Swiss mice were given intraperitoneal doses of aluminium sulphate of 0, 250 or 500 mg/kg body weight in 0.9% sodium chloride for two days, or mitomycin C doses of 1.5 mg/kg body weight as positive control (Roy et al. 1992). Six animals from each group were killed 24 and 48 hours after the last dose. The micronucleus frequency was determined in 1000 polychromatic erythrocytes (PCE) per animal and the normochromatic erythrocytes (NCE) were counted (up to 1000 per animal). The micronucleus frequency in the polychromatic cells of the animals given aluminium sulphate doses of 500 mg/kg body weight was significantly increased after 24 and 48 hours compared with that in the controls. The NCE:PCE ratio did not deviate from that in the control group. It was possible to reduce the micronucleus frequency in the animals treated with aluminium sulphate to the control level by previously giving the animals oral doses of water-soluble fruit extract from *Phyllanthus emblica* of 685 mg/kg body weight or ascorbic acid doses of 16.66 mg/kg body weight for seven days.

Aluminium sulphate doses of 0, 212, 265, 353, 530, 1060 or 2120 mg/kg body weight and day in distilled water (corresponding to aluminium doses of 0, 17, 22, 28, 43, 85 and 172 mg/kg body weight and day) or potassium aluminium sulfate (potassium alum) doses of 0, 503 or 764 mg/kg body weight and day (corresponding to aluminium doses of 28 and 43 mg/kg body weight and day) were administered orally to groups of 15 male rats (*Rattus norvegicus*) for up to 21 days. No positive controls were included. The mitosis index in the bone marrow cells of the femur was reduced in a dose dependent manner at all aluminium sulfate doses and over all treatment periods (Cochran-Armitage trend test $p < 0.001$). The frequency of cells with aberrations, pulverized cells and polyploid cells was increased in a dose-dependent manner after 7, 14 and 21 days (Cochran-Armitage trend test $p = 0.001$). The frequency of DNA breaks per cell was also increased in a dose-dependent manner (Cochran-Armitage trend test $p = 0.001$). The frequency of translocations was significantly increased only at the two high doses after 7 and 14 days, and also after 21 days at 265 mg/kg body weight. A comparison of the cytotoxic and clastogenic effects of aluminium sulfate (354 or 530 mg/kg body weight) and potassium aluminium sulfate (503 or 764 mg/kg body weight) at the same metal concentrations revealed no important differences, although the mitosis index was sporadically significantly lower after treatment with potassium aluminium sulfate (Roy et al. 1991).

5.7 Carcinogenicity

5.7.1 Short-term studies

Aluminium chloride or aluminium sulfate did not enhance transformation in Syrian hamster embryo cells treated with adeno viruses (SA7) (Casto et al. 1979).

In a transformation test carried out according to IARC test guidelines with the C3H10 T1/2F mouse fibroblast cell line, transformation frequency was not significantly increased at aluminium chloride concentrations of 0, 1, 10, 100 or 500 mg/ml. As positive control, 3-methylcholanthrene concentrations of 2.5 µg/ml were used. No foci of type II or type III were found after incubation of the fibroblasts with aluminium particles (> 5 µm) as used in periprosthetic tissue. Cytotoxicity was found at the highest concentration (Doran et al. 1998).

5.7.2 Long-term studies

After intratracheal instillation of 30 or 60 mg ultrafine aluminium oxide and aluminium silicates for two years, gross pathological examination revealed lung tumours in rats (Pott and Roller 2005). The tumours could have been formed as an effect of particle overloading as a result of the high doses administered (ILSI 2000) (see also documentation "Biopersistent granular dusts 2012 in German; English documentation to appear in 2013).

The carcinogenic potential of aluminium was investigated in $B6C3F_1$ mice in a long-term study. Groups of 60 males and 60 females were given 0, 1%, 2.5%, 5% or 10% (w/w) potassium alum, ($AlK(SO_4)_2 \times 12\ H_2O$) corresponding to aluminium doses of 0, 85, 212.5, 425 and 850 mg /kg body weight and day with the diet for 20 months. Survival in the male and female controls was 73.3% and 78.3%, respectively, and in the various dose groups 86.7% to 95% in male mice treated with potassium alum and 86.7% to 91.7% in the female mice. Body weight gains were slightly increased in the 1% and 2.5% dose groups compared with the values for the controls of both sexes, and slightly decreased in the 10% dose group, which was attributed by the authors to reduced palatability.

The absolute kidney and heart weights in the 5% dose group, the pituitary gland weights of the males in the 2.5% dose group and the brain weights of the females in the 1% dose group were significantly increased compared with the values for the control group. On the other hand, the absolute liver weights in the 5% and 10% dose groups and the heart and brain weights in the 10% dose group in both sexes, the absolute lung weights in males of the 10% dose group and the absolute spleen weights in females of the 10% dose group were significantly decreased. The following relative organ weight changes were obtained: a significant increase in kidney weights after doses of 5% and above in male mice and after doses of 10% in females, a significant decrease in liver weights in both sexes after doses of 5% and above and a significant decrease in spleen weights in female mice after doses of 10%.

The total incidence of tumour-bearing animals was 40.9%, 54.5%, 36.5%, 42.9% and 17.5% for male mice and 29.8%, 23.6%, 17.3 %, 11.5% and 13.5% (no other details) for females in the 0%, 1%, 2.5%, 5% and 10% dose groups, respectively. The frequency of hepatocellular carcinomas were for the males: 9/44 (controls) and 24/55, 15/52, 17/56 and 3/57 for the $AlK(SO_4)_2$ dose groups. The difference in

tumour incidence between the controls and the lowest $AlK(SO_4)_2$ dose group is statistically significant, but not considered relevant as there is no dose-effect relationship. In addition, a significantly reduced incidence of hepatocellular carcinomas was found in males of the high dose group compared with in the control group. As regards non-neoplastic changes, a significant increase in the incidence of myocardial eosinophilic cytoplasm was observed in males treated with doses of 2.5% and 5%. No other neoplastic or non-neoplastic changes were found. According to the authors, potassium alum does not have carcinogenic potential (Oneda et al. 1994).

In another study, potassium aluminium sulfate (corresponding to aluminium doses of 5 mg/kg body weight and day) was administered (no other details) with the drinking water to groups of 54 male and 54 female Swiss mice (Charles River SD). Between the age of 30 and 540 days, no deviations (no other details) were found in body weights compared with those of the controls. The incidence of lymphatic leukaemia and multiple tumours was significantly increased. The values for lymphatic leukaemia were: 3/47 in the control group and 10/41 in the group treated with $AlK(SO_4)_2$ ($p = 0.02$. The incidence of multiple tumours increased from 4/47 (controls) to 12/41 ($p = 0.013$) after treatment with $AlK(SO_4)_2$. Although the authors assign a weak tumorigenic effect to aluminium, the values are not reliable for two reasons. Tumours which are frequent in an animal strain, such as lymphatic leukaemia in the mouse, require a significance level of < 0.01; this was not obtained in this case. The incidence of lymphatic leukaemia was significantly increased (no other details) in the females. (Schroeder and Mitchener 1975). As only one value was given for lymphocytic leukaemia which, in addition, was not explained by the authors in greater detail (and also on account of the absence of data and insufficient documentation of the methods and conditions), this study cannot be used to evaluate the carcinogenicity of aluminium.

Groups of 30 female OF1 mice were given subcutaneous injections of 5 µmol of an iron-ATP complex (FeATP, group 1) or an aluminium-ATP complex (Al-ATP, group 2) every week for 4 months. Groups of 20 female OF1 mice were given 5 µmol sodium-ATP (ATP, group 3) according to the same schedule. By the end of treatment, every animal in groups 1 and 2 had received a total of 4.5 mg iron or 2.2 mg aluminium, and all treated animals 40.6 mg ATP each. The recovery period was 12 months. After 14 months, survival was 27% in the iron-ATP group, 40% in the aluminium-ATP group, 50% in the sodium-ATP group and 60% in the control group. In the region of the portal vein, the aluminium concentrations increased in the investigated tissues of liver, spleen and lymph nodes. In some of the mice treated with aluminium-ATP (no other details), microcytic and hypochromatic anaemia developed. In the groups treated with aluminium-ATP or iron-ATP, the first subcutaneous tumours were observed at the site of injection after 6 months, and tumours of the parotid and submandibular glands after 10 to 12 months. The histopathological examination of 12 of 15 subcutaneous tumours and one tumour of the submandibular glands of animals treated with aluminium-ATP or iron-ATP revealed extensive necrotic areas of well differentiated lymphatic tissue with

infiltrations into the surrounding normal tissue. These could probably be interpreted as well differentiated lymphomas. One of the two other subcutaneous tumours was a poorly differentiated spindle cell sarcoma and the second an adenocarcinoma. The two tumours of the parotid gland were described as well differentiated adenocarcinomas. The authors merely noted that the tumours induced by aluminium-ATP and iron-ATP showed similar histopathological characteristics (Anghileri et al. 2000). As it was not stated which of the tumours occurred in mice treated with iron-ATP and which with aluminium-ATP, this study cannot be used to evaluate the carcinogenic potential of aluminium.

No other evidence of carcinogenic effects of aluminium or aluminium compounds in animal studies is available. As a result of the high biopersistence, especially of corundum, particle-induced effects similar to those with other biopersistent granular dusts is to be expected at relevant doses (Lee et al. 1985; Greim et al. 2001). See Section III of the *List of MAK and BAT Values* for the carcinogenicity of inorganic fibre dusts containing aluminium oxide.

5.8 Other effects

The incubation of human fibroblasts obtained from skin biopsies with aluminium nitrate in concentrations of 50 to 2000 µg/l produced a significant, dose-dependent stimulation of DNA synthesis at concentrations of 100 µg/l and above. Cell cultivation for five days led to a time-dependent increase in ^{3}H-thymidine incorporation into DNA from incubation day 2. A slight, but not significant increase in mitosis frequency was observed only on days 5 and 8. The doses were selected on the basis of experience with uraemic patients, in whom aluminium-related intoxication was observed at aluminium ion concentrations in serum as low as 100 µg/l. Serum aluminium concentrations below 10 µg/l were considered normal (Dominguez et al. 2002). This study shows that aluminium ions are able to affect DNA synthesis, but not cell division.

In cells of the transformed UMR 106-01 animal cell line, an osteosarcoma cell line, aluminium chloride reduced ^{3}H-thymidine incorporation in the concentration range of 0.7 to 30 µM, and thus led to a lower rate of DNA synthesis (Blair et al. 1989).

The treatment of human peripheral blood monocytes for 24, 48 or 72 hours with aluminium sintered at 1450°C produced no change in vitality or in cell proliferation stimulated by concanavalin A. Only the release of interleukin-1α and interleukin-6, determined after incubation for 17 hours with aluminium in the presence of lipopolysaccharides, was changed compared with that in controls (Sudagidan et al. 2002).

High aluminium concentrations in the bones can decelerate osteoblastic and osteoclastic activities, producing osteomalacia and adynamic bone diseases as a result. In haematopoietic tissues, aluminium caused microcytic anaemia, which was

irreversible even after treatment with iron. *In vitro* investigations indicate that aluminium can produce an accumulation of excess iron.

6 Manifesto (MAK value, classification)

In humans, the lungs and the central nervous system are the main target organs after exposure to dusts containing aluminium, aluminium oxide and aluminium hydroxide.

No empirical data are available for humans from which an aluminium concentration without effects can be derived in the form of a NOAEL, as the epidemiological studies contain only inadequate data for the aluminium concentrations in air. High aluminium concentrations in workplace air, which in former years were frequently above the MAK value for dust containing aluminium valid up to 1997 (respirable fraction, average yearly value) of 6 mg/m^3, frequently caused lung fibrosis, so-called aluminosis. The aluminium concentrations in the urine observed in these cases were above the BAT value for aluminium of 200 µg/l urine. In a study with a collective of 62 persons from aluminium powder production previously exposed to high aluminium concentrations, radiological examinations revealed early stages of aluminosis in 15 persons. Taking the internal exposure level to aluminium determined at the time of diagnosis into account, the odds ratio for contracting aluminosis was significantly increased in persons with an aluminium concentration in urine of > 200 µg/l (OR 9.75) or 200 µg/g creatinine (OR 6.6) compared with in persons exposed to lower values.

For the formation of aluminosis there is not sufficient exposure data available at present to be able to determine a dose-effect relationship. Aluminosis has been observed at workplaces where exposure to stamped, non-greased (pyropowder) or only slightly greased aluminium powder is present. As a result of the exposure to a mixture of greased, non-greased, stamped and ground powders in the aluminium powder industry, it is at present not clear whether exposure to greased ground aluminium powder alone is capable of producing lung fibrosis.

In addition, reports are found in the literature of fibrotic lung diseases and obstructive respiratory diseases after exposure to grinding dusts containing aluminium, corundum, welding fumes containing aluminium and the smoke, fumes and dusts occurring in the aluminium-producing industry. As there is often simultaneous exposure to fluorides or ozone, it is at present not possible to clearly define the influence of aluminium in the induction of such lung diseases.

After the absorption of high levels of aluminium via contaminated dialysates or medication containing aluminium, aluminium-induced encephalopathy, also called dialysis encephalopathy, can occur in dialysis patients. Central nervous effects are observed also in workers exposed to aluminium at the workplace. It is, however not possible to evaluate such cases as a result of the absence of dose-effect relationships and exposure to a mixture of substances at the workplace with neuro-

toxic effects. There is no clear evidence that work-related exposure to aluminium produces Alzheimer's disease.

The existing MAK values for aluminium, aluminium oxide and aluminium hydroxide of 1.5 mg/m³ for the respirable fraction and of 4 mg/m³ for the inhalable fraction have therefore provisionally been retained, but apply only for dusts containing aluminium, aluminium hydroxide and aluminium oxide. The limitation of exposure peaks is described in Sections Vf) and Vg) of the *List of MAK and BAT Values*. Ultrafine aluminium particles, which occur for example during aluminium welding, are evaluated separately in the context of problems presented by ultrafine aerosol particles (see Section Vh) of the *List of MAK and BAT Values*.

Studies with rats and mice with oral, subcutaneous and intraperitoneal administration show that exposure to aluminium salts can impair sensorimotor and complex cognitive performance. These effects were observed in developing animals after perinatal exposure and also in adult animals after long-term exposure. As the studies have methodological shortcomings, it is not clear whether these effects are the result of developmental toxicity, neurotoxicity or other systemic effects. No inhalation studies of the toxic effects on development of dusts containing aluminium, aluminium oxide and aluminium hydroxide are available. No effects on dams and foetuses could be found in developmental toxicity studies with rats after oral administration of aluminium hydroxide (Gomez et al. 1990, 1991) and mice (Colomina et al. 1994), as the bioavailability of the substance, which is poorly soluble, is low after oral administration. Studies with soluble aluminium salts show, in rats and mice, that prenatal exposure at maternally toxic doses leads to disturbed ossification. Effects on reflex development, motor activity and behaviour were found in postnatal investigations. Delayed body weight development of the offspring was found to be the most sensitive parameter. In studies in which soluble aluminium lactate was administered by subcutaneous injection, a NOAEL corresponding to aluminium doses of 2.7 mg/kg body weight and day (Yokel 1985) was found for rabbits. In rats, however, aluminium doses of 0.2 mg/kg body weight and day was regarded as the LOAEL, as reduced body weight gains were found during lactation (Gonda and Lehotzky 1996; Gonda et al. 1996, 1997). Assuming a body weight of 70 kg in humans, the NOAEL in rabbits corresponds to an uptake of 189 mg aluminium per day and the LOAEL in the rats to 14 mg aluminium per day. The MAK value for dusts containing aluminium, aluminium oxide and aluminium hydroxide is 1.5 mg/m³ for the respirable (R) and 4 mg/m³ for the inhalable (I) dust fraction. Assuming an aluminium content in the dust of about 25% (see Tables 1 and Table 2), a volume of 10 m³ air inhaled over eight hours and systemic availability of 2% (see Section 3.1), with observance of the MAK value a daily aluminium uptake can be calculated of 0.075 mg (R) or 0.2 mg (I). The margin between this and 189 mg per day (the value derived from the NOAEL for rabbits for the daily uptake of aluminium without effects in humans would permit classification in Pregnancy Risk Group C. As, however, effects were observed in rat pups during lactation at the lowest dose, corresponding to a daily uptake of 14 mg alu-

minium in humans, dusts containing aluminium, aluminium oxide and aluminium hydroxide are classified in Pregnancy Risk Group D.

Dusts containing aluminium, aluminium oxide and aluminium hydroxide are not classified in any of the carcinogenicity categories. No evidence of carcinogenic potential was found in a long-term study with $B6C3F_1$ mice at concentrations of up to 10% aluminium potassium sulfate in the diet. Tumour-promoting effects were not investigated in this study.

With regard to genotoxicity, aluminium was not found to be mutagenic in bacterial mutagenicity tests and in mammalian cell mutagenicity tests. A number of studies do, however, demonstrate the induction of chromosome aberrations and micronuclei in cellular test systems. Effects were observed in experimental animals with regard to chromosome aberrations and micronuclei at high doses; lower doses were not tested, however. Overall, therefore, the findings can only be regarded as an indication of genotoxic effects *in vivo*. The discussed mechanisms of action point towards indirect effects, for which a (threshold) value without effects can be postulated, but not given from the available data. Aluminium has been detected in the seminal fluid and the spermatozoa of exposed workers. Nevertheless, there is not sufficient data available to be able to decide whether dusts containing aluminium, aluminium oxide and aluminium hydroxide should be classified in a category for germ cell mutagens.

Although there are numerous possibilities where exposure to aluminium, aluminium oxide and aluminium salts can occur, contact sensitization has been reported only in a few cases, sometimes even without demonstrated clinical relevance. In several cases, the sensitization was connected with the subcutaneous injection of aluminium oxide as a component of vaccines, which is not relevant for workplace conditions. Studies with animals of the sensitizing effects of aluminium yielded negative results. Although a large number of studies demonstrated the occurrence of allergic lung diseases after inhalation of large amounts of aluminium or aluminium oxide, reliable evidence of respiratory sensitization is not to be found in the available reports. Aluminium is therefore not designated with either an “Sh” or “Sa”.

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