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145. Aluminium and aluminium compounds

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Preface

An agreement has been signed by the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council of the Netherlands and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the agreement is to write joint scientific criteria documents, which could be used by the national regulatory authorities in both the Netherlands and in the Nordic countries.

The document on aluminium and aluminium compounds has been reviewed by DECOS as well as by NEG. The members of both committees are listed in Appendix 2. The first draft of this report was prepared by G Schaafsma, S Dekkers, WR Leeman, ED Kroese, and JHE Arts from TNO Quality of life, Zeist, the Netherlands. The joint document is published separately by DECOS and NEG. The NEG version presented herein has been adapted to the requirements of NEG and the format of Arbete och Hälsa. The editorial work and technical editing have been carried out by Anna-Karin Alexandrie and Jill Järnberg, scientific secretaries of NEG, at the Swedish Work Environment Authority.

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Contents

Abbreviations and acronyms

AAS	atomic absorption spectrometry
ACGIH	American Conference of Governmental Industrial Hygienists
AES	atomic emission spectrometry
AM	arithmetic mean
AMS	accelerator mass spectrometry
ATP	adenosine 5'-triphosphate
ATSDR	Agency for Toxic Substances and Disease Registry
BAT	Biologischer Arbeitsstoff-Toleranz (biological tolerance)
bw	body weight
CAS	Chemical Abstracts Service
cGMP	cyclic guanosine monophosphate
DECOS	Dutch Expert Committee on Occupational Safety
DFG	Deutsche Forschungsgemeinschaft
EEG	electroencephalography
EU	European Union
FAAS	flame atomic absorption spectrometry
$FEF_{25–75}$	mean forced expiratory flow during mid-half (25–75 %) of FVC
FEV_1	forced expiratory volume in 1 second (1^{st} second after full aspiration)
FVC	forced vital capacity
GFAAS	graphite furnace atomic absorption spectrometry
GM	geometric mean
HRCT	high-resolution computed tomography
HSE	Health and Safety Executive
IARC	International Agency for Research on Cancer
ICP	inductively coupled plasma
LD_{50}	lethal dose for 50 % of the exposed animals at single administration
LOAEL	lowest observed adverse effect level
MAK	Maximale Arbeitsplatzkonzentration
MEF_x	maximal expiratory flow at x % of FVC
MIG	metal inert gas
MMAD	mass median aerodynamic diameter
MS	mass spectrometry
NAA	neutron activation analysis
NEG	Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
PAH	polycyclic aromatic hydrocarbon
PEF	peak expiratory flow
SCE	sister chromatid exchange
TIG	tungsten inert gas
TLV	threshold limit value

TNFα	tumour necrosis factor alpha
TWA	time-weighted average
UK	United Kingdom
US	United States
VC	vital capacity
WHO	World Health Organization

1. Introduction

Aluminium is silvery, light, malleable and ductile, and the most abundant metal in the earth's crust. Aluminium is used primarily for metallurgical purposes, especially to produce Al-based alloy castings and wrought Al. Aluminium compounds are found in consumer products such as antacids, astringents, buffered aspirin, food additives and antiperspirants.

The present document on aluminium and aluminium compounds is a co-production between the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG) and the Dutch Expert Committee on Occupational Safety (DECOS), hereafter called the committees. The joint document is published separately, and according to different formats, by DECOS (85) and NEG.

This evaluation builds largely on the review by the Agency for Toxic Substances and Disease Registry (ATSDR) from 1999 (13), which was superseded by an update in 2008 (14). The data on reproduction toxicity, however, have been extracted from the evaluation by DECOS's Subcommittee on the Classification of Reproduction Toxic Substances, published in 2009 (84). Additional data were obtained from on-line databases (Chapter 16).

Mostly, ATSDR data (13) are summarised first. The studies cited by ATSDR are referred to in the text by author name and year and are listed in Chapter 15. Additional studies, retrieved by the authors of the present document, are subsequently presented. These studies are referred to by numbers and are listed in Chapter 14.

Unless otherwise noted, the term aluminium in this document refers to aluminium metal and aluminium ions/compounds.

Data on the effects of engineered aluminium nanoparticles are not presented and discussed in this document since they have their own specific toxic properties.

2. Identity, properties and monitoring

2.1 Chemical identity

Chemical identification data are presented in Table 1.

2.2 Physical and chemical properties

Particles of metallic aluminium can only exist in a zero valence, free elemental state as long as they are shielded from oxygen. Aluminium atoms on the surface of the metal quickly combine with oxygen in the air to form a thin layer of aluminium oxide that protects from further oxidation (13).

In Table 2, the physical and chemical properties of aluminium and different aluminium compounds are presented. No data on physical and chemical properties of alchlor were available. Finely stamped aluminium powder is called aluminium pyro powder. The size of this powder is reported to vary from less than 5 to 200 μm in diameter and from 0.05 to 1 μm in thickness (13, 108).

Table 1. Chemical identification data of aluminium and aluminium compounds (13, 36, 97).

Chemical name/Synonyms	Chemical formula	CAS No.	EINECS No.	EEC No.	RTECS No.
Aluminium					
Alumina fibre; metana; aluminium bronze; aluminium dehydrated	Al	7429-90-5	231-072-3	013-001-00-6	BD330000
Aluminium carbonate					
	$Al_2O_3 \cdot CO_2$; $Al_2(CO_3)_3$ has not been identified	53547-27-6	-	-	-
Aluminium chloride					
Aluminium trichloride; trichloroaluminium; aluminium chloride (1:3)	$AlCl_3$	7446-70-0	231-208-1	013-003-00-7	BD0525000
Aluminium chloride, basic [a] *(unspecific)*					
Aluminium chlor(o)hydrate [b] Aluminium chloride hydroxide; aluminium hydroxychloride; aluminium chlor(o)hydroxide; aluminium chloride oxide; aluminium chlorohydrol; aluminium hydroxide chloride; aluminium oxychloride	Not available; [a] $Al_nCl_{(3n-m)}(OH)_m$; [c] $[Al_nCl_{(3n-m)}(OH)_m]x$; [c] $Al_yCl_z(OH)_{3y-z} \cdot nH_2O$	1327-41-9	215-477-2	-	BD0549500
Aluminium chloride hydroxide[a] *(anhydrous monomer)*					
Aluminium chlor(o)hydrate [b]; dialuminium chloride pentahydroxide; aluminium monochloride pentahydroxide; chloropentahydroxydi-aluminium; aluminium chlor(o)hydroxide; aluminium hydroxide chloride; aluminium hydroxychloride; basic aluminium chloride	$Al_2ClH_5O_5$; $Al_2Cl(OH)_5$	12042-91-0	234-933-1	-	BD0550000
Aluminium fluoride					
Aluminium trifluoride	AlF_3	7784-18-1	232-051-1	-	BD0725000
Aluminium hydroxide					
α-Alumina trihydrate; alumina hydrate; alumina hydrated; aluminium oxide trihydrate; aluminium oxide hydrate; aluminium(III)hydroxide; hydrated alumina; hydrated aluminium oxide; aluminium hydrate	$Al(OH)_3$	21645-51-2	244-492-7	-	BD0940000
Aluminium lactate					
Aluctyl; aluminium, tris(2-hydroxypropanoate-O^1,O^2); propanoic acid, 2-hydroxy-aluminium complex; aluminium tris(α-hydropropionate)	$Al[CH_3CH(OH)CO_2]_3$	18917-91-4	242-670-9	-	BD2214000
Aluminium nitrate					
Aluminium trinitrate; aluminium(III)nitrate (1:3); nitric acid, aluminium salt; nitric acid aluminium (3+) salt	$Al(NO_3)_3$	13473-90-0	236-751-8	-	BD1040000

Table 1. Chemical identification data of aluminium and aluminium compounds (13, 36, 97).

Chemical name/Synonyms	Chemical formula	CAS No.	EINECS No.	EEC No.	RTECS No.
Aluminium oxide					
Activated aluminium oxide; α-aluminium, α-aluminium oxide; alumina; aluminium sesquioxide; aluminium trioxide; β-aluminium oxide; γ-alumina; γ-aluminium oxide	Al_2O_3	1344-28-1	215-691-6	-	BD1200000
Aluminium phosphate					
Aluminium orthophosphate; phosphoric acid, aluminium salt (1:1); aluminium phosphate tribasic	$AlPO_4$	7784-30-7	232-056-9	-	-
Aluminium potassium sulphate					
Sulphuric acid, aluminium potassium salt (2:1:1)	$AlK(SO_4)_2$	10043-67-1	233-141-3	-	-
Aluminium sulphate					
Alum; peral alum; pickle alum; cake alum; filter alum; papermakers' alum; patent alum; aluminium sulphate (2:3); aluminium trisulphate; dialuminium sulphate; dialuminium trisulphate; sulphuric acid, aluminium salt (3:2)	$Al_2(SO_4)_3$	10043-01-3	233-135-0	-	BD1700000
Alchlor[d]					
	$Al_2(OH)_5Cl \cdot nH_2O \cdot mC_2H_6O_2$; $Al_2(OH)_5Cl \cdot nH_2O \cdot mC_3H_8O_2$; $Al_2(OH)_4Cl_2 \cdot nH_2O \cdot mC_2H_6O_2$; $Al_2(OH)_4Cl_2 \cdot nH_2O \cdot mC_3H_8O_2$	52231-93-3	-	-	-

[a] Data provided by CAS® Client Services in June 2009; other CAS numbers (e.g. 11097-68-0 and 84861-98-3) are listed as deleted registry numbers.
[b] Preferred name in document.
[c] $0 < m < 3n$.
[d] Alchlor is a propylene glycol complex of aluminium chloride hydroxide.

Table 2. Physical and chemical properties of aluminium and aluminium compounds (13, 36, 97).

Physical description	Colour	Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Density (kg/m^3, 25°C)	Solubility	Log P octanol/ water	Vapour pressure (kPa)	Relative density (air = 1)	Flash point (°C)	Odour threshold (mg/m^3)
Aluminium metal and aluminium oxide											
Aluminium											
Malleable, ductile metal, crystalline solid	Silvery, with bluish tint	26.98	660	2 450	2 700	Insoluble in water, soluble in alkali and acids	n.d.	0.13 at 1 284 °C	n.d.	645	n.d.
Aluminium oxide											
Crystalline powder	White	101.94	2 072	2 980	3 965	Practically insoluble in water and non-polar organic solvents, slowly soluble in aqueous alkaline solution	n.d.	0.13 at 2 158 °C	n.d.	Not combustible	n.d.
Aluminium compounds not or poorly soluble in water (except aluminium oxide)											
Aluminium carbonate											
Lumps or powder	White	145.97	n.d.	n.d.	n.d.	Insoluble in water, soluble in hot HCl (aq) or H_2SO_4	n.d.	n.d.	n.d.	n.d.	n.d.
Aluminium fluoride											
Hexagonal crystals	White	83.98	1 291	1 276 (sublimation); 1 537	2 880	Poorly soluble in water: 0.6 g/100 ml at 25 °C, sparingly soluble in acids and alkali, insoluble in alcohol and acetone	n.d.	0.13 at 1 238 °C	n.d.	Not flammable	n.d.
Aluminium hydroxide											
Bulky amorphous powder	White	77.99	300	n.d.	2 420	Insoluble in water and alcohol, soluble in acids	n.d.	n.d.	n.d.	n.d.	n.d.
Aluminium phosphate											
Infusible powder crystals	White	121.95	> 1 460	n.d.	2 560 at 23 °C	Insoluble in water, soluble in acids and alkali	n.d.	n.d.	n.d.	n.d.	n.d.

Table 2. Physical and chemical properties of aluminium and aluminium compounds (13, 36, 97).

Physical description	Colour	Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Density (kg/m^3, 25°C)	Solubility	Log P octanol/ water	Vapour pressure (kPa)	Relative density (air = 1)	Flash point (°C)	Odour threshold (mg/m^3)
Aluminium compounds soluble in water											
Aluminium chloride											
Crystals	White when pure, ordinarily grey or yellow-to-greenish	133.34	< -20; -12; 80	103	2 440	Reacts explosively with water evolving HCl gas	n.d.	0.13 at 100 °C	n.d.	Not combustible	n.d.
Aluminium chlorohydrate											
Solid	Glassy	174.46	n.d.	n.d.	n.d.	Soluble in water	n.d.	n.d.	n.d.	n.d.	n.d.
Aluminium lactate											
Powder	Colourless, white-yellow	294.18	n.d.	n.d.	n.d.	Freely soluble in water	n.d.	n.d.	n.d.	n.d.	n.d.
Aluminium nitrate											
Nonahydrate, deliquescent crystals	White	213	73	Decomposition at 135 °C	n.d.	Soluble in water: 64 g/100 ml at 25 °C, soluble in alkali, acetone and HNO_3	n.d.	n.d.	n.d.	Not flammable	n.d.
Aluminium potassium sulphate											
Powder	White	258.21	n.d.	n.d.	n.d.	Moderately soluble in water: 5 g/100 ml at 25 °C, insoluble in alcohol	n.d.	n.d.	n.d.	n.d.	n.d.
Aluminium sulphate											
Crystals, pieces, granules or powder	White, lustrous	342.14	Decomposition at 700 °C	n.d.	2 710	Soluble in 1 part water, soluble in dilute acids, practically insoluble in alkali	n.d.	Essentially zero	n.d.	Not flammable	n.d.

n.d.: no data, P: partition coefficient.

Table 3. EU classification (CLP regulation) of aluminium and aluminium compounds.

Aluminium compound	CAS No.	Classification[a, b]
Aluminium powder (pyrophoric[c])	7429-90-5	Water-react. 2 (H261); pyr. sol. 1 (H250)
Aluminium powder (stabilised)	-	Water-react. 2 (H261); flam. sol. 1 (H228)
Aluminium chloride	7446-70-0	Skin corr 1B (H314)

[a] *Hazard classes and category codes:* Flam. sol. 1: flammable solids in category 1, Pyr. sol.: pyrophoric solids, Skin corr: skin corrosion/irritation, Water-react.: substances and mixtures, which in contact with water, emit flammable gases.
[b] *Hazard statement codes:* H228: flammable solid, H250: catches fire spontaneously if exposed to air, H261: in contact with water releases flammable gases, H314: causes severe skin burns and eye damage.
[c] is, even in small quantities, liable of igniting within 5 minutes after coming into contact with air.
CLP: classification, labelling and packaging, EU: European Union.

2.3 European Union (EU) classification and labelling

Of the compounds mentioned in the previous sections, only aluminium (powder) and aluminium chloride are listed in Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures being in force since 20 January 2009, implementing the Globally Harmonised System, and replacing Directive 67/548/EEC (substances) and Directive 1999/45/EC (preparations) (60) (see Table 3). No concentration limits are specified for the different aluminium compounds.

2.4 Analytical methods

In this section, well-established, standard methods for detecting and/or measuring and monitoring aluminium and aluminium compounds in air and in biological samples are described.

Generally, because of the ubiquitous nature of aluminium, contamination is a major problem encountered in the analysis of aluminium by all methods except accelerator mass spectrometry (AMS) using radioactive ^{26}Al. When using other methods, all items used during collection, preparation and assay should be checked for aluminium contribution to the procedure. Only by taking these stringent precautions will accurate results be produced.

2.4.1 Occupational air monitoring

Aluminium in air is usually associated with particulate matter and therefore standard methods involve collection of air samples on membrane filters and acid extraction of the filters. In Table 4, a summary is presented of methods for determining aluminium and aluminium compounds in occupational air samples. In recent methods as described by the Nederlands Normalisatie-instituut (NEN) and the United States National Institute for Occupational Safety and Health (US NIOSH), inductively coupled plasma-atomic emission spectrometry (ICP-AES) for sample analysis is used.

Table 4. Analytical methods for determining aluminium and aluminium compounds, as Al, in air samples.

Method	Sampler	Sample preparation	Assay procedure	Limit of detection (µg/ml)	Reference
US NIOSH method 7013	Filter (0.8-µm cellulose ester membrane).	Collection of sample on cellulose filter and digestion with nitric acid.	FAAS	2 µg/sample	(138)
US NIOSH method 7300	Filter (0.8-µm cellulose ester membrane or 5.0-µm PCV membrane).	Collection of sample on cellulose filter and digestion with nitric acid.	ICP-AES	0.0046	(139)
US OSHA method ID-121	Personal air samples are collected on mixed cellulose ester filters using a calibrated sampling pump. Wipe or bulk samples are collected using grab sampling techniques.	Samples are desorbed or digested using water extractions or mineral acid digestions.	AAS or AES	0.002	(149)
US OSHA method ID-109-G, aluminium oxide	Filter (5-µm low ash PVC membrane).	Sample filters are fused with a flux consisting of $LiBO_2$, NH_4NO_3 and NaBr in Pt crucibles. The fused sample is then put into aqueous solution and analysed for Al.	FAAS	0.5	(148)
US OSHA method ID-198SG, aluminium oxide	Filter (0.8-µm cellulose ester membrane).	Filter is digested with acids using a micro-wave.	AAS	0.025	(147)
NEN-ISO 15202, airborne particulate matter	Depth filters, e.g. glass or quartz-fibre filters, and membrane filters, e.g. mixed cellulose ester mem-brane filters and membrane filters made from poly-mers such as PVC or PTFE.	Different acid extraction methods of filters are specified, but for Al, sample dissolution in a closed vessel microwave digestion system is recommended.	ICP-AES	Not specified	(135-137)
HSE-MDHS 14/3, respirable and inhalable Al dust	Filter.	-	Gravimetric analysis	Not specified [a]	(82)

[a] Determined by the length of the sampling period, the sensitivity of the balance, and the weight stability of the substrate (e.g. filter) used to collect and weigh the sample. These factors should be chosen to ensure that the limit of detection is an order of magnitude lower than the appropriate exposure limit.
AAS: atomic absorption spectrometry, AES: atomic emission spectrometry, FAAS: flame atomic absorption spectrometry, HSE-MDHS: Health and Safety Executive-Methods for the determination of hazardous substances, ICP: inductively coupled plasma, NEN-ISO: Nederlands Normalisatie-instituut-International Organization for Standardization, NIOSH: National Institute for Occupational Safety and Health, OSHA: Occupational Safety and Health Administration, Pt: platinum, PTFE: polytetra-fluoroethylene, PVC: polyvinyl chloride, US: United States.

2.4.2 Biological monitoring
ATSDR data
A variety of analytical methods have been used to measure aluminium levels in biological materials, including AMS, graphite furnace atomic absorption spectrometry (GFAAS), flame atomic absorption spectrometry (FAAS), neutron activation analysis (NAA), ICP-AES, inductively coupled plasma-mass spectrometry (ICP-MS) and laser ablation microprobe mass analysis (Maitani *et al* 1994, Owen *et al* 1994, Van Landeghem *et al* 1994). Front-end separation techniques such as chromatography are frequently coupled with analytical methods.

Table 5 summarises methods for measuring aluminium and aluminium compounds in biological materials.

3. Sources

3.1 Natural occurrence

ATSDR data
Aluminium is the most abundant metal and the third most abundant element, after oxygen and silicon, in the earth's crust. It is widely distributed and constitutes approximately 8 % of the earth's surface layer (Brusewitz 1984). Aluminium does not occur naturally in the metallic, elemental state. It is found combined with other elements, most commonly with oxygen, silicon and fluorine (Browning 1969, Dinman 1983, IARC 1984, NRC 1982). These compounds are commonly found in soil, minerals (e.g. sapphires, rubies, turquoise), rocks (especially igneous rocks) and clays. These are the natural forms of aluminium rather than the silvery metal. The metal is obtained from aluminium containing minerals, primarily bauxite. Small amounts of aluminium are even found in water in dissolved or ionic form. The most commonly found ionic forms of aluminium are complexes formed with hydroxy (hydrogen attached to oxygen) ions.

Additional data
No additional data were found.

3.2 Man-made sources

3.2.1 Production
ATSDR data
The most important raw material for the production of aluminium is bauxite, which contains 40–60 % aluminium oxide (Dinman 1983, IARC 1984). Other raw materials sometimes used in the production of aluminium include cryolite, aluminium fluoride, fluorspar, corundum and kaolin minerals (Browning 1969, Dinman 1983, IARC 1984).

The principal method used in producing *aluminium metal* involves three major steps: refining of bauxite by the Bayer process to produce aluminium oxide, electro-

Table 5. Analytical methods for determining aluminium and aluminium compounds, as Al, in biological samples. Data from ATSDR (13), unless otherwise noted.

Sample matrix	Sample preparation	Assay procedure	Limit of detection (µg/l)	Reference
Serum	Direct injection into atomiser	GFAAS	Low µg/l levels	King *et al* 1981
Serum	Dilution with water, addition of EDTA	GFAAS	2	Alderman and Gitelman 1980
Serum	Centrifugation and injection of supernatant	GFAAS	14.3	Bettinelli *et al* 1985
Serum	Precipitation of proteins in serum with ultra-pure nitric acid in the ratio of 1 to 20 (v/v) between the acid and serum	GFAAS	2	Ruangyuttikarn *et al* 1998 (168)
Serum	Dilution with ultrapure water	Double-focusing ICP-MS	No data	Muniz *et al* 1999 (131)
Serum (Al-organic acid species)	Addition of sodium bicarbonate, direct injection into chromatography column	HPLC, ICP-AES	No data	Maitani *et al* 1994
Serum (Al-organic acid species)	Dilution with mobile phase, fractions collected for analysis	HPLC, ETAAS	No data	Wróbel *et al* 1995
Serum (Al-organic acid species)	Addition of citrate buffer, direct injection into chromatography column	HPLC, ETAAS	0.12	Van Landeghem *et al* 1994
Plasma	Dilution	GFAAS	3–39	Wawschinek *et al* 1982
Whole blood, plasma, serum	Dilution with water	GFAAS	24	Gardiner *et al* 1981
Whole blood	Addition of sodium citrate, centrifugation, injection of supernatant	GFAAS	Low µg/l levels	Gorsky and Dietz 1978
Whole blood, plasma, serum	Dilution with Triton X-100	GFAAS	Serum: 1.9 Plasma: 1.8 Whole blood: 2.3	van der Voet *et al* 1985
Urine, blood	Dilution with water	GFAAS, ICP-AES	Low µg/l levels	Sanz-Medel *et al* 1987
Urine, blood	Dilution with water	ICP-AES	Urine: 1 Blood: 4	Allain and Mauras 1979

Table 5. Analytical methods for determining aluminium and aluminium compounds, as Al, in biological samples. Data from ATSDR (13), unless otherwise noted.

Sample matrix	Sample preparation	Assay procedure	Limit of detection (µg/l)	Reference
Urine	Digestion, ion-exchange clean-up	NAA	50	Blotcky *et al* 1976
Urine	Direct injection	GFAAS	Low µg/l levels	Gorsky and Dietz 1978
Urine	Addition of hydrogen peroxide, nitric acid and Triton X-100	ETAAS	No data	Campillo *et al* 1999 (34)
Blood, urine, serum, faeces	Acid digestion using Parr bomb technique, microwave or hot plate method	ICP-AES	1	Que Hee and Boyle 1988
Hair	Wash with isopropanol, digestion with nitric acid, dilution with water	GFAAS	0.65 µg/g	Chappuis *et al* 1988

AAS: atomic absorption spectrometry, AES: atomic emission spectrometry, ATSDR: Agency for Toxic Substances and Disease Registry, EDTA: ethylenediaminetetraacetic acid, ETAAS: electrothermal atomic absorption spectrometry, GFAAS: graphite furnace atomic absorption spectrometry, HPLC: high-performance liquid chromatography, ICP: inductively coupled plasma, MS: mass spectrometry, NAA: neutron activation analysis.

lytic reduction of aluminium oxide by the Hall-Heroult process to produce aluminium, and casting of aluminium into ingots (Browning 1969, Dinman 1983, IARC 1984).

The electrolytic reduction process of transforming aluminium oxide into aluminium is carried out in electrolytic cells or pots. The areas where this occurs are called potrooms. Two types of electrolytic cells may be used, a prebake or a Søderberg cell. The use of electrodes in aluminium reduction operations is associated with the generation of several types of wastes (Dinman 1983, IARC 1984). In aluminium reduction facilities using the prebake process, polycyclic aromatic hydrocarbons (PAHs) are generated. In aluminium reduction operations using the Søderberg cell process, considerable amounts of volatiles from coal tar pitch, petroleum coke and pitch, including PAHs, are generated.

Aluminium chloride is produced by a reaction of bauxite with coke and chlorine at about 875 ºC (HSDB 1995, Sax and Lewis 1987).

Aluminium fluoride is made by heating ammonium hexafluoroaluminate to red heat in a stream of nitrogen, by the action of fluorine or hydrogen fluoride gas on aluminium trihydrate at high temperatures, followed by calcining the hydrate formed, by fusing sodium fluoride with aluminium sulphate or by a reaction of fluosilicic acid on aluminium hydrate (HSDB 1995).

Aluminium hydroxide is produced from bauxite. The ore is dissolved in a solution of sodium hydroxide, and aluminium hydroxide is precipitated from the sodium aluminate solution by neutralisation (as with carbon dioxide) or by autoprecipitation (Bayer process) (HSDB 1995, Sax and Lewis 1987).

Aluminium nitrate is formed by dissolving aluminium or aluminium hydroxide in dilute nitric acid and allowing the resulting solution to crystallise (HSDB 1995).

Aluminium oxide is produced during the recovery of bauxite, which is crushed, ground, and kiln dried, followed by leaching with sodium hydroxide, forming sodium aluminate, from which aluminium hydroxide is precipitated and calcined (Bayer process) (HSDB 1995).

Aluminium sulphate is manufactured by reacting freshly precipitated pure aluminium hydroxide, bauxite or kaolin, with an appropriate quantity of sulphuric acid. The resulting solution is evaporated and allowed to crystallise (HSDB 1995).

Additional data

No additional data were found.

3.2.2 Use

ATSDR data

Aluminium metal and compounds have a wide variety of uses (Anusavice 1985, Browning 1969, Budavari *et al* 1989, Hawley 1977, HSDB 1995, Locock 1971, Staley and Haupin 1992, Stokinger 1981, Venugopal and Lucky 1978). Most primary *aluminium* is used for metallurgical purposes; 85–90 % of these uses are in the production of aluminium-based alloy castings and wrought aluminium products. Pure aluminium is soft and lacks strength. By forming alloys, the strength,

hardness and other useful properties of the metal can be increased while building on the inherent properties of aluminium of low density, high electrical and thermal conductivity, high reflectivity and corrosion resistance.

The major uses of aluminium and its alloys are in packaging, building and construction, transportation and electrical applications. Over 95 % of beer and carbonated drinks are packaged in twopiece aluminium cans. Aluminium sheet and foil are used in pie plates, frozen food trays and other packaging applications. In construction, aluminium is used for siding and roofing, doors and windows. Aluminium is used in the bodies, trim and mechanical parts of cars, trucks, airplanes, ships and boats, as well as other transportation-related structures and products such as bridges and highway signs. Electrical applications include overhead transmission lines, cable sheathing, and wiring. Other applications of aluminium include die-cast auto parts, corrosion-resistant chemical equipment, cooking utensils, decorations, fencing, sporting equipment, toys, lawn furniture, jewellery, paint and in dental alloys for crowns and dentures. Other uses include absorbing occluded gases in the manufacture of steel, testing for gold, arsenic and mercury, precipitating copper, as a reducer for determining nitrates and nitrites, in coagulating colloidal solutions of arsenic or antimony, in explosives and in flashes for photography. Aluminium powder is used in paints, protective coatings and fireworks.

Aluminium compounds and materials also have a wide range of uses (Anusavice 1985, Browning 1969, Budavari *et al* 1989, Hawley 1977, Locock 1971, Sax and Lewis 1987, Stokinger 1981, Venugopal and Lucky 1978). Naturally occurring aluminium-containing minerals, such as bentonite and zeolite, are used in water purification, sugar refining and in the brewing and paper industries. A variety of aluminium compounds is used in industrial, domestic, consumer and medicinal products.

Aluminium chloride is used as an acid catalyst (especially in Friedel-Crafts-type reactions), as a chemical intermediate for other aluminium compounds, in the cracking of petroleum, in the manufacture of rubbers and lubricants, and as an antiperspirant (HSDB 1995). The hexahydrate form is used in preserving wood, disinfecting stables and slaughterhouses, in deodorants and antiperspirants, in cosmetics as a topical astringent, in refining crude oil, dyeing fabrics and manufacturing parchment paper (Budavari *et al* 1989).

Aluminium chlorohydrate is the active ingredient in many antiperspirants and deodorants (Budavari *et al* 1989, Hawley 1977, Sax and Lewis 1987).

Aluminium hydroxide is used in stomach antacids as a desiccant powder, in antiperspirants and dentifrices, in packaging materials, as a chemical intermediate, as a filler in plastics, rubber, cosmetics and paper, as a soft abrasive for brass and plastics, as a glass additive to increase mechanical strength and resistance to thermal shock, weathering and chemicals, and in ceramics (HSDB 1995). Aluminium hydroxide is also used pharmaceutically to lower the plasma phosphorus levels of patients with renal failure (Budavari *et al* 1989, Sax and Lewis 1987).

Aluminium nitrate is used in antiperspirants, for tanning leather, as a corrosion inhibitor, in the preparation of insulating papers, on transformer core laminates, in incandescent filaments and in cathode ray tube heating elements (HSDB 1995).

Aluminium oxide is used in the production of aluminium, manufacture of abrasives, refractories, ceramics, electrical insulators, catalyst and catalyst supports, paper, spark plugs, crucibles, and laboratory works, adsorbent for gases and water vapours, chromatographic analysis, fluxes, light bulbs, artificial gems, heat resistant fibres, food additive (dispersing agent) and in hollow-fibre membrane units used in water desalination, industrial ultra filtration and haemodialysis (HSDB 1995). An application of aluminium oxide, which may have wide occupational use in the future, is as a dosimeter for measuring personnel radiation exposure (McKeever *et al* 1995, Radiation Safety Guide 1999, Radiation Safety Newsletter 1998).

Aluminium phosphate is used in over-the-counter stomach antacids (Budavari *et al* 1989, Sax and Lewis 1987).

Aluminium sulphate is used primarily for water purification systems and sewage treatment systems as a flocculent, in the paper and pulp industry, in fireproofing and waterproofing cloth, clarifying oils and fats, waterproofing concrete, in antiperspirants, in tanning leather, as a mordant in dyeing, in agricultural pesticides, as an intermediate in the manufacture of other chemicals, as a soil conditioner to increase acidity for plants (e.g. rhododendrons, azaleas, camellias and blueberries), and in cosmetics and soap. A saturated solution of aluminium sulphate is employed as a mild caustic. Solutions containing 5–10 % aluminium sulphate have been used as local applications to ulcers and to arrest foul discharges from mucous surfaces. Aluminium sulphate is also used in the preparation of aluminium acetate ear drops (HSDB 1995).

Additional data

Aluminium salts have become the standard adjuvant in vaccines such as those against diphtheria, tetanus and pertussis (DTP), *Haemophilus* influenzae type b, *pneumococcus* conjugates, and hepatitis A and B. Aluminium salts are added to vaccines in the form of aluminium potassium sulphate, aluminium sulphate or aluminium hydroxide. The last seems to be the most immunogenic, especially during immunisation (99).

With regard to (veterinary) medical purposes in the Netherlands, different drugs are registered which contain aluminium and aluminium compounds as the active substance (37). According to the Veterinary Medicinal Products Unit, which is responsible for the authorisation of veterinary medicines in the Netherlands, aluminium and aluminium hydroxide are used as active substances in veterinary medicines (30). In the agriculture sector in the Netherlands, aluminium sulphate is used as an active substance in biocides and pesticides (38).

In the Nordic countries, the largest reported uses of aluminium and aluminium compounds are for aluminium oxide, aluminium hydroxide, aluminium sulphate, and aluminium chlorohydrate. The latter is mainly used as a complexing or

flocculating agent in water purification and sewage treatment, and in the pulp and paper industry (189).

4. Exposure

4.1 General population

ATSDR data

Aluminium is found naturally in the environment. The general population may be exposed to aluminium by eating food (due to its natural occurrence in edible plants and its use as food additives and in food and beverage packaging and cooking utensils), drinking water (due to its use in municipal water treatment compounds), ingesting medicinal products (like certain antacids and buffered analgesics that contain aluminium) or breathing air. Skin contact with soil, water, aluminium metal, antiperspirants, food additives (e.g. some baking powders) or other substances that contain aluminium may also occur.

Aluminium is the most abundant metal in the earth's crust. Its concentration in soils varies widely, ranging from about 700 to over 100 000 mg/kg soil (Shacklette and Boerngen 1984, Sorensen *et al* 1974) and the typical concentration is about 71 000 mg/kg soil (Frink 1996).

Most of the aluminium in the air is in the form of small suspended particles of soil (dust). Levels of atmospheric aluminium vary depending on location, weather conditions and the level of industrial activity or traffic in the area. High levels of aluminium in dust are found in areas where the air is dusty, where aluminium is mined or processed into aluminium metal, or near certain hazardous waste sites. Background levels of aluminium in the air are generally 0.005–0.18 ng/m^3 (Hoffman *et al* 1969, Pötzl 1970, Sorensen *et al* 1974). Aluminium levels in US urban and industrial areas can range from 0.4 to 10 ng/m^3 (Cooper *et al* 1979, Dzubay 1980, Kowalczyk *et al* 1982, Lewis and Macias 1980, Moyers *et al* 1977, Ondov *et al* 1982, Pillay and Thomas 1971, Sorenson *et al* 1974, Stevens *et al* 1978).

The concentration of aluminium in natural waters is generally below 0.1 mg/l water unless the water is very acidic (Brusewitz 1984, Miller *et al* 1984, Sorenson *et al* 1974, Taylor and Symons 1984). People generally consume very little aluminium from drinking water. Drinking water is sometimes treated with aluminium salts, but even then aluminium levels generally do not exceed 0.1 mg/l although levels of 0.4–1 mg/l of aluminium in drinking water have been reported (Schenck *et al* 1989).

Aluminium occurs naturally in many edible plants and is added to many processed foods. The concentrations in foods and beverages vary widely, depending upon the food product, the type of processing used and the geographical areas in which food crops are grown (Brusewitz 1984, Sorenson *et al* 1974). In general, the foods highest in aluminium are those that contain aluminium additives (e.g. processed cheese, grain products and grain-based desserts) (Greger 1992, Pennington 1987). Most unprocessed foods like fresh fruits, vegetables and meat

contain very little aluminium at amounts < 5 mg/kg (Greger 1992, Pennington 1987, Schenck *et al* 1989). In processed foods (e.g. processed cheeses, baked goods, non-dairy cream substitutes), aluminium concentrations resulting from the introduction of aluminium-containing food additives may amount to ca. 2 300 mg/kg (baking powder) (Greger *et al* 1985, Pennington 1987, Sorensen *et al* 1974).

While tea leaves may contain aluminium levels up to 10 000 mg/kg (Lewis 1989), aluminium concentrations in tea steeped from tea bags may range from 0.4 to 4.3 mg/l (Greger *et al* 1985, Schenck *et al* 1989). Aluminium concentrations in brewed coffee (3 % extract) and instant coffee (1 % solution) may range from ca. 0.2 to 1.2 and ca. 0.02–0.6 mg/l, respectively (Schenk *et al* 1989), in alcoholic beverages (wine, beer, spirits) from ca. 0.07 to 3.2 mg/l (Pennington 1987, Schenck *et al* 1989), and in fruit juices and soft drinks from ca. 0.04 to 4.1 and 0.1–2.1 mg/l, respectively (Schenck *et al* 1989).

Cow's milk-based and soy-based infant formulae may contain aluminium levels up to ca. 0.7 and 2.5 mg/l (Baxter *et al* 1991, Simmer *et al* 1990).

Generally, preparing food or beverages in aluminium cookware and storing them in aluminium foils or cans may increase the aluminium content (Abercrombie and Fowler 1997, Greger *et al* 1985, King *et al* 1981, Muller *et al* 1993b, Nagy and Nikdel 1986).

Most adults consume 1–10 mg aluminium per day from natural sources (Greger 1992).

People are exposed to aluminium in some cosmetics such as deodorants and in pharmaceuticals such as antacids, buffered aspirin and intravenous fluids. Buffered aspirin and antacid preparations may contain aluminium compounds at amounts of 20 and 200 mg aluminium per dose (tablet, capsule, etc.), respectively, which may result in daily intakes of as much as 700 and 5 000 mg, respectively (Brusewitz 1984, Lione 1985, NRC 1982, Schenck *et al* 1989, Shore and Wyatt, 1983).

Additional data

In the so-called "Total Diet Study", which is an important part of the United Kingdom (UK) Government's surveillance programme for chemicals in food, the mean total dietary exposure (i.e. not including the contribution from drinking water) for adults to aluminium was estimated to be 12 mg/day (upper range 29 mg/day). This figure was estimated from the mean concentrations of aluminium (limit of detection: 0.27 mg/kg fresh weight) in 20 food groups and the average consumption of each food group from a national food survey (203).

Aluminium was not listed in the European Pollutant Emission Register (EPER). This register contains data on the emissions in air and water of 50 pollutants reported by about 12 000 large and medium-sized industrial facilities, among which aluminium-producing and aluminium-processing ones, in the 25 EU member states and Norway (59).

4.2 Working population

ATSDR data

Occupational exposure to aluminium occurs not only in the refining of the primary metal, but also in secondary industries that use aluminium products (e.g. aircraft, automotive, and metal products) and aluminium welding (Nieboer *et al* 1995). Three major steps are involved in primary aluminium production (see Section 3.2.1). Aluminium is first extracted with caustic soda from bauxite ore, precipitated as aluminium hydroxide, and subsequently converted to aluminium oxide in a calcination process. In the second step, the oxide is dissolved in molten cryolite (Na_3AlF_6) and electrolysed to yield the pure molten metal. The electrolytic cells are called pots and the work area is called the potroom. Casting is the final step in the process where molten aluminium is poured into ingots in the foundry.

In the initial extraction and purification process, exposure is primarily to aluminium hydroxide and oxide; in the potroom, to aluminium oxide and aluminium fluoride (as well as to tar-pitch volatiles including PAHs); and in the foundry, to partially oxidised aluminium metal fumes (Drabløs *et al* 1992, IARC 1984, Nieboer *et al* 1995). Drabløs *et al* (1992) studied aluminium concentrations in workers at an aluminium fluoride plant. Mean aluminium levels in urine were 0.011 ± 0.007 mg/l (range 0.002–0.046 mg/l) for 15 plant workers, 0.032 ± 0.023 mg/l (0.006–0.136 mg/l) for 7 foundry workers, and 0.054 ± 0.063 mg/l (0.005–0.492 mg/l) for 12 potroom workers as compared to 0.005 ± 0.003 mg/l (0.001–0.037 mg/l) for 230 unexposed controls.

Most of the studies of occupational exposure (aluminium refining and metal industry workers) to aluminium have dealt with inhalation of aluminium-containing dust particles. Rarely is a worker exposed solely to aluminium-containing dust. Exposure to mixtures of aluminium with fine respirable particles or other toxic chemicals is more prevalent, e.g. PAHs in coal tar pitch.

According to the US National Occupational Exposure Survey conducted by NIOSH from 1981 to 1983 (NIOSH 1988, 1991), the industries with the largest numbers of workers potentially exposed to aluminium and aluminium compounds include: plumbing, heating and air conditioning, masonry and other stonework, electrical work, machinery except electrical, certified air transportation equipment, electrical components, fabricated wire products, general medical and surgical hospitals, industrial buildings and warehouses, and special dies, tools, jigs and fixtures.

Additional data

In an aluminium powder producing and processing plant in Erlangen-Nüremberg, Germany, aluminium dust concentrations were between 5 and 21 mg/m^3 during the production of aluminium powder. The peak values were observed with sieving of aluminium powder. The aluminium dust concentrations were much lower in the area of paste production (1.1–3.8 mg/m^3). The values from workplaces not directly exposed to aluminium were below 0.4 mg/m^3 (117).

In a comprehensive survey, exposure to chemical agents in Swedish aluminium foundries and aluminium-remelting plants were investigated. The industrial hygiene measurements were performed from 1992 to 1995. Concentrations of aluminium in total dust ranged from < 0.001–0.94 mg/m^3 (mean 0.029) in foundries and from 0.002–0.54 mg/m^3 (mean 0.057) in remelting plants (198, 199).

In a study by Röllin *et al*, the changes in ambient aluminium levels in the potrooms of a modern aluminium smelter in South Africa during the plant construction stage and one year into full production were investigated. Aluminium present in the total ambient air fraction in potrooms during construction ranged from 0 to 2.1 mg/m^3, with the highest median concentration of 0.17 mg/m^3 being recorded at 17 months. At 24 months, when full production was attained, the aluminium content in the total fraction obtained by personal monitoring reached median levels of 0.03 mg/m^3. At 36 months, i.e. one year into production, the median total airborne and respirable fraction samples were 0.08 and 0.03 mg/m^3, respectively. The aluminium concentration in the respirable dust fraction was 44 % of the aluminium found in the total inhalable fraction measured at the same time (169).

Healy *et al* investigated inhalation exposure at seven secondary aluminium smelters in the UK to quantify the main exposures and identify their sources. The results showed that people were exposed to a range of workplace air pollutants. The substances monitored were amongst others total inhalable dust and aluminium. The mean sampling time was 280 minutes. Personal exposure results for total inhalable dust were between 0.7 and 5.6 mg/m^3. The aluminium personal exposure ranged from 0.04 to 0.9 mg/m^3 (mean 0.31). The average proportion of aluminium in total inhalable dust samples was 13 % and rotary furnace processes generated the most dust. From a total of 33 results, this proportion varied between 5 and 27 %, with a standard deviation (SD) of 5 %. If it is assumed that aluminium is present as the oxide, the average proportion of Al_2O_3 in the dust sampled was 25 %. The composition of the remaining 75 % of the dust is uncertain, although the metal analysis suggested that other metal oxides alone could not account for the shortfall (86).

Matczak *et al* evaluated occupational exposure to welding fumes and its elements in aluminium welders in the Polish industry. The study included 34 total dust and 12 respirable dust samples from metal inert gas (MIG) welders and fitters in two plants and 15 total dust and 3 respirable dust samples from tungsten inert gas (TIG) welders and fitters in another plant. Air samples, covering 6–7 hours out of the 8-hour work shift (including breaks) were collected in the breathing zone of welders, who all used welder's hand shields. Effective welding times were about 6 and about 3 hours for welders and fitters, respectively. Total and respirable dust concentrations were determined gravimetrically and the elements in the collected dust by atomic absorption spectrometry (AAS). For MIG welding, the mean time-weighted average (TWA) concentrations were 6.0 mg/m^3 (range 0.8–17.8) for total dust, with mean concentrations for aluminium, which was the major component of these welding dust/fumes, of 2.1 mg/m^3 (range 0.1–7.7), i.e. 29.4 % (8.9–55.7 %) of total MIG, and 2.6 mg/m^3 (0.7–6) for respirable dust, with mean

concentrations for aluminium of 0.8 mg/m^3 (0.2–2.2). For TIG welding, the mean TWA concentrations were 0.7 mg/m^3 (0.3–1.4) for total dust, with mean concentrations of aluminium of 0.17 mg/m^3 (0.07–0.50, i.e. 23.9 % (12.5–40.2 %) of total TIG), and 0.8 mg/m^3 (0.3–1.9) for respirable dust, with mean concentrations for aluminium of 0.3 mg/m^3 (0.07–0.6) (122).

In German automobile industry and train body and truck trailer construction, total respirable dust exposure of welders, measured in five consecutive samplings (breathing zone, 120–240 minutes) from 1999 to 2003, ranged from 0.11 to 15.6 mg/m^3(165).

Riihimäki *et al* assessed airborne aluminium exposure in MIG welding and grinding shipyard workers in Finland. The welding fumes contained aluminium oxide particles with diameters < 0.1 μm and their aggregates. Mean 8-hour TWA concentrations, measured inside of the welding helmet, ranged from 0.2 to 10.0 mg/m^3 for total dust and from 0.008 to 2.4 mg/m^3 for aluminium. Generally, high concentrations were encountered during welding in confined compartments and in plasma cutting. When using no respiratory protection, total dust and aluminium breathing zone air levels were 1.2–13.6 and 0.3–6.1 mg/m^3, respectively (162).

In the breathing zone air of workers exposed to bauxite (mainly aluminium hydroxide) and aluminium sulphate particles with diameters of 1–10 μm in a Finnish aluminium sulphate-producing facility, mean 8-hour TWA total dust and aluminium levels were 0.3–4.4 and 0.02–0.5 mg/m^3, respectively (162).

Delgado *et al* assessed potential dermal exposure to the non-volatile fractions of paints during the painting process in car-body repair shops with water-based paints containing aluminium (amounts of aluminium in paints not reported). The measurements were done during filling of the spray gun, paint spraying and cleaning of the gun. Potential dermal exposure was assessed using patches and gloves as dosimeters and analysing deposits of aluminium, which was used as a chemical tracer. For the exposure scenarios mentioned above, the potential dermal exposure was expressed as μg paint/cm^2/min and μg aluminium/cm^2/min. The body region areas used in the calculations were 18 720 cm^2 for total body area without hands and 410 cm^2 for the area of each hand. Potential dermal exposure of the hands to aluminium during filling of the spray gun ranged from 0.021 to 13.4 μg/cm^2/min (median 0.49, arithmetic mean (AM) 2.03, geometric mean (GM) 0.62). During spraying, the potential dermal exposure to aluminium ranged from 0.004 to 0.12 μg/cm^2/min (mean 0.021, AM 0.031, GM 0.022) for the body and 0.01 to 0.59 μg/cm^2/min (mean 0.068, AM 0.10, GM 0.067) for the hands. With cleaning of the spray gun, the hands were the principal area exposed, with values ranging from 0.017 to 4.10 μg/cm^2/min (AM 0.83, GM 0.42) (44).

5. Kinetics

5.1 Absorption

ATSDR data

Evidence for absorption of aluminium after inhalation exposure in humans is available from several occupational studies. Occupational exposure to aluminium fumes, dusts and flakes has resulted in increases in aluminium levels in serum, tissue and urine. The percentage of aluminium absorbed following inhalation exposure was not reported in the occupational toxicokinetic studies (Gitelman *et al* 1995, Mussi *et al* 1984, Pierre *et al* 1995, Sjögren *et al* 1985, 1988). Data from Mussi *et al* (1984) suggest that the fractional absorption of aluminium from lung to blood is higher in individuals exposed to aluminium fumes as compared to aluminium dust. However, it is not known if a possible difference in particle size between the aluminium fumes and aluminium dust influenced absorption.

Several animal studies indicated that aluminium is retained in the lung after inhalation exposure to aluminium oxide (Christie *et al* 1963, Thomson *et al* 1986) and aluminium chlorohydrate (Steinhagen *et al* 1978, Stone *et al* 1979). However, no significant increases in aluminium in tissues or serum were seen, indicating that lung retention rather than absorption was taking place (Steinhagen *et al* 1978, Stone *et al* 1979).

Mechanisms of inhalation absorption of aluminium are not well characterised, although it seems likely that relatively large aluminium-containing particles retained in the respiratory tract are cleared to the gastrointestinal tract by ciliary action. As has been observed with typical particulates (ICRP 1994), it is hypothesised that aluminium particles that are small enough (< 5 μm diameter) to reach the lungs may contribute to overall body levels by dissolution and direct uptake into the blood stream or by macrophage phagocytosis (Priest 1993, Reiber *et al* 1995).

Studies by Perl and Good (1987) and Zatta *et al* (1993) have demonstrated that aluminium may directly enter the brain via the olfactory tract. The aluminium crosses the nasal epithelium and reaches the brain via axonal transport.

No human or reliable experimental animal studies were located regarding aluminium absorption after dermal exposure to aluminium or its compounds.

Gastrointestinal absorption of aluminium is low, generally in the range of 0.1–0.6 %, but absorption of poorly bioavailable forms such as aluminium hydroxide can be less than 0.01 % (Day *et al* 1991, DeVoto and Yokel 1994, Ganrot 1986, Greger and Baier 1983, Hohl *et al* 1994, Jones and Bennett 1986, Nieboer *et al* 1995, Priest *et al* 1998). Gastrointestinal absorption is complex and is, amongst others, determined by the chemical form (type of anion) of the ingested compound and the presence of complexing ligands in the diet which can either enhance (e.g. carboxylic acids such as lactic and, especially, citric acid) or reduce (e.g. phosphate or dissolved silicate) uptake (DeVoto and Yokel 1994, Reiber *et al* 1995).

Additional data

From a few studies in workers exposed to aluminium, the percentage of aluminium absorbed from the lung was estimated to be ca. 2 %, based on data on daily urinary aluminium excretion and on aluminium concentrations in occupational air. In two human volunteers, exposed by inhalation to ^{26}Al-labelled aluminium oxide particles with a mean aerodynamic diameter of 1.2 μm, the fraction of aluminium absorbed was calculated to be 1.9 % (181).

Riihimäki *et al* examined aluminium exposure and kinetics in 12 welding and grinding shipyard workers and 5 aluminium sulphate-production workers. The shipyard workers were exposed to welding fumes containing aluminium oxide particles with diameters < 0.1 μm and their aggregates at mean 8-hour TWA concentrations of aluminium of 1.1 mg/m^3 (range 0.008–6.1). The aluminium sulphate-production workers were exposed to bauxite (mainly aluminium hydroxide) and aluminium sulphate with diameters of 1–10 μm at mean 8-hour TWA aluminium concentrations of 0.13 mg/m^3 (range 0.02–0.5). In welders, about 1 % of welding fume aluminium was estimated to be rapidly absorbed from the lungs, whereas an undetermined fraction was retained forming a lung burden. In the production workers, the fractional absorption could not be quantified but might be higher than that in the welders without evidence of a lung burden (162).

Sjögren *et al* exposed 3 previously unexposed male volunteers to welding fumes for 8 hours (mean 8-hour TWA aluminium concentration: 2.4 mg/m^3, range 0.3–10.2) and estimated that 0.1–0.3 % of the amount of aluminium inhaled was excreted in the urine within the next two days after exposure (183).

Röllin *et al* investigated the bioaccumulation and excretion patterns of aluminium in 115 newly employed potroom workers of a modern aluminium smelter in South Africa at various intervals during the plant construction stage and one year into full production (i.e. over a total period of 36 months). As none of the subjects had ever worked in the aluminium industry before, they served as their own controls and the first blood and urine specimens were collected before commencement of employment. Aluminium present in the total ambient air fraction in potrooms during construction ranged from 0 to 2.1 mg/m^3, with the highest median concentration equalling 0.173 mg/m^3 being recorded at 17 months. After 12 months, the mean ± SD concentration of aluminium in serum had almost doubled (month 0: 3.33 ± 2.13 μg/l, month 12: 6.37 ± 3.98 μg/l), thereafter it levelled off (169).

A case report of severe hyperaluminaemia in a 43-year-old woman using a 20 % aluminium chlorohydrate-containing antiperspirant cream on each underarm daily for 4 years suggested dermal absorption of aluminium. Application of 1 g of this cream would result in a daily external dermal dose of 0.11 g of aluminium (III), amounting to 157 g over the 4-year period (80).

5.2 Distribution

5.2.1 Distribution through the body

ATSDR data

Aluminium occurs normally in the body tissues of humans (Ganrot 1986). The total body burden of aluminium in healthy human subjects is approximately 30–50 mg (Alfrey 1981, 1984, Alfrey *et al* 1980, Cournot-Witmer *et al* 1981, Ganrot 1986, Hamilton *et al* 1973, Tipton and Cook 1963). Of the total body burden of aluminium, about one-half is in the skeleton, and about one-fourth is in the lungs (Ganrot 1986). Most of the aluminium detected in lungs is probably due to accumulation of insoluble aluminium compounds that have entered the body via the airways. The normal level of aluminium in adult human lungs is about 20 mg/kg wet weight and increases with age due to an accumulation of insoluble aluminium compounds (Ganrot 1986). Most of the aluminium in other parts of the body probably originates from food intake. Reported normal levels in human bone tissue range from 5 to 10 mg/kg (Alfrey 1980, Alfrey *et al* 1980, Cournot-Witmer *et al* 1981, Flendrig *et al* 1976, Hamilton *et al* 1973, Tipton and Cook 1963). Aluminium is also found in human skin (Alfrey 1980, Tipton and Cook 1963), lower gastrointestinal tract (Tipton and Cook 1963), lymph nodes (Hamilton *et al* 1973), adrenals (Stitch 1957, Tipton and Cook 1963) and parathyroid glands (Cann *et al* 1979). Low aluminium levels (0.3–0.8 mg/kg wet weight) are found in most soft tissue organs, other than the lungs (Hamilton *et al* 1973, Tipton and Cook 1963). The normal level of aluminium in the human brain ranges from 0.25 to 0.75 mg/kg wet weight, with gray matter containing about twice the concentration found in white matter (Alfrey *et al* 1976, Arieff *et al* 1979, McDermott *et al* 1978). There is evidence that with increasing age, aluminium concentrations may increase in the brain tissue (Alfrey 1980, Crapper and DeBoni 1978, Markesbery *et al* 1981, McDermott *et al* 1979, Stitch 1957, Tipton and Shafer 1964). Aluminium levels in serum may also increase with ageing (Zapatero *et al* 1995).

Aluminium binds to various ligands in the blood and distributes to every organ, with highest concentrations found in bone and lung tissues. Aluminium can form complexes with many molecules in the body (organic acids, amino acids, nucleotides, phosphates, carbohydrates, macromolecules). Free aluminium ions (e.g. $Al(H_2O)_6^{3+}$) occur in very low concentrations.

Ohman and Martin (1994) showed that 89 % of the aluminium in serum is bound to transferrin. There are *in vitro* data indicating that aluminium can bind to the iron-binding sites of transferrin (Moshtaghie and Skillen 1986), and that Al^{3+} may compete with similar ions in binding to transferrin (Ganrot 1986). Al^{3+} is also known to bind to a considerable extent to bone tissue, primarily in the metabolically active areas of the bone (Ganrot 1986).

Cellular uptake of aluminium by organs and tissues is believed to be relatively slow and most likely occurs from the aluminium bound to transferrin (Ganrot 1986). It is likely that the density of transferring receptors in different organs influences the distribution of aluminium to organs. Within cells, Al^{3+} accumulates in the lysosomes, cell nucleus and chromatin.

Additional data

Roider and Drasch investigated aluminium concentrations in human tissues (five different parts of the brain, lung, kidney, liver and spleen) in a not occupationally exposed population in Southern Bavaria (Germany). Tissue samples from 140 adults were obtained from autopsies and analysed by GFAAS. As far as the criteria sex and age were concerned, a balanced distribution was achieved (10 females and 10 males for each age decade). The highest aluminium concentration was found in the lung (GM 5.55 mg Al/kg wet weight), followed by the liver (0.43 mg Al/kg), the spleen (0.29 mg Al/kg) and the kidney (0.24 mg Al/kg). The content in the brain averaged 0.31 mg Al/kg, but aluminium was not evenly distributed in the brain. The concentration was highest in the grey matter of cerebrum (0.34 mg Al/kg) and lowest in the white matter (0.19 mg Al/kg). A positive correlation was observed among aluminium concentrations in all tissues (Spearman rank correlations, $p < 0.001$). Aluminium levels were age-dependent; the concentration in tissues increased with age. Aluminium levels in the lung depended on the locality where the person lived. Males living in rural areas had a higher amount of aluminium deposited in their lungs (164).

The effect of stress on brain distribution of aluminium was tested in three groups of adult mice given 0, 300 and 600 mg Al/kg body weight (bw)/day in drinking water for 2 weeks (Appendix 1, Table VI). One-half of the animals in each group were concurrently subjected to restraint stress during 1 hour/day throughout the study. At the end of the behavioural testing period, mice were killed and aluminium concentrations were determined in a number of tissues. The levels of aluminium in whole brain and cerebellum were significantly enhanced in mice exposed to aluminium plus restraint (41).

In a study by Ogasawara (Appendix 1, Table VI-VII), aluminium was administered orally, intravenously and intraperitoneally to rats, in the absence or presence of citric acid or maltol. Oral administration of aluminium hydroxide or aluminium chloride with citric acid for 7 weeks was not found to increase brain aluminium levels. Similarly, a single intravenous injection of aluminium chloride in the presence or absence of either citric acid or maltol did not alter brain aluminium levels after 48 hours. Only daily intraperitoneal injections of aluminium chloride (8 mg Al/kg bw) and an equimolar amount of maltol over a 14-day period enhanced accumulation of aluminium in rat brain. No significant increases were observed for the experimental groups receiving intraperitoneal aluminium chloride alone or with citric acid. According to the authors, these results suggested that the chemical form of aluminium strongly influenced its bioavailability (143).

Chronic subcutaneous injection of aluminium-L-glutamate in young mature rats showed that aluminium accumulated especially in the striatum and hippocampus (45).

5.2.2 Placental transfer

ATSDR data

There is limited animal evidence indicating that aluminium has the potential to cross the placenta and accumulate in the foetus following oral or intraperitoneal exposure to aluminium (Cranmer *et al* 1986). Increased concentrations of aluminium were detected in both foetuses and placentas of mice treated throughout gestation with aluminium chloride (Cranmer *et al* 1986).

Additional data

After exposure of female rats (sperm positive) to doses of aluminium chloride of 345 mg/kg bw/day on gestational days 0–16 and postnatal days 0–16, significantly high concentrations of aluminium were observed in the placenta and in the brains of foetuses and sucklings (173).

5.3 Metabolism

No information was available on the biotransformation of aluminium and aluminium compounds in the body. However, as an element, aluminium is always found attached to other chemicals and these affinities can change within the body. The complexes formed are metabolically active.

ATSDR data

In living organisms, aluminium is believed to exist in four different forms: as free ions, as low-molecular-weight complexes, as physically bound macromolecular complexes and as covalently bound macromolecular complexes (Ganrot 1986). The free ion, Al^{3+}, is easily bound to many substances and structures. Therefore, its fate is determined by its affinity to each of the ligands and their relative amounts and metabolism. Aluminium may also form low-molecular-weight complexes with organic acids, amino acids, nucleotides, phosphates and carbohydrates. These low-molecular-weight complexes are often chelates and may be very stable. The complexes are metabolically active, particularly the non-polar ones. Because aluminium has a very high affinity for proteins, polynucleotides and glycosaminoglycans, much of the aluminium in the body may exist as physically bound macromolecular complexes with these substances. Metabolically, these macromolecular complexes would be expected to be much less active than the smaller, low-molecular-weight complexes.

Additional data

No additional data were found.

5.4 Excretion

5.4.1 Excretion from the body

ATSDR data

In humans, the kidney is the major route of excretion of absorbed aluminium after inhalation and oral exposure. The unabsorbed aluminium is excreted primarily in the faeces after oral exposure. No studies were located regarding excretion in animals after inhalation exposure to aluminium or its compounds.

With regard to inhalation exposure, studies indicated that urinary levels were related to exposure concentration. However, quantitative correlations, as well as elimination of aluminium in the faeces, were not reported. A relationship between the duration of aluminium exposure and urinary concentrations has been found in humans (Sjögren *et al* 1985, 1988). Welders exposed to 0.2–5.3 mg/m^3 (8-hour work shift) for more than ten years had a urinary aluminium half-time of at least 6 months compared to 9 days for individuals exposed for less than one year (Sjögren *et al* 1988). The excretion half-time was 8 hours following a single exposure to aluminium welding fumes (Sjögren *et al* 1985). A half-time of 7.5 hours was estimated in workers exposed to aluminium dust (Pierre *et al* 1995). However, if urinary concentrations were measured after an exposure-free period, the level was related to the total number of exposed years. Apparently, the longer the exposure, the greater the retention of aluminium in humans.

When humans ingested 1.71 µg Al/kg bw/day as aluminium lactate in addition to 0.07 mg Al/kg bw/day in the basal diet for 20 days, 0.09 and 96 % of the daily aluminium intake was cleared through the urine and faeces, respectively (Greger and Baier 1983). Excretion data collected in animal studies are consistent with the results from human studies. Sprague Dawley rats administered a single dose of one of eight aluminium compounds (all contained 35 mg aluminium) excreted 0.015–2.27 % of the initial dose in the urine (Froment *et al* 1989). The difference in the excretion rates most likely reflected differences in gastrointestinal absorption.

Additional data

Letzel *et al* examined renal excretion kinetics by determination of biological half-time of aluminium in aluminium welders in automobile industry in Germany. Spontaneous urine samples from 16 welders with aluminium concentrations > 50 µg/l were collected before and after an exposure-free period (24–45 days). During the exposure-free interval, median urinary aluminium levels significantly decreased from 178.7 µg/l (or 118.1 µg/g creatinine) to 55.6 µg/l (or 52.7 µg/g creatinine). Biological half-times of 23.6 days (range 8.8–64.9) and 30.4 days (12.9–214.9) were calculated related to µg/l and µg/g creatinine, respectively. There was no relationship between the half-times and the age of the persons, the duration of previous exposure or of the exposure-free interval and the current concentration of aluminium in urine before the exposure-free interval. On a group basis, there was a tendency of having a somewhat longer biological half-time for persons with a higher cumulative exposure index (118).

Ljunggren *et al* studied the elimination kinetics of aluminium in workers (n = 13) in aluminium powder production. From aluminium concentrations determined in urine samples collected before and after a 4–5-week exposure-free period, half-times of 5–6 weeks were calculated. Among a separate group of workers (n = 10), who had been retired for 6 months to 14 years, half-times varied from 8 months to 8 years and were related to the number of years since retirement (120).

Other reports on individuals or groups of workers exposed to aluminium welding fumes or aluminium powders showed similar results suggesting accumulation of aluminium in the body from which it is eliminated very slowly (57, 65, 162, 165, 169, 171, 184).

5.4.2 Excretion in human milk

ATSDR data

Different studies indicated that aluminium can be excreted in human milk. The median aluminium level in breast milk collected from 12 Canadian women was reported to be 14 µg/l (range < 5–45) (Koo *et al* 1988). In an Australian study, Weintraub *et al* (1986) reported human breast milk concentrations of 30 µg/l in nursing mothers. More recently, Simmer *et al* (1990) reported a mean aluminium concentration of 49 µg/l in breast milk collected from Australian women. In the UK, one study found aluminium levels in human breast milk in the range of 3–79 µg/l (mean 27) (Baxter *et al* 1991), while another study reported mean aluminium concentrations of 9.2 µg/l (95 % CI 5.6–12.7, collected from 15 nursing mothers) (Hawkins *et al* 1994). The aluminium content of human milk from 42 nursing Croatian women in the winter of 1992–1993 ranged from 4 to 2 670 µg/l with a mean of 380 µg/l (Mandić *et al* 1995). While some differences in aluminium content of milk were found depending on the participant's age, number of deliveries, post-partum days, weight gain during pregnancy, refugee status and smoking status, correlations with these factors were not statistically significant. Mandić *et al* (1995) were unable to explain the high values obtained for aluminium in the milk of the Croatian women, especially since there was no data on aluminium in Croatian foodstuffs. No information on occupational exposure was provided. Since the measurements using standard reference serum were acceptable, contamination in the analytical procedure was ruled out. While steps were taken to avoid contamination in the collection process, no controls to gauge the effectiveness of these steps were reported.

There is limited animal evidence indicating that aluminium has the potential to be distributed to some extent to the milk of lactating mothers. The concentration of aluminium in milk of rats that ingested 420 mg Al/kg bw/day as aluminium lactate in the diet during gestation and lactation increased at least 4-fold beginning on postnatal day 12 (Golub *et al* 1996). Peak concentrations of aluminium were detected in the milk of lactating rabbits 12–24 hours after a single large gavage dose of aluminium lactate. However, the amount of aluminium in milk as a percentage of the total oral dose was not reported (Yokel and McNamara 1985). Although levels of aluminium in breast milk were elevated in aluminium-exposed

rabbits, the concentrations in the pups were not significantly different from control levels, suggesting that the aluminium was poorly absorbed (Yokel 1985).

Additional data
In a study assessing reference values for various minor and trace elements in human milk of Italian urban and rural populations (subdivided into smokers and non-smokers and not professionally exposed to chemicals), Coni *et al* found aluminium concentrations ranging between 39 and 1 413 µg/g (n = 59, mean 239 µg/l, no SD given). No individual levels were given, but in the groups of urban smoking mothers and of rural non-smoking mothers, maximum levels were 1 115 and 1 413 µg/g, respectively. Coni *et al* used a strategy to minimise the risk of chemical contamination by cleansing the nipple and the areola with doubly distilled water before sampling (43).

Krachler *et al* found aluminium concentrations of < 10–380 µg/l (median 67 µg/l) in breast milk samples obtained from 27 Austrian mothers. Before collecting the milk, breasts were cleaned with doubly distilled water and air dried. Krachler stated that the highest level might be due to contamination of the specimen during collection or sample preparation (106).

DECOS's Subcommittee on the Classification of Reproduction Toxic Substances (84) noted that in some of these studies (Coni *et al* (43), Mandić *et al* 1995) levels exceeded 710 µg aluminium per litre of breast milk which is a level the subcommittee considered to be tolerable based on a provisional tolerable weekly intake of 1.0 mg/kg bw as recommended by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (100).

5.5 Possibilities for biological exposure monitoring

ATSDR data
Aluminium can be measured in the blood, urine and faeces. Since aluminium is found naturally in a great number of foods, it is found in everyone. Unfortunately, exposure levels cannot be related to serum or urine levels very accurately, primarily because aluminium is very poorly absorbed by any route and its oral absorption in particular can be quite affected by other concurrent intakes. There is an indication that high exposure levels are reflected in urine levels, but this cannot be well quantified as much of the aluminium may be rapidly excreted. Aluminium can also be measured in the faeces, but this cannot be used to estimate absorption.

Additional data
The concentrations of aluminium in blood and urine are affected by short-term and long-term occupational exposure (98). Samples collected immediately after a work shift are strongly related to the current exposure, whereas samples taken later in the period after exposure reflect cumulative exposure (104). It is not known how well concentrations of aluminium in blood and urine reflect the concentrations in the target tissues, such as the brain (98). Riihimäki *et al* also mentioned that it is uncertain how representative the surrogates aluminium in serum and in urine

are for the metal concentration in the brain. They hypothesised that they are of value since results demonstrated an almost doubling of aluminium in serum in rabbits exposed to fine aluminium oxide dust over 5 months in a dusting chamber, and the level of aluminium in the brain was more than doubled (161).

In order to evaluate aluminium exposure and to assess aluminium concentrations in plasma and urine, a reference group of persons from the urban region Erlangen-Nüremberg, Germany, without occupational aluminium exposure (13 men and 26 women) and a group of employees of a plant producing and processing aluminium powder (143 men and 26 women) were investigated. The group of employees consisted of 54 persons working in the area of aluminium powder production, 48 in the production of special pastes containing aluminium powder, 24 in administration, 15 in maintenance, 8 in diverse laboratories and 20 at other workplaces without direct contact with aluminium. The highest aluminium dust concentrations, measured by personal breathing zone air sampling (sampling time: 1–6 hours), were found in the powder-production area with levels between 5 and 21 mg/m^3, the peak levels occurring when sieving aluminium powder. Concentrations in the paste production ranged from 1 to 4 mg/m^3 and were below 0.4 mg/m^3 in the other areas. The powder-production workers had higher internal aluminium levels when compared to those of the paste-production workers. The aluminium concentrations in the plasma of the powder-production workers varied between < 1.5 and 88.8 µg/l (mean 14.2, median 8.5) and in the urine between 3.1 and 1 477 µg/l (mean 132.6, median 69.6) and 8.5 and 935 µg/g creatinine (mean 102.8, median 63.0), respectively. In the paste-production workers, aluminium levels in plasma ranged from 2.3 to 30.0 µg/l (mean 8.9, median 7.3) and in urine from 1.4 to 159.4 µg/l (mean 29.3, median 19.4) and from 3.9 to 159.4 µg/g creatinine (mean 32.8, median 22.6). The aluminium concentrations in the plasma of the unexposed reference subjects varied between < 1.5 and 11.0 µg/l and in the urine between 2.4 and 30.8 µg/l and 1.9 to 20.2 µg/g creatinine, respectively. There was a statistically significant ($p < 0.05$) linear correlation between the aluminium concentrations in the plasma and urine for the total exposed group ($r = 0.714$) and the employees from the area of powder production ($r = 0.849$). For the workplaces with a lower exposure and for the reference group, no significant relationship could be determined. According to the authors, besides urine values, plasma values should be included in the evaluation of the exposure in the aluminium powder industry, due to the great danger of contamination of urine samples on site (117).

A group of 62 aluminium welders (age in 1999: 23–51 years, median: 35 years) in German automobile industry and train body and truck trailer construction was surveyed annually from 1999 to 2003 by determination of pre- and post-shift aluminium in urine and plasma to evaluate an adequate strategy for biological monitoring of aluminium (165). Biomonitoring was supplemented by personal air measurements of the total dust concentration. The welders' internal exposure was compared to the exposure of 60 non-exposed assembly workers (age in 1999: 21–51 years, median: 36 years) who were surveyed in 1999, 2001 and 2003.

Total respirable dust exposure of the welders measured in 5 consecutive samplings (breathing zone, 120–240 minutes) from 1999 to 2003 ranged from 0.11 to 15.6 mg/m^3. According to the annual median values, which ranged from 0.44 to 0.72 mg/m^3, only minor fluctuations in external exposure occurred. No information on co-exposure was reported.

Median concentrations of aluminium in urine of the welders decreased from 40.1 to 19.8 µg/g creatinine and in plasma from 8.7 to 4.6 µg/l. For the control group, the median levels of aluminium in urine ranged from 4.8 to 5.2 µg/g creatinine and in plasma from 2.4 to 4.3 µg/l, indicating a higher sensitivity for the marker aluminium in urine. No systematic differences have been found between pre- and post-shift levels of aluminium in urine. According to the authors, this might be caused by the slow elimination kinetics and low systemic bioavailability of aluminium. A correlation analysis did not yield close relationships between dust exposure, aluminium in plasma and aluminium in urine (165).

Riihimäki *et al* investigated changes in serum and urinary aluminium concentrations in 12 welding and grinding shipyard workers and 5 aluminium sulphate-producing workers over a short time (2 workdays) and a long time (2 years, in 8 shipyard workers only). The shipyard workers were exposed to welding fumes containing aluminium oxide particles at mean 8-hour TWA concentrations of aluminium of 1.1 mg/m^3. The aluminium sulphate-production workers were exposed to bauxite (mainly aluminium hydroxide) and aluminium sulphate at mean 8-hour TWA aluminium concentrations of 0.13 mg/m^3 (see also Section 5.1). The mean post-shift serum and urinary aluminium levels in the shipyard welders were 6 and 92 µg/l, respectively, in the aluminium sulphate workers 3.5 and 16 µg/l, respectively. Between two shifts, the aluminium concentration in the serum of the welders decreased by about 50 % ($p < 0.01$) while that in their urine did not change ($p = 0.64$). No such changes were seen in the production workers. One year later when aluminium welding at the shipyard had ceased and the workers involved had no longer been working with aluminium for 1–5 months, the median aluminium concentration in the serum decreased by about 50 % ($p = 0.007$) with no change in urinary aluminium concentration ($p = 0.75$). Two years after the start of the study, aluminium serum concentrations in 7 out of the 8 workers for whom samples were available were < 2.7 µg/l, i.e. the 95th percentile of the normal distribution in Finnish adult city residents without occupational exposure to aluminium. However, urinary levels were higher than "normal" values (162).

In its 2009 evaluation of a biological tolerance level (BAT value) for aluminium, the Working Group on the Derivation of Threshold Values in Biological Materials of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (a commission of the German Research Foundation (Deutsche Forschungsgemeinschaft (DFG)) concluded that, from human data, a relationship between (indicators of) internal exposure (aluminium concentration in plasma/serum and urine) and effects could not be assessed. Therefore, it was not possible to derive a BAT value based on a relationship between internal exposure and effects. This should therefore be based on relationships between external and

internal exposure taking the German occupational exposure limit of 1.5 mg/m^3 (see Table 6, Section 9.2) as a reference point.

With respect to the indicators for internal exposure, the working group stated that the studies in German automobile industry and train body and truck trailer construction (see references (28, 29, 101, 102, 115, 165)) confirmed that there is no clear correlation between the aluminium concentration in plasma and total dust concentration at the workplace. Furthermore, aluminium concentrations in plasma of occupationally exposed groups with values < 10 µg/l differ only slightly from values that can be expected in the general population (< 5 µg/l). Therefore, the working group considered determination of aluminium concentrations in plasma not appropriate as an indicator of occupational exposure.

According to the working group, the study by Rossbach *et al* (165) suggested that for the assessment of occupational aluminium exposure, aluminium in urine would be a more robust and sensitive parameter compared to aluminium in plasma. Since urinary aluminium concentrations expressed per gramme creatinine correlated better with aluminium concentrations in air compared to urinary concentrations in litres, the working group decided to use µg aluminium/g creatinine as the indicator of choice for internal exposure. From data presented by Mussi *et al* (133), Sjögren *et al* (179), and in the aforementioned German studies, the working group calculated that exposure to 1.5 mg/m^3 would lead to an aluminium excretion in the urine of ca. 50–67 µg/g creatinine and set a BAT value of 60 µg Al/g creatinine. Because of the long biological half-time following chronic cumulative exposure to aluminium, there was no need to fix the sampling time. The working group noted that the BAT value is related to urine with creatinine concentrations of 0.5–2.5 g/l (114).

The American Conference of Governmental Industrial Hygienists (ACGIH) has not specified a Biological Exposure Index (BEI) for biological monitoring of occupational exposure to aluminium and its compounds (4).

5.6 Possibilities for biological effect monitoring

ATSDR data

There are no known simple, non-invasive tests that can be used as biomarkers of effects caused by aluminium.

Additional data

No additional data were found.

5.7 Summary

Inhalation and dermal absorption have not been studied in detail. The percentage of aluminium absorbed following inhalation might be about 2 %, whereas the percentage for dermal exposure is not reported. Welding of aluminium creates submicron-sized particles that are easily inhaled and reach the alveoli. Animal studies showed no significant increases in aluminium in tissues or serum after

inhalation exposure to aluminium oxide and aluminium chlorohydrate, indicating that lung retention rather than absorption was taking place.

After oral exposure, 0.1–1 % of aluminium is absorbed (depending on the aluminium compound ingested and the diet composition). Furthermore, aluminium may directly enter the brain via the olfactory tract. The aluminium crosses the nasal epithelium and reaches the brain via axonal transport.

Aluminium may exist as free ions (very low concentrations) but mainly forms complexes with various ligands in the blood and distributes to every organ, with highest concentrations found in bone and lung tissues. In animals, elevated levels of aluminium in the foetus were observed following oral or intraperitoneal exposure, providing evidence of transplacental transfer of aluminium.

The kidney is the major route of excretion of systemically available aluminium after inhalation and oral exposure. No data were available on excretion after dermal exposure. With regard to inhalation exposure, longer exposure times are associated with a decreased rate of clearance of aluminium by the kidney. Unabsorbed aluminium is excreted primarily in the faeces after oral exposure. Several studies indicated that aluminium can be excreted in human milk, in some of them exceeding levels which are considered to be safe.

The concentrations of aluminium in blood and urine are affected by short-term and long-term occupational exposure. Samples collected immediately after a work shift are mainly related to the most recent exposure, whereas samples taken later in the period after exposure reflect cumulative exposure. The most suitable biological parameter for biological monitoring of persons occupationally exposed to aluminium is the aluminium concentration in urine (expressed as µg Al/g creatinine).

It is not known how well concentrations of aluminium in blood and urine reflect the concentrations in the target tissues, such as the brain.

6. Mechanisms of action

ATSDR data

In cases in which human aluminium toxicity has occurred, the target organs appear to be the lung, the central nervous system and the bone. No specific molecular mechanisms have been elucidated for human toxicity to aluminium, but the element is known to compete in biological systems with cations, especially magnesium (Macdonald and Martin 1988) despite an oxidation state difference, and to bind to transferrin and citrate in the blood stream (Ganrot 1986). It may also affect second messenger systems and calcium availability (Birchall and Chappell 1988) and irreversibly bind to cell nucleus components (Crapper-McLachlan 1989, Dyrssen *et al* 1987). Aluminium has also been shown to inhibit neuronal microtubule formation.

In animal models, aluminium can also produce lung, central nervous system, and bone effects, as well as developmental effects in offspring.

6.1 Lung toxicity

ATSDR data
There have been several cases of lung fibrosis in humans as the result of occupational exposure to aluminium dusts (Jordan 1961, Mitchell *et al* 1961), and signs of lung damage have also been produced in rats, hamsters and guinea pigs after exposure to aluminium flakes and dusts of alchlor, aluminium fluoride, aluminium chloride or aluminium chlorohydrate (Drew *et al* 1974, Finelli *et al* 1981, Gross *et al* 1973, Steinhagen *et al* 1978, Thomson *et al* 1986).

The lung effects observed in humans and animals are suggestive of dust overload. Dust overload occurs when the volume of dust in the lungs markedly impairs pulmonary clearance mechanisms. Lung overload is not dependent on the inherent toxicity of the compound, and dust overloading has been shown to modify both the dosimetry and toxicological effects of the compound. When excessive amounts of widely considered benign dusts are persistently retained in the lungs, the resultant lung effects are similar to those observed following exposure to highly toxic dusts. The excessive levels of dust in the lung lead to excessive engulfment of particles by alveolar macrophages resulting in a progressive loss of alveolar macrophage mobility and an aggregation of alveolar macrophages (Morrow 1992). The relative or complete loss of alveolar macrophage mobility increases the likelihood of direct particle-epithelial cell interactions, often resulting in a prolonged inflammatory response, and interstitial localisation of dust particles.

Additional data
No additional data were found.

6.2 Neurotoxicity

ATSDR data
Numerous mechanistic studies of aluminium neurotoxicity have been performed but no single unifying mechanism has been identified (Erasmus *et al* 1993, Jope and Johnson 1992, Strong *et al* 1996). The main sites of action of aluminium are difficult to discern because the studies have been performed using a variety of exposure methods (including a number of different *in vivo* injections and *in vitro* systems) and animal species, and a number of typical effects are not common to all species and exposure circumstances (i.e. are only expressed using certain models of neurotoxicity). Although available data are insufficient to fully understand the mechanism(s) of aluminium toxicity, some processes that are involved have been identified.

Some of the neurotoxic effects of aluminium can be partially explained by its genotoxic and subcellular effects on DNA in neurons and other cells demonstrated *in vitro*. These effects include nuclear effects such as binding to DNA phosphates and bases, increasing histone-DNA binding, altering sister chromatid exchange (SCE), and decreasing cell division (Crapper-McLachlan 1989, Crapper-McLachlan and Farnell 1985). Cytoplasmic effects include conformational changes

in calmodulin and increasing intracellular calcium. Although these effects may not specifically be caused by interactions with DNA, they will significantly affect neuronal functions. Since aluminium accumulates in DNA structures in the cell nucleus, it may alter protein-DNA interactions. This is particularly important for the calcium-binding protein, calmodulin. This can affect the calcium-modulated second messenger system which is activated by neurotransmitters. Interference with DNA and protein synthesis may also be part of the mechanism that is involved in the creation of the neural filaments that compose the neurofibrillary tangles seen in Alzheimer's patients (Bertholf 1987).

Changes in cytoskeletal proteins, manifested as hyperphosphorylated neurofilamentous aggregates within the brain cells, is a characteristic response to aluminium in certain species (e.g. rabbits, cats, ferrets and non-human primates) and exposure situations (e.g. intracerebral and intracisternal administration). Similar neurofibrillary pathological changes have been associated with several neurodegenerative disorders, suggesting that the cause of aluminium-related abnormal neuronal function may involve changes in cytoskeletal protein-functions in affected cells. The neurofilamentous aggregates appear to result mainly from altered phosphorylation, apparently by post-translational modifications in protein synthesis, but may also involve proteolysis, transport and synthesis (Jope and Johnson 1992, Strong *et al* 1996). Each of the processes can be influenced by kinases, some of which are activated by second messenger systems. For example, aluminium appears to influence calcium homeostasis and calcium-dependent processes in the brain via impairment of the phosphoinositide second messenger producing system (which modulates intracellular calcium concentrations). Calcium-activated proteinases may be affected which could alter the distribution and concentration of cytoskeletal proteins and other substrates (Jope and Johnson 1992).

The species (rodents) in which aluminium-induced neurobehavioural effects (e.g. changes in locomotor activity, learning and memory) have been observed fail to develop significant cytoskeletal pathology, but exhibit a number of neurochemical alterations following *in vivo* or *in vitro* exposure (Erasmus *et al* 1993, Strong *et al* 1996). Studies in these animals indicate that exposure to aluminium can affect permeability of the blood-brain barrier, cholinergic activity, signal transduction pathways, lipid peroxidation and glucose metabolism as well as interfere with metabolism of essential trace elements (e.g. iron) because of similar coordination chemistries and consequent competitive interactions. Signal pathways are important in all cells and control differentiation and proliferation, neurotransmitter release and synaptic plasticity. Glucose metabolism may be affected by aluminium due to specific inhibition of hexokinase and glucose-6-phosphate dehydrogenase (Erasmus *et al* 1993, Strong *et al* 1996).

It is not known whether the potential mechanisms of aluminium neurotoxicity identified in adults parallel those active in the developing foetus and/or young animal. For example, aluminium competition for essential element uptake could be important during the development of the nervous system but less important for nervous system function in an adult animal (Strong *et al* 1996).

Additional data

Schetinger *et al* showed that aluminium interferes with δ-aminolevulinate dehydratase activity *in vitro* in the brain of adult mice (Swiss albino) (see Appendix 1, Table IV) (172).

Chronic administration of aluminium in the drinking water (2.5 % aluminium sulphate) reduced the basal activity of guanylate cyclase and impaired the glutamate-nitric oxide-cyclic guanosine monophosphate (cGMP) pathway in the cerebellum in rats (see Appendix 1, Table VI) (87).

Low molecular mass aluminium complexes induce calcium overload in heart and brain. The efficiency of this process depends on the nature of the ligand. Adenosine 5'-triphosphate (ATP) seems to play an important role in this process (9).

Exley has proposed a mechanism through which chronic exposure to aluminium would bring about subtle and persistent changes in neurotransmission. This mechanism involves the potentiation of the activities of neurotransmitters by the action of aluminium-ATP at ATP receptors in the brain (61).

Kohila and Tähti reported decreases in ATPase activity and cellular ATP in animal cells (*in vitro*) after exposure to aluminium lactate (see Appendix 1, Table IV) (105).

Tsunoda and Sharma reported lower dopamine, dihydroxyphenylacetic acid and homovanillic acid levels in the hypothalamus of mice treated with aluminium ammonium sulphate. According to the authors, changes in the concentration of dopamine and its metabolites measured in the hypothalamus suggest an inhibition of dopamine synthesis by aluminium (see Appendix 1, Table VI) (195).

Fattoretti *et al* suggested that the ageing central nervous system of rats is particularly susceptible to aluminium ($AlCl_3 \times 6\ H_2O$) toxic effects which may increase the cell load of oxidative stress (see Appendix 1, Table VI) (63).

Tsunoda and Sharma reported a significantly increased expression of tumour necrosis factor alpha (TNFα) mRNA in cerebrum of mice treated with aluminium ammonium sulphate. In peripheral cells, there were no significant differences of cytokine mRNA expressions. According to the authors, increased expression of TNFα mRNA by aluminium in cerebrum may reflect activation of microglia, a major source of TNFα in this brain region (see Appendix 1, Table VI) (196).

Data suggest that Al^{3+} ions bind to calmodulin in the presence of Ca^{2+} ions, leading to an inactive, reversible conformation, instead of its physiological active form, which may lead to the impairment of protein flexibility and to the loss of its ability to interact with several other proteins, which may decrease or inhibit the regulatory character of calmodulin in cellular processes (119).

6.3 Bone toxicity

ATSDR data

Two types of osteomalacia have been associated with aluminium exposure. The first type has been observed in healthy individuals using aluminium-containing antacids to relieve the symptoms of gastrointestinal disorders such as ulcers, colic

or gastritis. The aluminium in the antacids binds with dietary phosphorus and impairs gastrointestinal absorption of phosphorus. The observed osteomalacia and rickets is directly related to the decreased phosphate body burden.

Furthermore, osteomalacia is well documented in dialysed uraemic patients exposed to aluminium via dialysis fluid or orally administered aluminium used to control hyperphosphataemia. In the case of the uraemic patient, bone aluminium levels are markedly increased and the aluminium is present between the junction of calcified and non-calcified bone (Alfrey 1993). The osteomalacia is characterised by increased mineralisation lag time, osteoid surface and osteoid area, relatively low parathyroid hormone levels and mildly elevated serum calcium levels.

Additional data
No additional data were found.

6.4 Pro-oxidant activity

ATSDR data
No data were available.

Additional data
Diseases associated with high aluminium concentrations could be partially mediated by an increase in oxidative damage (formation of reactive oxygen species) to cell components. Aluminium could induce oxidative stress through its capacity to interact with active oxygen species, increasing their oxidant activity, or by affecting membrane rheology. Furthermore, aluminium-membrane interactions can also affect signalling cascades; an increase in intracellular oxidant levels can trigger redox-sensitive transcription factors involved in the decision of the cell to proliferate or undergo apoptosis (150).

Campbell *et al* reported significant increases in reactive oxygen species production and a significant decrease in glutathione content in glioma cells after 48-hour exposure to 500 µM aluminium sulphate (see Appendix 1, Table IV) (33). El-Demerdash observed that aluminium chloride (oral dose of 34 mg/kg bw/day) induced the formation of free radicals in male rats after exposure for 30 days (see Appendix 1, Table VI) (56). Furthermore, treatment (intraperitoneal injection) with 3 mg aluminium over a 3-week period increased both cortical levels of glutathione and the rates of generation of reactive oxygen species in brains of rats. Aluminium dosing elevated glutamine synthetase activity in the cortex. Levels of creatine kinase, another enzyme susceptible to oxidative stress, were also elevated in cortices of aluminium-treated rats. Aluminium treatment had very minor effects on hepatic parameters of oxidative events (see Appendix 1, Table VII) (27).

Exley proposed a mechanism which may help to explain the pro-oxidant activity of aluminium. Central to this mechanism is the formation of an aluminium superoxide semi-reduced radical ion, $AlO_2^{\bullet 2+}$. While the existence of this radical remains to be confirmed, there are strong chemical precedents to support its formation and

its oxidising potential. It is predicted to potentiate superoxide-driven biological oxidation, such as the oxidation of nicotinamide adenine dinucleotide (NADH), and accelerate ion-driven biological oxidation, such as the peroxidation of lipids. It is expected to form under physiological conditions when the concentration of free Al^{3+} is lower than nanomolar though its formation will likely be in competition with the dismutation of $O_2^{\bullet -}$. *In vivo*, the formation of $AlO_2^{\bullet 2+}$ would be expected to facilitate the direct activities of $O_2^{\bullet -}$ in both physiological and pathological processes and further aggravate oxidative damage by enhancing the formation of $HO^{\bullet}$ via the Fenton reaction. These activities may be more pronounced in disease states in which aluminium has been implicated (62).

Accumulating evidence suggests that aluminium can potentiate oxidative (formation of reactive oxygen species) and inflammatory events, leading to tissue damage and neurological disorders. Aluminium can potentiate iron-induced oxidative events and aluminium may exacerbate intrinsic inflammatory activity, mediated by interleukins and other inflammatory cytokines, providing an irresolvable chronic stimulus for microglial and phagocytic activation within the brain (21, 32).

6.5 Summary of the mechanisms of action of aluminium

The target organs of aluminium appear to be the lung, the central nervous system, and bone. Diseases associated with high aluminium concentrations could be partially mediated by an increase in oxidative damage (formation of reactive oxygen species) to cell components. Furthermore, aluminium-membrane interactions can affect signalling cascades.

There have been several cases of lung fibrosis in humans as the result of occupational exposure to aluminium dusts, and signs of lung damage have also been produced in rats, hamsters and guinea pigs after exposure to several aluminium compounds. The inflammatory responses and fibrosis may be caused by accumulation of particles in the lungs (dust overload) and impairment of pulmonary clearance mechanisms which may result from exposure to high levels of aluminium dusts.

Some processes that are involved in aluminium neurotoxicity have been identified. Some of the neurotoxic effects of aluminium can be partially explained by its effects on DNA in neurons and other cells demonstrated *in vitro*. Another one of these is changes in cytoskeletal protein functions, manifested as hyperphosphorylated neurofilamentous aggregates within the brain cells. Studies in animals indicate that exposure to aluminium can affect permeability of the blood-brain barrier, potentiation of the activities of neurotransmitters by the action of aluminium-ATP at ATP receptors, cholinergic activity, inhibition of dopamine synthesis, signal transduction pathways such as the glutamate-nitric oxide-cGMP pathway, lipid peroxidation, and glucose metabolism as well as interfere with metabolism of essential trace elements (such as calcium). Alteration of the conformation of calmodulin, leading to an inactive, reversible conformation, instead

of its physiological active form, caused by aluminium binding may also have possible implications in the neurotoxic effects of aluminium. Furthermore, aluminium has been implicated in a variety of neurological disorders that have been associated with an increase in the formation of reactive oxygen species. Besides, accumulating evidence suggests that the metal can potentiate inflammatory events, leading to tissue damage.

Osteomalacia has been associated with aluminium exposure. Aluminium in antacids, which are ingested to relieve gastrointestinal disorders, binds with dietary phosphorus and impairs gastrointestinal absorption of phosphorus. Furthermore, osteomalacia is well documented in dialysed uraemic patients exposed to aluminium via dialysis fluid or orally administered aluminium used to control hyperphosphataemia.

7. Effects in humans

Effects of aluminium and aluminium compounds in humans are summarised in Appendix 1, Table I (case reports), Table II (non-carcinogenic respiratory effects after long-term exposure) and Table III (neurotoxic effects after long-term exposure). The most important studies are described below.

7.1 Irritation and sensitisation

7.1.1 Respiratory tract

No studies were located on local effects on the respiratory tract after acute exposure. Local effects on the respiratory tract after long-term exposure are described in Section 7.3.

7.1.2 Skin

ATSDR data

No studies were located regarding dermal effects in humans after dermal exposure to various forms of aluminium.

Aluminium compounds are widely used in antiperspirants without harmful effects to the skin (Sorenson *et al* 1974). Some people, however, are unusually sensitive to some types of antiperspirants and develop skin rashes, which may be caused by aluminium (Brusewitz 1984).

Several children and one adult who had previous injections of vaccines or allergens in an aluminium based vehicle showed hypersensitivity to aluminium chloride (soluble) in a patch test (Böhler-Sommeregger and Lindemayr 1986, Veien *et al* 1986).

Additional data

Additional human data regarding local skin effects are summarised in Appendix 1, Table I.

A 43-year-old women did not have any rash or skin irritation due to daily application of 1 g of an antiperspirant cream containing 20 % aluminium chlorohydrate (soluble) on each underarm for 4 years (80).

Several case reports involving injections of vaccines in an aluminium-based vehicle showed local skin reactions/hypersensitivity to aluminium and aluminium hydroxide (insoluble) (185).

A 34-year-old man with a 2-year history of eczema of both hands and the right elbow flexure had used at work a compressor air pistol with his right hand to blow fillings out of newly milled narrow aluminium threads. Aluminium particles were thus impelled at high speed into the right hand. Clinically, there was erythema, hyperkeratosis, fissuring and partial desquamation on the hand. Patch testing was positive for aluminium (152).

In general, sensitisation to aluminium is very rare despite its wide distribution in cosmetics and its extensive use in several industries (7). As described above, aluminium is used as an adjuvant in most commonly used hyposensitisation extracts, as aluminium prolongs the period of absorption and increases the immunological response. Several studies have been published in the literature in which sensitisation to aluminium has been caused by repeated injections of substances containing aluminium given over a prolonged period in the course of hyposensitisation therapy. Children with aluminium sensitivity have been reported to develop persistent subcutaneous nodules at the sites of hyposensitisation therapy (7).

Although aluminium injected as hydroxide in an absorbed vaccine and antigen extracts can cause granulomas, the small number of reports of aluminium allergy from the aluminium industry indicated that epicutaneous application of aluminium is not strongly sensitising.

7.1.3 Eyes

ATSDR data

No studies were located regarding ocular effects in humans following acute- or intermediate-duration inhalation exposure to various forms of aluminium. Following the cessation of exposure, normal eye examination results were reported in a man chronically exposed to metallic aluminium and aluminium oxide powders in air (De Vuyst *et al* 1987).

Additional data

No additional studies were located on effects on the eyes.

7.2 General systemic toxicity

Since human data suggest that the respiratory tract and the nervous system may be the most sensitive organs of occupational aluminium exposure, the corresponding studies are discussed in separate sections (7.3 and 7.4, respectively).

ATSDR data

No studies were presented regarding mortality and cardiovascular, gastrointestinal, haematological, musculoskeletal, hepatic, renal and endocrine effects after acute inhalation or dermal exposure to aluminium and aluminium compounds in occupational settings.

Following repeated exposure, mortality has been reported in workers exposed to finely powdered metallic aluminium (aluminium concentrations: ca. 650 mg/m^3 as total dust, ca. 50 mg/m^3 as respirable dust) or to aluminium flake powder. Both mortality and the heart effects observed in these workers were considered to be secondary to severe pulmonary fibrosis and poor pulmonary function (McLaughlin *et al* 1962, Mitchell *et al* 1961).

Epidemiological studies in cohorts ranging from 340 to 21 829 men working in aluminium industry failed to identify increased mortality from cardiovascular disease (Milham 1979, Mur *et al* 1987, Rockette and Arena 1983, Theriault *et al* 1984). In a study on cardiovascular tests (electrocardiogram, blood pressure), there were no differences between the results of 22 aluminium workers exposed for 10 years or more and those of 16 unexposed controls (Bast-Pettersen *et al* 1994).

No adverse haematological effects were observed in a group of 7 workers following a 6-month exposure to aluminium fumes or dusts at breathing zone air levels of 1–6.2 mg Al/m^3 (mainly aluminium oxide) (Mussi *et al* 1984). In 30 out of 36 workers with long-term exposure to aluminium oxide dust, prolongation of prothrombin time was seen (Waldron-Edward *et al* 1971).

Bone mineral content, assessed by osteodensitometry, was not significantly changed in workers exposed to average concentrations of aluminium powder of 12 mg/m^3 for an average of about 12–13 years (Schmid *et al* 1995).

In the aforementioned group of 7 workers, there was no effect on liver function or on hepatic microanatomy (determined from biopsy samples) (Mussi *et al* 1984).

No adverse effects were observed on renal function and standard urine tests in the aforementioned group (Mussi *et al* 1984) or in other groups chronically exposed to aluminium powder (De Vuyst *et al* 1987, McLaughlin *et al* 1962).

No studies were reported on gastrointestinal and endocrine effects in repeatedly exposed groups of workers.

With regard to oral exposure, dietary intake of aluminium, recently estimated to be in the 0.10–0.12 mg Al/kg bw/day range in adults (Pennington and Schoen 1995), has not been of historical concern with regard to toxicity due to its presence in food and the generally recognised as safe (GRAS) status of aluminium-containing food additives by the US Food and Drug Administration (FDA). Users of aluminium-containing medications that are healthy (i.e. have normal kidney function) can ingest much larger amounts of aluminium than in the diet, possibly as high as 12–71 mg Al/kg bw/day from antacid/anti-ulcer products and 2–10 mg Al/kg bw/day from buffered analgesics when taken at recommended doses (Lione 1985).

Additional data
No additional key studies were identified on the effects of aluminium and aluminium compounds after single inhalation, dermal or oral exposure.

An increased risk of coronary heart disease has been observed in two studies of aluminium production (smelters) workers but not in another study. Air pollutant particles in general, and not aluminium *per se*, were considered to be responsible for the effect observed (181).

No other studies on effects following repeated occupational exposure were found.

7.3 Respiratory tract toxicity

ATSDR data
The most convincing evidence that aluminium exposure results in respiratory effects in humans comes from studies of workers exposed to fine aluminium dust (pyro powder) or aluminium oxide (insoluble). The early studies deal with aluminium powder workers exposed years ago when exposure conditions were not typical of today's conditions. Although detailed exposure data are lacking, there is reason to believe that exposure levels at which the above mentioned effects occurred were extremely high. Random tests with filter papers and impingers have shown the dust content in air to be in general between 4 and 50 mg/m^3 and occasionally several times higher. Today, the exposure is thought to be much lower after technical improvements.

In a number of studies, the potential for airborne aluminium to induce respiratory effects in chronically exposed workers were examined. Exposure to aluminium fumes and dust occurs in potrooms. Wheezing, dyspnoea and impaired lung function have been observed in potroom workers. Because these workers were also exposed to a number of other toxic chemicals, including sulphur dioxide, PAHs, carbon monoxide and hydrogen fluoride, it is difficult to ascribe the respiratory effects to aluminium only.

Lung fibrosis is the most commonly reported respiratory effect observed in workers exposed to fine aluminium dust (pyro powder), aluminium oxide (insoluble) or bauxite. However, reports on the fibrogenic potential of aluminium are conflicting, most probably due to differences in the lubricant used to retard surface oxidation during milling (Dinman 1987). The lung fibrosis has only been associated with pyro powders utilising non-polar aliphatic oil lubricants to retard surface oxidation such as mineral oil (Edling 1961, McLaughlin *et al* 1962, Mitchell *et al* 1961, Ueda *et al* 1958) and this process is no longer used. Exposure to pyro powder which used stearic acid as a lubricant did not result in fibrosis (Crombie *et al* 1944, Meiklejohn and Posner 1957, Posner and Kennedy 1967).

Additional data
Additional data with regard to effects on the respiratory tract are summarised in Appendix 1, Table II.

Potroom and foundry workers

Workers in aluminium potrooms are exposed to various air pollutants, and 26 substances to which exposure can occur have been listed, such as dusts (aluminium, cryolite (a fluorinated compound of sodium and aluminium), carbon dust and fluorides), fumes and gases (mainly hydrogen fluorides and sulphur dioxide) (121, 157, 187, 188). As the concentrations of several pollutants are correlated to each other, it has been difficult to identify the causal agent of potroom asthma, although a number of authors have suggested fluoride compounds to be the major candidate (178, 187, 188). Furthermore, smoking and former exposures were found to be risk factors. High blood eosinophil count, atopic history, exposure duration and level of exposure were also found to be risk factors (187, 188).

Negative findings in studies on lung function impairment could be due to a healthy worker effect (157).

Aluminium metal dust and aluminium oxide

Between 1944 and 1979, McIntyre powder, which was reported to contain 15 % elemental aluminium and 85 % aluminium oxide, was used as a prophylactic agent against silicotic disease in mines in Ontario, Canada (160). Miners inhaled the aluminium particles for 10 or 20 minutes before each underground shift. The estimated concentration to which the miners were exposed during 10 minutes was about 350 mg/m^3. For a 10-minute exposure at this concentration, the amount of aluminium retained in the lung is calculated to be about 20 mg, assuming an effective tidal volume of 450 cm^3/breathe and 12 breaths/minute. This corresponds to 2 mg/m^3 over an 8-hour working day assuming the conventional inhalation volume of 10 m^3. With regard to respiratory effects, no adverse health effects on the lung were observed (22).

Aluminium welding fumes

Hull and Abraham reported the clinical, radiographic, microscopic and micro-analytic results of 2 co-workers who were chronically exposed to high unspecified concentrations of fumes during aluminium arc welding and died of complications from aluminium welding fume-induced lung fibrosis. The individuals worked at the same aluminium shipbuilding facility. The severe lung fibrosis was characterised by diffuse pulmonary accumulation of aluminium metal and a corresponding reduction in lung function. Scanning electron microscopy and energy dispersive X-ray analysis of the exogenous particle content in the lung tissue of these cases revealed the highest concentrations of aluminium particles (average of 9.26 billion aluminium particles per cm^3 of lung tissue) among 812 similar analyses in a pneumoconiosis database of the authors. One patient had an original clinical diagnosis of sarcoidosis but no evidence of granulomatous inflammation (91) (Appendix 1, Table I).

In a cross-sectional study by Abbate *et al*, a group of 50 male shipyard welders who were exposed to aluminium underwent medical examination, standard chest X-rays and spirometry. Environmental monitoring displayed concentrations of

6.2–20.2 mg/m^3 for five different areas. Five samplings were performed, each lasting 120 minutes. The welding aerosol contained mainly breathable aluminium-bearing particles. The chemical characterisation of the welding aerosol caused aluminium to be fully oxidised. No information on co-exposure was reported. The data were compared with those of a homogeneous group of controls, all with blood aluminium levels below 7.5 µg/l. Subjects with a history of allergic and/or respiratory disorders and those who smoked over three cigarettes per day were excluded from the study. Statistical analysis was performed on the following spirometric parameters: vital capacity (VC), forced vital capacity (FVC), maximum forced expiratory volume in 1 second (FEV_1), and mean forced expiratory flow during mid-half of FVC ($FEF_{25–75}$). Fifty male workers with an average age of 31.8 ± 5.1 years, occupational exposure of 11.8 ± 3.7 years, presented with average aluminium blood levels of 32.6 ± 8.7 µg/l (measured on Monday morning at the beginning of the working week). Unexposed subjects had blood aluminium levels below 7.5 µg/l. Clinical and radiographic examination did not reveal pathological conditions affecting the respiratory apparatus. Statistical comparison of the spirometric parameters showed a decrease in the examined values in exposed workers. This decrease was found to be directly proportional to the blood aluminium level (1).

Letzel *et al* (115) performed a longitudinal study of about 4 years with three cross-sectional studies integrated within intervals of two years each (1999, 2001, 2003). Two study groups were formed. For the first group, 101 aluminium welders (median age at the start of the study: 35 years, range 23–51 years; total duration of welding at the start of the study: 7–118 months; 83 % smokers and ex-smokers) in the car-body construction industry were selected of which 98 completed the first investigation. The control group consisted of 50 non-exposed car-production workers of the same plant. There was no relevant loss of test persons during the course of the study. However, in 2003, only 68 of them were still working as welders. The medical programme included, amongst others, standardised medical history, physical examination, parameters of pulmonary function, high-resolution computed tomography (HRCT) of the lung of welders and biomonitoring of aluminium levels in urine and plasma. Air monitoring consisted of measurement of aluminium (as total dust with personal air sampler "Alpha 1" with a welding fume sampling head) and ozone. In 1999, 2001 and 2003, the median (range) dust levels were 0.47 mg/m^3 (0.1–6.2), 0.67 mg/m^3 (0.2–1.5) and 0.55 mg/m^3 (0.15–0.96), respectively. Median (of average of pre- and post-shift) levels in urine were 57.6, 52.4 and 19.7 µg/l, respectively.

Compared to the controls, welders reported, partly significantly, more respiratory symptoms. In the 2003 investigation, a decrease in complaints was observed. Analyses of the results of pulmonary function parameters did not show clear evidence of an increased occurrence of restrictive pulmonary ventilation disorders. However, welders had worse results in the flow-volume curve, especially for the maximal expiratory flow at 25 and 50 % of FVC (MEF_{25} and MEF_{50}) at all investigations. No changes were observed in FEV_1 and VC. HRCT revealed an

increase in the incidence of emphysematous lung changes during the observation period (1999: 31.7 %, 2003: 58.8 %), while in one welder, signs suspicious of an early stage of lung fibrosis were observed.

The second group consisted of 46 aluminium welders (median age 1999: 40 years) from five different companies in the field of railway vehicle engineering and special vehicle production and 37 non-exposed controls (median age 1999: 38 years). During the course of the study, there was a decrease in the study population. Median dust levels were about 5–7 mg/m^3 with maximum levels of ca. 20–50 mg/m^3 (in 2001, a maximum level of 273 mg/m^3 was reported). Median urine concentrations ranged from ca. 120 to 150 µg/l with maximum values of ca. 650 µg/l. Results were similar as those seen in the first group of welders in the motor car industry. The welders reported more respiratory symptoms than controls. The results of pulmonary function tests were not consistent: in some tests (e.g. peak expiratory flow – PEF – in 2001), results were better for the welders, in other worse (e.g. MEF_{25} in 2001). Generally, higher exposed welders had worse results than less exposed workers. From HRCT, an increase in the incidence of emphysematous lung changes during the observation period (1999: 37.2 %, 2003: 50 %) was seen, while there were signs suspicious of an early stage of lung fibrosis in 8 welders.

The authors concluded that in this study inflammatory changes were found in the lungs of especially "high" exposed aluminium welders. However, a causal relationship with aluminium could not be established, because of the co-exposure to ozone and because the changes observed in HRCT mainly concerned smokers and ex-smokers (115).

Aluminium pyro powder

Kraus *et al* noted that since the beginning of the 1990s, several new – severe – cases of aluminium-induced lung fibrosis have been reported in aluminium powder industry in Germany (107, 108). After having established in a case report that HRCT is suitable and more sensitive for detecting early stages of aluminium dust-induced lung disease (108), Kraus *et al* performed a cross-sectional study among a group of 62 male workers from eight departments of two aluminium powder-producing plants. The investigation included a standardised questionnaire, physical examination, lung function analysis (VC, FEV_1, total resistance), total lung capacity, biological monitoring of aluminium in plasma and urine, chest X-ray, HRTC, and a great number of immunological tests. Workplace air was not monitored. The median exposure duration was 123 months (range 13–360). The median (range) concentrations of aluminium were 104 µg/g creatinine (7.9–821) or 83.3 µg/l (3.7–630) in urine and 12.5 µg/l (2.5–84.4) in plasma. There were no clinically relevant findings from immunological tests. Chronic bronchitis was observed in 15 workers (24 %) and dyspnoea during exercise in four (6.5 %). HRTC revealed aluminium-induced changes in the lungs, characterised by small rounded and ill-defined centrilobular nodular opacities mainly in the upper lobes, in 15 workers (5 and 4 of the affected workers reported chronic bronchitis and

dyspnoea, respectively). Affected workers had higher concentrations of aluminium in urine (340 vs. 135 µg/g creatinine in non-affected workers, $p = 0.007$) and plasma (33.5 vs. 15.4 µg/l, $p = 0.01$) (10 workers had urinary levels > 200 µg/l, the German biological limit value at the time of the study). With respect to lung function analysis, affected workers only showed differences in VC (decrease, $p = 0.01$) when compared to non-affected workers. Years of exposure and concentration of aluminium in urine and plasma were found to be the best predictors for HRCT findings. Age and decreased VC were of borderline significance. Finally, Kraus *et al* noted that all participants were exposed to non-greased and at least barely greased aluminium powder. Affected workers were mainly workers exposed to barely or non-greased powders in the stamping workplace with the highest levels of aluminium dust, most of it being respirable with diameters < 5 µm (107).

Letzel found decreases in FEV_1, MEF_{25}, MEF_{50} and MEF_{75} in a group of 32 workers exposed to aluminium in an aluminium powder plant compared to 30 non-exposed workers from the same facility. Further analysis revealed that smoking contributed more to the statistically significance difference in FEV_1 and MEF_{25} than exposure to aluminium. Exploratory personal air sampling showed maximum total dust levels of 33.6 mg/m^3 of which 62 % consisted of aluminium. The exposed workers had aluminium concentrations between 5.0 and 337 µg/l in urine and between 5.1 and 25.9 µg/l in plasma (113).

Other

Six and seven cases of asthma developed in 1975 and 1976, respectively, in a group of 35–40 workers of a Swedish aluminium fluoride-producing facility exposed to mean aluminium fluoride concentrations (personal air sampling) of 5.5 and 2.6 mg/m^3, respectively. During 1978–1980, when measures resulted in lower concentrations of 0.4–1.0 mg/m^3, two new cases appeared, while none occurred in 1981 and 1982 (no exposure levels reported) (177).

Four cases of short-lasting asthma occurred during 1971–1980 in a group of 37 workers of a Swedish aluminium sulphate-producing facility exposed to average aluminium sulphate concentrations varying between 0.2 and 4 mg/m^3. The induction of asthma was reported to be related to "heavy" dust exposure during rinsing or repair work (177).

Hjortsberg *et al* reported an increase of bronchial reactivity in small airways due to exposure to potassium aluminium tetrafluoride used as a flux for soldering aluminium. Median exposure levels of respirable dust and of respirable particulate fluoride were 1.1 and 0.3 mg/m^3, respectively, while subsequent measures lowered levels to 0.7 and 0.1 mg/m^3, respectively (88).

7.4 Neurotoxicity

ATSDR data

No studies were presented regarding neurological effects in humans following acute or short-term inhalation exposure to various forms of aluminium. A number of occupational studies have investigated the neurotoxic potential of airborne

aluminium in chronically exposed workers. The workers were exposed to aluminium dust in the form of McIntyre powder (which was reported to contain 15 % elemental aluminium and 85 % aluminium oxide), aluminium dust and fumes in potrooms and foundries, and aluminium fumes during welding. With the exception of some isolated cases (e.g. McLaughlin *et al* 1962), inhalation exposure has not been associated with overt signs or symptoms of neurotoxicity. However, in some of the studies, subclinical neurological effects such as impairment on neurobehavioural tests for psychomotor and cognitive performance and an increased incidence of subjective neurological symptoms (Hänninen *et al* 1994, Hosovski *et al* 1990, Rifat *et al* 1990, Sim *et al* 1997, Sjögren *et al* 1996, White *et al* 1992) were found. Further details of some important studies are described in the section "Additional data" below. In general, these occupational studies poorly characterise aluminium exposure. The lack of adequate exposure monitoring data and the different types of aluminium exposure makes it difficult to compare these studies and draw conclusions regarding the neurotoxic potential of inhaled aluminium in workers.

Evidence is equivocal on the possible relationship between aluminium and Alzheimer's disease. Epidemiology and case-control studies that examined the possible relationship between Alzheimer's disease and aluminium report conflicting results. No increases in Alzheimer's disease-related deaths were observed in workers exposed to airborne aluminium (Salib and Hillier 1996). Some studies designed to show the possible relationship between oral exposure to aluminium and the incidence of Alzheimer's disease have found significant associations. There is no consensus on whether, collectively, the human studies provide sufficient evidence for suggesting an association between aluminium and Alzheimer's disease.

Graves *et al* (1990) examined the association between Alzheimer's disease and the use of aluminium-containing antiperspirants in a case-control study using 130 matched pairs. The Alzheimer's disease was clinically diagnosed at two geriatric psychiatric centres. The controls were friends or non-blood relatives of the Alzheimer patients. Information on life-time use of antiperspirants/deodorants was collected via a telephone interview with the subject's spouse. No association was found between Alzheimer's disease and antiperspirant/deodorant use, regardless of aluminium content (odds ratio (OR) 1.2, 95 % confidence interval (CI) 0.6–2.4). When only users of aluminium-containing antiperspirants/deodorants were examined, the adjusted OR was 1.6 (95 % CI 1.04–2.4). A trend ($p = 0.03$) toward a higher risk of Alzheimer's with increasing use of aluminium-containing antiperspirants/deodorants was also found.

Additional data

Additional data on central nervous system effects are summarised in Appendix 1, Table III.

Potroom and foundry workers

Exposure in potrooms is primarily to aluminium oxide and aluminium fluoride and exposure in foundries is partially to oxidised aluminium metal fumes (see Chapter 4).

Studies demonstrated neurological effects like slower psychomotor reactions and reduced coordination, as well as memory problems and other mental disturbances. Furthermore, an increase of the prevalence of neurological symptoms (coordination problems, difficulty buttoning, and depression) was reported.

However, workers in aluminium potrooms and foundries are not only exposed to aluminium compounds. Exposure occurs to various air pollutants and over 20 substances to which exposure can occur have been listed, such as dusts (aluminium, cryolite (a fluorinated compound of sodium and aluminium), carbon dust and fluorides), fumes and gases (mainly hydrogen fluorides and sulphur dioxide) (121, 157, 187, 188). Several pollutants are correlated to each other (178). Röllin *et al* reported that the aluminium concentration in the respirable dust fraction amounted to 44 % of the aluminium found in the total inhalable fraction measured at the same time in the potrooms of a modern aluminium smelter in South Africa (169).

Healy *et al* investigated inhalation exposure at seven secondary aluminium smelters in the UK. The substances monitored were, amongst others, total inhalable dust and aluminium. Personal exposure results for total inhalable dust were 0.7–56 mg/m^3. The aluminium personal exposure ranged from 0.04 to 0.9 (mean 0.3) mg/m^3. The average proportion of aluminium in total inhalable dust samples was 13 %. From a total of 33 results, this proportion varied between 5 and 27 %, with a standard deviation of 5 %. If it is assumed that aluminium is present as the oxide, the average proportion of Al_2O_3 in the dust sampled was 25 %. The composition of the remaining 75 % of the dust was uncertain, although the metal analysis suggested that other metal oxides alone could not account for the shortfall according to the authors (86).

Information in the toxicological profile of the ATSDR (13, 14) reported that in aluminium reduction facilities using the prebake process, PAHs are generated. Furthermore, in aluminium reduction operations using the Søderberg cell process, considerable amounts of volatiles from coal tar pitch, petroleum coke, and pitch, including PAHs, are generated.

Because the concomitant exposure to these other compounds, it is not possible to attribute the observed effects to aluminium specifically.

Aluminium metal dust and aluminium oxide

There were no significant differences in diagnoses of neurological disorder between miners inhaling Mclntyre powder as a prophylactic agent against silicotic disease (see Section 7.3) and those who did not. Performance of a group of 261 miners exposed to aluminium was compared to that of 346 unexposed miners in three cognitive tests. A higher proportion of miners with impaired cognitive

functions were reported among those with longer lasting treatment periods (160), but re-design and re-analysis of the study did not confirm the results (142).

Two cross-sectional studies were conducted by Letzel *et al* at a German aluminium powder plant to evaluate possible nervous system effects from occupational aluminium exposure. The investigation included biological monitoring, a neuropsychological test battery and event-related P300 potentials. The first examination involved 32 aluminium dust-exposed workers (median exposure time: 12.6 years, range 2–41.3) and 30 unexposed controls from the same plant who were matched for age, gender, professional training, and education level. Exposed workers had median (range) aluminium concentrations in urine of 87.6 µg/g creatinine (4.6–605) or 110 µg/l (5.0–337) and in plasma of 8.7 µg/l (5.1–25) (it was not mentioned at which time points aluminium sampling in serum and urine were performed). Unexposed workers had median aluminium (range) concentrations of 9.0 µg/g creatinine (1.9–51.8) or 7.6 µg/l (2.6–73.8) in urine and of 4.3 µg/l (1.6–7.1) in plasma. No information on co-exposure was reported. High alcohol consumption reported in some workers in the two groups could mask mild aluminium-induced central nervous changes. There was no dose-effect relationship for the length of exposure or internal aluminium concentrations in plasma or urine and any of the primary neurological variables (110, 116). Five years later, all available workers from both groups, viz. 21 exposed (15 still exposed, 6 formerly exposed, median exposure time: 16 years, range 2–41.2 years) and 15 unexposed controls were re-assessed using the same methods except for the P300 potentials. The other persons were no longer willing to participate in the voluntary follow-up investigation or had left the plant. A shift in age between the exposed and control groups (self-selection) was reported. There was no evidence that persons with a below-average test performance or high or long exposure to aluminium did not participate in the follow-up examination. A tendency for persons who admitted to high alcohol consumption in the first evaluation not to participate in the follow-up evaluation was observed. Exposed workers had median (range) aluminium concentrations of 19.8 µg/g creatinine (3–203) and of 24.1 µg/l (3.4–219) in urine and of 6.7 µg/l (1.6–20.6) in plasma. For unexposed workers, figures were 4.5 µg/g creatinine (2.2–15.9) and 6.5 µg/l (2–25.4) in urine and 4.3 µg/l (1.9–12.9) in plasma. As with the first examination, no significant exposure-related differences between the two study groups were found for the primary neurological variables. Longitudinal comparison of the two examinations showed a significant reduction in the renal aluminium excretion (likely to be the result of improved occupational hygienic measures taken after the first investigation) (116).

Aluminium pyro powders

Iregren *et al* examined possible neurotoxic effects in a small group of workers (n = 16, median age: 34.7 years (range 22–48), median seniority: 8 years (range 2–22), median alcohol index: 1 (range 0–5)) exposed to aluminium in the production of flake powder (exposed years not specified). Exposure to aluminium was evaluated with aluminium concentrations in blood and urine as well as a

questionnaire. The samples from most of the flake powder-production workers were collected after five exposure-free days. The groups exposed to aluminium were compared with a group of 39 mild steel welders (median (range) age 39 (23–59) years, median seniority 12 (5–30) years, median alcohol index 2 (0–5)). The two study groups were homogeneous. Neurotoxic effects were studied with mood and symptom questionnaires and several psychological and neurophysiological tests. Flake powder producers had median (range) aluminium levels in urine of 59.0 µg/g creatinine (12–139) and of 83.0 µg/l (12–282) and in blood of 9.0 µg/l (< 1–21). Mild steel welders had median (range) aluminium concentration in urine of 4.7 µg/g creatinine (< 1–25) and of 3.0 µg/l (< 1–26) and in blood of 1.0 µg/l (< 1–11). Aluminium was not found to affect the functioning of the nervous system in flake powder producers (98).

Aluminium welding fumes

In a study to investigate prevalences of symptoms for groups of welders with different exposures, responses from 282 workers were analysed, among them 65 welding aluminium. All welders responded to the Q16 symptom questionnaire. Two symptoms were specifically related to exposure to aluminium ("do you often have problems with concentrating?" and "do you often feel depressed without reason?"). Furthermore, welders reporting exposure to aluminium fumes for more than 20 000 hours (corresponding to about 13 years of full-time exposure) had a doubled risk for reporting more than three symptoms in this questionnaire (OR 2.79, 95 % CI 1.08–7.21) (180).

Hänninen *et al* investigated 17 male aluminium welders in a shipyard (mean age: 37 years, range 24–48) who had been engaged in welding for 5–27 years (mean 15 years) but had been MIG welding on aluminium for only about the last 4 years. Central nervous system functions were examined with neuropsychological tests, symptom and mood questionnaires, quantitative electroencephalography (EEG), and P300 evoked responses. No control group was included. The mean serum and urine aluminium concentrations were 5.7 µg/l (range 0.8–17.3) and 75.5 µg/l (range 24.3–164.6), respectively. Although the welders performed normally on the neuropsychological tests, there was a negative association between all four memory tests and urinary aluminium and a positive association between the variability of visual reaction times and serum aluminium concentration. The neuropsychological assessment suggested disturbing effects of aluminium on short-term memory, learning, and attention. In the quantitative EEG, a corresponding exposure-effect relationship was found for activity in the frontal region (93).

Akila *et al* performed a cross-sectional study of asymptomatic MIG aluminium welders (history of aluminium welding for up to 23 years) and a reference group of mild steel welders. Subjects underwent a semi-structural interview by a physician to provide details on age, education, health, smoking, alcohol consumption, etc. A comprehensive neuropsychological examination was undertaken to assess psychomotor function, simple visual reaction time, attention related tasks, verbal

and visual or visuospatial abilities, verbal and visual learning, and memory. Levels of aluminium were determined in urine and serum, and of lead in blood. Urine samples were collected after two consecutive exposure-free days and blood samples were taken in the morning of the test day. Based on urinary aluminium concentrations, welders were classified into a reference and a low- and high-exposure group (n = 28, 27 and 24, respectively). There was no evidence of concurrent exposure to other neurotoxins. Each company was visited to ensure that there were no potentially confounding exposures. Blood lead levels were all in the normal range of 0.1–0.4 μmol/l. There was no current or recent use of antacids containing aluminium. The mean urinary aluminium concentrations were 12, 60 and 269 μg/l, respectively. No urine concentrations corrected for creatinine clearance were reported. The mean serum aluminium concentrations were 2.4, 4.6 and 14.3 μg/l, respectively.

Aluminium welders showed no impairment on the finger tapping, Santa Ana dexterity, simple visual reaction times, any of the verbal memory tasks, the similarities subtest of Wechsler adult intelligence scale or the Stroop task. However, the low-exposure group performed poorer on the memory for designs and on more difficult block design items demanding preliminary visuospatial analysis. The time limited synonym task, embedded figures, digit symbol speed, and the backward counting component of the divided attention task showed exposure-response relations with statistically significant effects in the high-exposure group. The impairments found were circumscribed. Overall, the performance difficulties were mainly detected in tasks demanding complex attention, requiring working memory, and particularly in time limited tasks involving visually presented material (6).

Riihimäki *et al* analysed essentially the same study population, which consisted, however, of more welders and less referents. The study population was divided into three subgroups: a referent group (n = 25, median age: 37.4 years, median Al serum and urine levels: 2.2 and 11 μg/l, respectively), a low-exposed group (n = 29, median age: 35.7 years, median Al serum and urine levels: 3.8 and 49 μg/l, respectively), and a high-exposed group (n = 30, median age: 43.9 years, median Al serum and urine levels: 12.4 and 192 μg/l, respectively). Age was a potential confounder and was controlled for in the statistical analyses. The final study population was homogenous in terms of ethnic and cultural background, education, social status, social consumption of alcohol, occupation and the main job characteristics. There were no heavy drinkers, psychotropic drug users or users of aluminium-containing antacids. Blood lead levels (< 0.4 μmol/l) were in the normal range.

Comparison of the symptom scales by covariance analysis, with age as a covariate, revealed significant differences between the high-exposure group and the control group for memory and concentration difficulties ($p = 0.004$), fatigue ($p = 0.027$) and emotional lability ($p = 0.045$). Similarly, significant differences were found for 6 out of 18 neuropsychological tests (Bourbon-Wiersma dot cancellation accuracy, $p = 0.0497$; counting backwards, $p = 0.042$; dual-task cancellation

speed, p = 0.047; dual-task counting speed, p = 0.021; synonyms, p = 0.011; and memory for designs, p = 0.030). The test results indicated a circumscribed effect of aluminium, mainly in tasks demanding complex attention and the processing of information in the working memory system and in the analysis and recall of abstract visual patterns. The visual EEG analysis revealed mild diffuse abnormalities in 17 % of the low-exposure group and in 27 % of the high-exposure group, and mild to moderate epileptiform abnormalities in 7 % and 17 %, respectively (161).

Kilburn noticed that it was not reported whether manganese exposure as a result of welding was taken into account. According to Kilburn, most commercial aluminium is alloyed with copper, manganese or zinc. Studies have described effects on the central nervous system after exposure to aluminium-manganese from remelting and welding. Therefore, dose effects attributed solely to aluminium in the present study should probably be interpreted as applying to aluminium-manganese mixtures, since exposure to manganese alone slows visual reaction times, disturbs head steadiness and eye-hand coordination, and impairs short-term memory (104).

Sjögren *et al* examined the effects on the nervous system in 38 welders exposed to aluminium (years worked with welding: 17.1 years). According to a questionnaire, the welders had welded lead or high alloy manganese steel for a total of less than 10 hours. As a control group, 39 railway track welders were included (years worked with welding 13.8 years). None of the participants had been occupationally exposed to solvents. Two control welders had been exposed to solvents to some extent during leisure activities. Previous head trauma was somewhat more common among control welders. This was not taken into account in the analysis, and the effect, probably minor, would have underestimated group differences. The only subject who had ingested antacids containing aluminium daily during the past 10 years was a control welder (highest urinary concentration of aluminium – 26 µg/l – among the controls). The investigation included four different questionnaires on peripheral and central nervous system symptoms, psychological and neurophysiological tests and determination of blood and urine concentrations of aluminium, lead and manganese. One sample of blood and one sample of urine were taken from each participant. Some samples were taken several hours post-shift. The urinary concentrations were therefore recalculated to correspond to concentrations immediately after the shift. The median (range) concentrations of aluminium in urine were 24 µg/g creatinine (4.5–162) and 22 µg/l (4–255) and in blood 3 µg/l (< 1–27). The welders had about 6–7 times higher concentrations of aluminium in urine than the controls (median (range) 4.7 (< 1–24.9) µg/g creatinine and 3 µg/l (< 1–26) µg/l). Median blood concentrations of controls were 1 (range < 1–11) µg/l. The median exposure time of aluminium welders was 7 065 hours (range 1 766–21 980). Blood lead and manganese levels were comparable between the welders and referents.

Regarding the symptom questionnaires, aluminium welders reported statistically significantly more symptoms of the nervous system (especially fatigue) at the time of test (as well as fewer symptoms of pain during the past 6 months) than the controls. In addition, aluminium welders scored significantly lower in 4 out of 20

psychological tests (non-dominant hand tapping speed, Luria-Nebraska motor scale task No. 3 and No. 4, dominant-hand pegboard) and had significantly higher amplitude of the dominant hand in the diadochokinesis test. For the symptoms and two of the five tests, the effect was dose-related (182). However, when Sjögren and colleagues re-analysed their data together with two other aluminium-exposed groups (smelters and flake production workers) by controlling for age and multiple comparisons (Bonferroni), the above mentioned significant differences disappeared (98).

In a cross-sectional study, Bast-Petterson *et al* tested 20 aluminium welders (mean age: 33 years, range 21–52), having been exposed to aluminium for an average of 8.1 years (range 2–21), for tremor and reaction time and screened for neuropsychiatric symptoms. Exclusion criteria were exposure to solvents (not further specified by the authors), disease which could affect the central nervous system, including cancer, cerebrovascular diseases, neurological diseases and diabetes. Alcohol consumption was slightly (not significantly) higher among the referents. The similarity in the distribution of background variables indicated that the construction workers were suitable as referents. The welders were instructed to void the first morning urine at home and the first post-shift urine after changing to their own clothes. The number of collected urine samples was 189. The mean number of urine samples was 9.5 (range 4–10) for each exposed subject. The median urinary aluminium concentration for each individual was used for further statistical calculations. The median (range) urinary aluminium concentrations were 36 (14–110) µg/g creatinine and 41 (19–130) µg/l.

With regard to exposure, during the MIG and pulsed metal active gas (MAG) welding operations, the electrodes were consumed under a protected layer of argon/carbon dioxide shielding gas. The welding aerosol contained mainly respirable aluminium-containing particles. Chemical characterisation of the welding aerosol and mass balance consideration showed that aluminium was fully oxidised. Nitrogen oxides and ozone were also emitted. Aluminium in air was measured inside the respiratory protection of 17 welders. Each worker wore his equipment for an average of 4 days (range 2–5 days). Sixty-nine measurements were performed and the concentrations of airborne aluminium were based on the individual median concentrations. The mean and median airborne aluminium concentrations inside the protection were 1.18 and 0.91 mg/m^3 (range 0.57–3.77), respectively.

The welders were compared with 20 age-matched construction workers. The welders reported more neuropsychiatric symptoms (median: 2 vs. 1, $p = 0.047$). Although the welders as a group performed better than the referents on a tremor test, years of exposure, but not age, was predictive of poorer performance. The welders' reaction times were rapid by clinical standards (mean simple reaction time: 221 milliseconds; mean continuous performance test: 364 milliseconds). In addition, the welders had more rapid reaction times than the referents. However, there was a statistically significant relation between longer reaction times and aluminium in air. The relations between hand steadiness and years exposed, and between reaction time and aluminium in air, could indicate slight effects from

exposure to aluminium. The possibility of selection of workers with high manual skills into welding work and a possible job-related training effect, might partly serve to explain the good performance among the welders. Furthermore, performance on reaction time tasks may be sensitive to motivational factors and the exposed welders could have been more motivated to perform well, since they were more concerned about an effect of welding on the nervous system (18).

In Germany, a longitudinal study of about 4 years with three cross-sectional studies integrated within intervals of two years each (1999, 2001, 2003) was performed. Two study groups were formed. For the first group, 101 aluminium welders (median age at the start of the study: 35 years (range 23–51), total duration of welding at the start of the study: 7–118 months, 83 % smokers and ex-smokers) in the car-body construction industry were selected of which 98 completed the first investigation. The control group with a similar structure consisted of 50 non-exposed car-production workers of the same plant. There was no relevant loss of test persons during the course of the study. However, in 2003, only 68 of them were still working as welders. The examination programme consisted, amongst others, of a standardised medical history, physical examination, neurobehavioural tests to evaluate the level of neurotoxic symptoms, premorbid intelligence and deficits in the domains of motor performance, logical thinking, short-term and working memory, perceptual speed, and switching attention. Furthermore, aluminium levels were determined in urine and plasma and in air (as total dust with personal air sampler "Alpha 1" with a welding fume sampling head) and ozone. In 1999, 2001 and 2003, the median (range) dust levels were 0.47 mg/m^3 (0.1–6.17), 0.67 mg/m^3 (0.2–1.5) and 0.55 mg/m^3 (0.15–0.96), respectively. Median (of average of pre- and post-shift) levels in urine were 57.6, 52.4 and 19.7 µg/l, respectively. Welders did not report more symptoms in the modified Q16 when compared to controls. Furthermore, no statistically significant differences in psychomotor performance and other neurobehavioural tasks were detected. Some small changes in reaction time between welders and non-welders were observed comparing data from the investigations in 1999 and 2001, but they were not seen in 2003, and therefore not considered to be relevant (28, 101, 115).

The second group started with 46 aluminium welders (median age 1999: 40 years) from five different companies in the field of railway vehicle engineering and special vehicle production and 37 non-exposed controls (median age 1999: 38 years). During the course of the study, there was a decrease in the study population, leaving 75 % (n = 33) of the exposed and 70 % (n = 26) of the controls in 2001, and 45 % (n = 20) and 32 % (n = 12), respectively, in 2003. The longitudinal study compared repeatedly measured exposure data and neurobehavioural data of 20 male aluminium welders (mean (± SD) aluminium-welding years 14.8 ± 4.1 years, mean age 43.3 ± 7.4 years, mean education index 1.4 ± 0.4, mean plasma carbohydrate-deficient transferrin 4.3 ± 4.2 U/l) with data of 12 controls (mean age: 42.9 ± 5.7 years, mean education index: 1.2 ± 0.4, mean plasma carbohydrate-deficient transferrin: 2.9 ± 5.5 U/l) on the basis of three investigations over a 4-year period. The second group underwent the same examinations as the first

group. The characteristics of the biological monitoring data and the relationship to neurobehavioural data were examined with correlation and regression analysis. The courses of neurobehavioural changes were analysed with multivariate covariance-analytical methods (MANCOVA) considering the covariates age, indicators of "a priori" intelligence differences (education or "premorbid" intelligence) and alcohol consumption (carbohydrate-deficient transferrin levels).

The mean total dust levels, measured near to the routinely worn ventilated helmets, were in the range of 5–8 mg/m^3 (with the minium level at the second examination and the maximum at the third). Pre-shift levels of aluminium in urine had a maximum at the second examination and a minimum at the third examination (140 and 88 µg/g creatinine, respectively, $p < 0.001$). Plasma levels rose from about 13 µg/l at the first examination to about 16 µg/l at both other examinations (not significant). Post-shift urine and plasma values were higher than pre-shift values by 30 µg/g creatinine and 3.5 µg/l, respectively. Statistical analysis of the biological monitoring data showed high long-term stability and sensitivity to acute shift-dependent exposure changes. When compared to controls, the welders showed no differences in symptom scores or in neurobehavioural performance courses during the 4-year period. There was no correlation between biological monitoring and performance variables. Explorative modelling indicated that the structure of neurobehavioural outcomes could be determined by possible indicators of "a priori" intelligence differences between subjects, but not by their exposure information (102) (see also (29, 115)).

7.5 Carcinogenicity

ATSDR data

No studies were presented regarding carcinogenic effects in humans following inhalation, dermal or oral exposure to various forms of aluminium. In studies on workers in the aluminium-production industry, increased cancer mortality rates were observed, but other compounds to which the workers were exposed, such as PAHs and tobacco smoke, were considered to be the causative agents (Gibbs and Horowitz 1979, Milham 1979, Mur *et al* 1987, Rockette and Arena 1983, Thériault *et al* 1984).

Additional data

The studies mentioned above and additional epidemiological studies in workers in aluminium industry were evaluated by the International Agency for Research on Cancer (IARC) in 2005. In a summary, IARC mentioned that the first reports on risks of cancer associated with work in the aluminium production industry were made in the 1970s in the former Soviet Union. Further, in a series of Canadian reports from Québec, statistically significant excess risks and positive exposure-response relationships were observed for lung and urinary bladder cancer after adjustment for tobacco smoking. A study of another Canadian aluminium production plant in British Columbia showed statistically significant exposure-related trends in both lung and urinary bladder cancer risks. A French study reported

excesses in lung and urinary bladder cancer risks. In a Norwegian cohort study, there was an increased risk for urinary bladder cancer but not for lung cancer. A study in multiple US plants showed a lung cancer risk close to that expected but a statistically significant excess risk for urinary bladder cancer. In a meta-analysis of studies that used benzo[a]pyrene as an index of exposure to PAHs, results were pooled from eight cohort studies of lung cancer and six of urinary cancer in aluminium workers. Pooled risk estimates indicated a positive exposure-response relationship between cumulative exposure to benzo[a]pyrene and both urinary bladder and lung cancer.

In addition, two studies demonstrated statistically significantly increased incidences of lymphatic and haematopoietic cancers while there was a small excess risk in a third study. Finally, an increased risk for pancreatic cancer was found in two studies (94).

Studies among workers involved in the manufacture of synthetic abrasive materials, containing amongst others aluminium oxide and silicon carbide, showed an increased risk of stomach cancer in a Swedish and a US study and of lung cancer in a Canadian study. Among silicon carbide-production workers, with co-exposure to crystalline silica, increased risks of cancer of the lungs were reported in a Canadian and a Norwegian study and of the stomach in a Norwegian study (see Sjögren *et al* (181)).

7.6 Reproduction toxicity

The effects of exposure to aluminium and aluminium compounds on reproduction have been reviewed and separately published by DECOS's Subcommittee on the Classification of Reproduction Toxic Substances. Data and conclusions of the subcommittee are summarised below. For detailed information on individual studies, it is referred to the subcommittee's report (84).

7.6.1 Fertility

Hovatta *et al* studied the effect of aluminium on semen quality by comparing semen of a group consisting of 27 employees of a Finnish refinery and a polyolefin factory (mean age: 34 years) with semen of a group consisting of 45 sperm donor candidates of a Finnish sperm bank (mean age: 28 years). A statistically significant inverse correlation was observed between aluminium concentration in the spermatozoa and sperm motility and sperm morphology, but no correlation was observed between the concentration of aluminium in seminal plasma and sperm parameters. Hovatta *et al* did not present data on occupational exposures (compounds, concentrations). They stated that the factories were situated in a rural area, that most of the employees lived in the countryside, and that the sperm bank donor candidates were from the urban Helsinki area (90).

7.6.2 Developmental effects

Apart from a statistically significant incidence of children showing clubfoot (4 cases vs. 1 control), Golding *et al* did not find effects when comparing outcome

of all singleton pregnancies (n = 92) in an area in north Cornwall, England, with high drinking water concentrations of aluminium sulphate resulting from a water pollution incident (not specified) with the outcome of two control groups. The control groups consisted of pregnancies completed before the pollution incident (n = 68) and of pregnancies in a neighbouring area (n = 193) (66). The Golding study was one of a number of studies investigating the potential health effects of chemical exposure, viz. aluminium, sulphate, copper, zinc, lead, iron and manganese, resulting from the water pollution incident. A specially convened subgroup of the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment of the UK Department of Health, concluded that no delayed or persistent harm was expected as a consequence of the exposure to the chemicals from this incident (42).

Morton *et al* determined the concentrations of 20 trace elements by AAS, and examined the associations between the presence of trace elements found in representative samples of tap water collected from 48 local authority areas in South Wales and central nervous system malformation rates for the areas. They found a statistically significant positive association for aluminium (129). The subcommittee of DECOS questioned the relevance of these findings noting that the mean concentrations of aluminium in morning (n = 48) and evening (n = 48) samples were 0.061 and 0.049 mg/l, respectively, i.e. below the drinking water guideline value of 0.2 mg/l. Assuming a daily water consumption of 1.5 litres, daily intake of aluminium from these sources would amount to 0.09 mg, which is far below the daily dietary exposure (3.2 mg, from the UK Total Diet Study 1976 to 1997 (203)) and the daily amount that would be tolerable according to the World Health Organization (WHO) (9 mg/day, calculated from a provisional tolerable weekly intake of 1 mg/kg bw) (100).

7.7 Immunotoxicity

ATSDR data

Sarcoid-like epithelioid granulomas were found in the lungs of a 32-year-old man chronically exposed to metallic aluminium and aluminium dust. Immunological testing failed to confirm sarcoidosis, but did find helper T-lymphocyte alveolitis and blastic transformation of peripheral blood lymphocytes in presence of the soluble aluminium compound. Additional testing one year after termination of exposure indicated that the man no longer had alveolitis. However, this patient had also been exposed to cobalt, vanadium, manganese, palladium and silica (De Vuyst *et al* 1987).

Additional data

No additional information was found on immunological effects of aluminium and aluminium compounds in humans.

7.8 Summary and evaluation

No human data were available on the irritation of skin, eyes and respiratory tract following acute or single occupational exposure to metallic aluminium or aluminium compounds.

Although widely and extensively used in industries and cosmetics, sensitisation to aluminium or its compounds is generally rare. Several of the positive reports concern the use of aluminium (hydroxide) in vaccines or in hyposensitisation therapy which is of little relevance for extrapolation to workplace conditions.

There were no data indicative of toxicologically relevant systemic health effects following acute exposure to aluminium or its compounds.

In a great number of studies, the potential effects of occupational exposure to aluminium on the nervous system and the respiratory tract have been examined in potroom and foundry workers, aluminium powder plant workers, aluminium welders, and miners who used the so-called McIntyre powder (15 % elemental aluminium and 85 % aluminium oxide) as a prophylactic agent against silicosis.

In none of the studies addressing neurotoxicity were overt signs or symptoms of neurotoxicity reported. However, in some of them, subclinical effects were observed. They included increased incidences of subjective neurological symptoms, impaired performance in tests concerning reaction time, eye-hand coordination, memory, and/or motor skills and changes in quantitative EEG. Only in a few studies were concentrations of aluminium in workplace air presented, mostly single observations at the time of investigation, but data from the past when exposure may have been much higher were lacking. Among the few studies examining the potential association between neurotoxic effects and aluminium concentrations in blood or urine, some found a significant association while others did not.

Respiratory effects, especially impaired lung function and pulmonary fibrosis, have been observed in several groups of workers exposed to aluminium dust or fumes under several working conditions. In recent German studies in welders and workers in aluminium powder industry, the use of HRCT revealed increased incidences of emphysematous lung changes. However, generally, no exposure data, especially those from the past, were given. In addition, there was frequently exposure to other compounds (e.g. ozone and manganese in welders, hydrogen fluoride and hydrogen chloride in potroom/foundry workers).

Increased cancer mortality rates were found in studies in workers in the aluminium production industry where there was co-exposure to carcinogenic compounds such as PAHs.

There were no studies on the effects of occupational exposure to aluminium or aluminium compounds on reproductive capacity, pregnancy outcome or post-natal development.

In a Finnish study, the effect of aluminium on semen quality was examined comparing a group of workers potentially exposed to aluminium with a group of semen donor candidates. Generally, the donor candidates had higher aluminium levels in spermatozoa and seminal plasma. A statistically significant inverse correlation was observed between aluminium concentration in the spermatozoa and

sperm motility and sperm morphology, but no correlation was observed between the concentration of aluminium in seminal plasma and sperm parameters.

8. Animal and *in vitro* experiments

8.1 Irritation and sensitisation

8.1.1 Respiratory tract
ATSDR data
Rats exposed for 4 hours to 200 and 1 000 mg/m^3 aluminium flakes developed microgranulomata in the respiratory tract at 14 days post-exposure. The microgranulomata were persistent, i.e. still present at 3 and 6 months post-exposure. No effects were observed at 10, 50 and 100 mg/m^3 (Thomson *et al* 1986).

Additional data
No additional studies on local effects on the respiratory tract were located.

8.1.2 Skin
ATSDR data
Skin damage has been observed in female TF1 Carworth mice, New Zealand rabbits and Large White pigs following the application of 10 % aluminium chloride (soluble) (0.5–100 mg Al) or aluminium nitrate (soluble) (0.6–13 mg Al) for 5 days. The damage consisted of hyperplasia, microabscess formation, dermal inflammatory cell infiltration and occasional ulceration. Aluminium sulphate (soluble), chlorohydrate (soluble) or hydroxide (insoluble) did not cause skin effects (Lansdown 1973).

Additional data
Aluminium chloride (soluble) was negative when tested in a local lymph node assay with mice (CBA/Ca, n = 4) at concentrations of 5, 10 or 25 % (vehicle: petrolatum) (16, 17). The committees note that, generally, this test is considered less appropriate for detecting sensitising capacity of metals.

8.1.3 Eyes
ATSDR data
No data on the irritating potential following instillation of aluminium or its compounds into the eyes of animals were presented. No (histological) effects were seen on the eyes of rats and guinea pigs exposed to aluminium chlorohydrate (soluble) concentrations of 25 mg/m^3 (6.1 mg Al/m^3) (for details, see Section 8.3.2) (Steinhagen *et al* 1978).

Additional data
No behaviour suggesting irritation of the eyes was noted in rats exposed to concentrations of aerosolised aluminium chlorohydrate (soluble) in a silicone-ethanol

vehicle of 0.34 (± 0.22) and 2.50 (± 0.37) mg/m^3, 4 hours/day, 5 days/week for 22 days (see Section 8.3.1) (193). No other studies on local effects on the eyes were located.

8.2 Toxicity due to single exposure

ATSDR data
Lethal concentrations for 50 % of the animals at single exposure (LC_{50}s) for inhalation exposure were not presented. Exposure for 4 hours to up to 1 000 mg Al/m^3 as aluminium oxide did not induce mortality in groups of 12–18 male Fischer 344 rats (Thomson *et al* 1986).

No quantitative data on acute dermal toxicity were found.

Data on acute lethality of ingested aluminium are available, but actual oral doses are unclear due to insufficient information on aluminium intake from the base diet. For aluminium nitrate (soluble), lethal doses for 50 % of the exposed animals at single administration (LD_{50}s) of 261 and 286 mg Al/kg bw have been reported for Sprague Dawley rats and Swiss Webster mice, respectively (Llobet *et al* 1987). For aluminium chloride (soluble), LD_{50} values of 370, 222 and 770 mg Al/kg bw have been reported for Sprague Dawley rats, Swiss Webster mice and male Dobra Voda mice, respectively (Llobet *et al* 1987, Ondreicka *et al* 1966). The LD_{50} for aluminium sulphate (soluble) in male Dobra Voda mice was 980 mg Al/kg bw (Ondreicka *et al* 1966). Time to death and clinical signs were not given. A single gavage exposure to 540 mg Al/kg bw as aluminium lactate (soluble) was fatal to 5/5 lactating female New Zealand rabbits (Yokel and McNamara 1985). Time to death was reported to be 8–48 hours.

Furthermore, there are no indications of other toxicologically relevant systemic health effects after acute inhalation, dermal and oral exposure to aluminium and aluminium compounds.

Additional data
Kumar exposed male Wistar rats to doses of aluminium chloride ($AlCl_3 \times 6\ H_2O$, water soluble) of 0, 1 600, 2 560, 4 069 and 6 553 mg/kg bw (i.e. ca. 180, 280, 450 and 720 mg Al/kg bw). A median oral lethal dose of 3 630 mg/kg bw (i.e. ca. 400 mg Al/kg bw) was estimated. Toxic effects at the two higher doses were lethargy, reduced spontaneous movement and lachrymation. Difficulty in breathing followed by death after 3 hours was observed in 50 %, 75 %, and 100 % of the animals at 2 560, 4 069 and 6 553 mg/kg bw, respectively (109).

8.3 Toxicity due to repeated exposure

8.3.1 General toxicity studies
ATSDR data
There are no indications of toxicologically relevant systemic health effects in animals after inhalation, dermal and oral short-term exposure to aluminium and aluminium compounds. In guinea pigs and rats exposed to concentrations of

aluminium chlorohydrate (soluble) of 25 mg/m^3 (6.1 mg Al/m^3), apart from decreased body weights in rats and effects on the lungs, no effects were seen on organ weights or upon pathological or haematological examinations (for details, see Section 8.3.2) (Steinhagen *et al* 1978).

Additional data

Tansy *et al* exposed groups of rats (Sprague Dawley, n = 15/sex/group) to concentrations of aerosolised aluminium chlorohydrate (soluble, presumably $Al_{13}O_4(OH)_{24}(H_2O)_{12}Cl_7$) in a silicone-ethanol vehicle of 0.34 (± 0.22) and 2.50 (± 0.37) mg/m^3, 4 hours/day, 5 days/week for 22 days. The mass median aerodynamic diameters (MMADs) were 1.57 (± 0.45) and 4.28 (± 0.93) µm, respectively. Sham and propellant/vehicle control groups were included. There was no mortality in any of the groups. Exposure to aluminium chlorohydrate did not induce changes on serum analyses data, body and organ weights. Mean aluminium tissue concentrations of the liver, gastric mucosa and parathyroid glands did not show any consistent relationship between exposure conditions and measured aluminium concentrations. No remarkable abnormalities were seen upon gross post-mortem examinations, or upon histological examination conducted on the livers, kidneys, adrenals and parathyroids of 6 animals/sex/group (see Section 8.3.2) (193).

In the environmental health criteria monograph on aluminium of the IPCS/WHO (1997) additional information to the ATSDR was found. Adequate inhalation studies were not identified. However, following intratracheal administration of aluminium oxide, particle-associated fibrosis was observed, similar to that found in other studies on silica and coal dust. In oral short-term studies in which an adequate range of endpoints was examined following exposure of rats, mice or dogs to various aluminium compounds (sodium aluminium phosphate (soluble), aluminium hydroxide (insoluble), aluminium nitrate (soluble)) in the diet or drinking-water, only minimal effects (decreases in body weight gain generally associated with decreases in food consumption or mild histological effects) have been observed at the highest administered doses (70–300 mg Al/kg bw/day). Systemic effects following parenteral administration also included kidney dysfunction (96).

Yousef reported effects of aluminium on haemato-biochemical parameters, lipid peroxidation and enzyme activities in male rabbits (New Zealand, n = 6/group) given oral doses of aluminium chloride (soluble) of 34 mg/kg bw/day (i.e. ca 7 mg Al/kg bw/day), every other day for 16 weeks. Concomitant administration of ascorbic acid (40 mg/kg bw/day) generally reduced the effects induced by aluminium (202).

8.3.2 Respiratory effects

ATSDR data

There are limited data on the pulmonary toxicity of aluminium in animals following chronic exposure. A biologically significant increase in relative lung weights have been observed in rats and guinea pigs exposed to 25 mg/m^3 aluminium chlorohydrate (soluble, unspecified), 6 hours/day, 5 days/week for

approximately 2 years. Lung weights were not affected at 2.5 mg/m^3. The lungs were not histologically examined (Stone *et al* 1979).

Pigott *et al* (1981) did not find evidence of lung fibrosis in rats exposed to 2.18 or 2.45 mg/m^3 manufactured or aged Saffil alumina fibres (a refractory material containing aluminium oxide (insoluble) and about 4 % silica). The animals were exposed for 86 weeks followed by a 42-week observation period.

Additional data

No additional data were found on respiratory effects after exposure to aluminium and aluminium compounds. However, relevant studies presented by ATSDR are described in this section.

In the study by Tansy *et al*, no histological effects were observed in the nasal mucosa and lungs of rats exposed to concentrations of aerosolised aluminium chlorohydrate (soluble) in a silicone-ethanol vehicle of 0.34 (± 0.22) and 2.50 (± 0.37) mg/m^3, 4 hours/day, 5 days/week for 22 days. Mean aluminium concentrations in the lungs of exposed animals did not differ from those of controls (see Section 8.3.1) (193).

Steinhagen *et al* exposed groups of weanling Fischer 344 rats and Hartley strain guinea pigs (n = 10/ species/sex/group) by inhalation to nominal concentrations of soluble aluminium chlorohydrate ($Al_2(OH)_5Cl \times xH_2O$) of 0, 0.25, 2.5 and 25 mg/m^3, 6 hours/day, 5 days/week for 6 months. Analysis of the chlorohydrate used showed it to contain 24.5 % aluminium, i.e. exposure levels were 0, 0.061, 0.61 and 6.1 mg Al/m^3. Aluminium chlorohydrate was generated as a particulate dry dust using a Wright dust feed mechanism. Actual concentrations were 0.245 (± 0.46), 2.63 (± 0.92) and 21.18 (± 2.75) mg/m^3. The MMADs were 1.6, 1.20 and 1.53 µm, respectively; the 84 % diameters 6.20, 5.78 and 5.34 µm, respectively. (The geometric SDs were 3.88, 4.82 and 3.49, respectively). After 6 months of exposure, 5 animals/species/sex/group were sacrificed for pathological examinations and the remainder for haematology and tissue aluminium concentration determinations. There was no effect on haematology endpoints. Exposure to 25 mg/m^3 caused significant decreases in body weights in male and female rats while no body weight effects were seen in the other exposed groups. Absolute and relative weights of heart, liver, kidney, spleen or brains were not affected. In the groups exposed to 25 mg/m^3, statistically significant ($p < 0.01$) increases in relative lung weights were observed in all rats and all guinea pigs (in absolute lung weights only in rats) while no lung weight changes were seen at 0.25 and 2.5 mg/m^3. In both rats and guinea pigs, there was a significant dose-related increase in the amount of aluminium in the lungs (as µg Al/g wet tissue). Upon pathological examination, only effects in the respiratory tract were seen. In the animals exposed to 0.25 mg/m^3, there were slight exposure-related changes in 3 (out of 10) guinea pigs, characterised by an increase in alveolar macrophages which were more diffusively distributed when compared to control animals. Also in rats, alveolar macrophages were increased slightly, while there was an indication of granulomatous change in the peribronchial lymph node of one rat. In the groups

exposed to 2.5 or 25 mg/m^3, all rats and guinea pigs had multifocal granulomatous pneumonia characterised by proliferation and/or infiltration of mononuclear inflammatory cells and large macrophages in alveoli around the termination of air passage ways. In addition, in the peribronchial lymph nodes, there were micro-granulomas composed of large cells with eosinophilic cytoplasm but not containing vacuoles or other evidence of phagocytised material. Further, in the high-concentration groups, the number of goblet cells was increased in the nasal cavities. In the trachea, no lesions were observed (190).

Drew *et al* observed acute bronchopneumonia and moderate thickening of the alveolar walls in hamsters exposed for 3 days to 164 mg/m^3 of alchlor (a propylene glycol complex of aluminium-chloride-hydroxide) (6 hours on day 1 and 4 hours on days 2 and 3) and in rabbits exposed to 212 mg/m^3, 4 hours/day for 5 days. Ten, 20 or 30 6-hour exposures to 52 mg/m^3 alchlor caused granulomatous inflammation in the lungs that persisted through a 6-week post-exposure period (55).

Finelli *et al* exposed male rats (Sprague Dawley, n = 50/group) to respirable dust (< 10 µm) concentrations of aluminium chloride (soluble) and aluminium fluoride (poorly soluble) of 1.83 and 1.28 mg/m^3 (0.37 and 0.41 mg Al/m^3), respectively, 6 hours/day, 5 days/week for 5 months. A control group exposed to filtered air was included. Groups of 10 animals were sacrificed at study week 5, 9, 13, 18 and 26 (i.e. after an exposure-free period of 63 days). Besides body weights and (relative) weights of kidney, liver, lungs and brain, only a selected number of lung parameters thought to provide early warning of any pathological effects were determined. There were no differences in mean body weights and relative lung and brain weights between the three groups. At study weeks 13 and 18, increases of about 10 % were observed in relative liver and/or kidney weights [due to confusing reporting, these changes cannot be related specifically to the aluminium fluoride or aluminium chloride group]. In both groups, there was evidence suggestive of damage to alveolar macrophages (increases in lysozyme levels, protein levels) (aluminium chloride only) and to type II cells (increased alkaline phosphatase activity) (both compounds) in the lavage fluid (64).

Exposure to aqueous aerosol concentrations of aluminium sulphate (soluble) of 2 mg/m^3 (no data on exposure conditions and particle size given) were reported to affect the lungs of rats: increases in the number of pulmonary alveolar macrophages and of distorted, oversized pulmonary alveolar macrophages and granulocytes and in the permeability of the alveolar wall; increased lung weights, stiffer lungs and fibrosis (at the level of the terminal and respiratory bronchioles); decreased levels of copper, zinc and iron. Comparison with the results from similar, concurrent studies with sulphuric acid and potassium sulphate suggested that the aluminium ion was the toxic factor (no more data presented) (64).

8.3.3 Neurological effects

ATSDR data

No studies were presented regarding neurological effects in animals following acute inhalation exposure to various forms of aluminium. No brain weight or histological changes were observed in Fischer 344 rats or Hartley guinea pigs exposed to up to 6.1 mg Al/m^3 as aluminium chlorohydrate (soluble) (25 mg/m^3) for 6 months (Steinhagen *et al* 1978). No brain weight effects were observed in Sprague Dawley rats exposed by inhalation to 0.37 mg Al/m^3 as aluminium chloride (soluble) or 0.41 mg Al/m^3 as aluminium fluoride (poorly soluble) for 5 months, although tissues were not examined histologically (Finelli *et al* 1981). No differences in brain weights were observed in Fischer 344 rats or Hartley guinea pigs exposed by inhalation to 25 mg/m^3 of aluminium chlorohydrate (soluble) for up to 24 months (Stone *et al* 1979).

With regard to oral exposure, the lowest tested reliable neurotoxic doses (i.e. among those that include base dietary aluminium) are in mice. The most frequently affected neurobehavioural endpoints in mice exposed as adults, or exposed during development and tested as adults, included decreases in motor activity, grip strength and startle responsiveness, and effects most commonly found in exposed weanlings and young mice included increases in grip strength and landing foot splay and decreased thermal sensitivity, indicating that the spectrum of effects is different in adult and developing animals (Donald *et al* 1989, Golub and Germann 1998, Golub *et al* 1987, 1989, 1992a, 1992b, 1994, 1995) (see also Section 8.5.2). Neurobehavioural effects that have been associated with oral exposure to aluminium in rats include impaired motor coordination and operant learning (Bernuzzi *et al* 1989a, 1989b, Bilkei-Gorzo 1993, Cherroret *et al* 1992, Commissaris *et al* 1982, Muller *et al* 1990, 1993a, Thorne *et al* 1986, 1987).

A lowest observed adverse effect level (LOAEL) of 130 mg Al/kg bw/day was identified for decreased spontaneous motor activity in adult mice that were exposed to dietary aluminium lactate (soluble) for 6 weeks (Golub *et al* 1989). Aluminium lactate is a representative form of aluminium that is intermediate in bioavailability between inorganic complexes such as aluminium hydroxide and carboxylic acid complexes such as aluminium citrate. Overall activity was reduced about 20 % compared to controls due to less frequent occurrence of the highest activity states, which usually occurred during the diurnal period of peak activity. The duration of peak activity periods was also reduced (about 35 % compared to controls) and vertical movement (primarily rearing and feeding) was more affected than horizontal movement (primarily locomotion), but there was no shift in the diurnal activity cycle or any prolonged periods of inactivity. No effects on motor activity occurred at 62 mg Al/kg bw/day. Mice that ingested doses higher than 130 mg Al/kg bw/day as aluminium chloride (soluble) for 49 days or aluminium lactate for 90 days, and were tested using a standardised neurotoxicity screening battery, also showed decreased motor activity, as well as decreased grip strength and startle responsiveness (Golub *et al* 1992a, Oteiza *et al* 1993).

Depressed motor activity has also been observed in exposed adult rats, suggesting that this effect is a consistent neurobehavioural outcome associated with ingested aluminium (Golub *et al* 1992b).

Other studies found histological changes in the brain of rats exposed by diet to 92 mg Al/kg bw/day as aluminium chloride (soluble) in combination with an unnaturally high level of citrate for 6 months (Florence *et al* 1994) or to 12 mg Al/kg bw/day as aluminium fluoride (poorly soluble) in drinking water and the base diet for 45–52 weeks (Varner *et al* 1993, 1994, 1998). Unusual exposure conditions preclude identifying relevant LOAELs for brain histopathology from these studies. In particular, the effects appear to be due to greatly enhanced bioavailability because both studies were designed to maximise the uptake of aluminium (i.e. by the massive co-exposure to citrate, and the use of aluminium fluoride to form an optimum fluoro-aluminium species capable of crossing the gut and blood-brain vascular barriers).

Neurodegenerative changes in the brain, manifested as intraneuronal hyperphosphorylated neurofilamentous aggregates, is a characteristic response to aluminium in certain species and non-natural exposure situations generally involving direct application to brain tissue, particularly intracerebral and intracisternal administration and *in vitro* incubation in rabbits, cats, ferrets and non-human primates (Erasmus *et al* 1993, Jope and Johnson 1992).

Additional data

During exposure to concentrations of aerosolised aluminium chlorohydrate in a silicone-ethanol vehicle of 0.34 (± 0.22) and 2.50 (± 0.37) mg/m^3, 4 hours/day, 5 days/week for 22 days, rats began to huddle after a few minutes. For the rest of the exposure period, the majority huddled. Some of them exhibited a bout of preening, but otherwise behaviour was essentially unremarkable (for details, see Section 8.3.1) (193).

Three groups of adult mice were given 0, 300 and 600 mg Al/kg bw/day as aluminium nitrate nonahydrate (soluble) in drinking water for 2 weeks. One-half of the animals in each group were concurrently subjected to restraint stress during 1 hour/day throughout the study. After cessation of treatment, open-field activity, active avoidance learning, and motor resistance and coordination of the animals were evaluated. At the end of the behavioural testing period, mice were killed and aluminium concentrations were determined in a number of tissues. There were no remarkable effects of aluminium, restraint stress or their combined administration on either open-field activity or on the number of avoidances in an automatic reflex conditioner. However, a lower motor resistance and coordination in a rotarod were observed following exposure to 600 mg Al/kg bw/day, restraint alone, or to aluminium (300 and 600 mg/kg bw/day) plus restraint stress. The levels of aluminium in whole brain and cerebellum were significantly enhanced in mice exposed to aluminium plus restraint (41).

Groups of male BALB/c mice were administered aluminium ammonium sulphate dodecahydrate (soluble) in drinking water *ad libitum* at 0, 5, 25 and 125

mg Al/l (estimated to be ca. 0, 1, 4 and 21 mg Al/kg bw/day) for 1 month. An additional group received 250 mg/l ammonium as ammonium sulphate (soluble). In addition, all groups received ca. 22 mg Al/kg bw/day via the diet. No signs of gross behavioural alterations were observed (196).

8.3.4 Immunological effects

ATSDR data

In rats exposed to aluminium flakes for 5 days, there were multifocal micro-granulomas in the lungs and hilar lymph nodes at 200 mg Al/m^3, but not at 100 mg/m^3 (Thomson *et al* 1986). An increase in granulomatous lesions in the lungs and peribronchial lymph nodes were also observed in rats and guinea pigs exposed to 0.61 or 6.1 mg Al/m^3 as aluminium chlorohydrate (soluble) for 6 hours/day, 5 days/week for 6 months (Steinhagen *et al* 1978). There is some evidence that developmental exposure to aluminium may adversely affect the immune system in young animals. A 19 % increase in spleen weights, depressed spleen cell concentrations of interleukin-2, interferon-γ, and TNFα, and a deficiency of CD4+ cells in T-cell populations were observed in Swiss Webster mice that were exposed to aluminium from conception through 6 months of age (Golub *et al* 1993). The maternal animals consumed 200 mg Al/kg/day as aluminium lactate (soluble) in the diet from conception through lactation and the offspring were subsequently fed the same diet as the dams. Susceptibility to bacterial infection was increased in offspring of Swiss Webster mice that were exposed to dietary aluminium lactate (soluble) in a dose of 155 mg Al/kg bw from conception through 10 days of age, but not in 6-week-old mice exposed to 195 mg Al/kg bw/day for 6 weeks (Yoshida *et al* 1989). Susceptibility to infection was evaluated by assessing survival following intravenous inoculation with *Listeria monocytogenes* at the end of the exposure periods.

Additional data

No additional data were found on immunological effects after exposure to aluminium and aluminium compounds.

8.3.5 Carcinogenicity

ATSDR data

No carcinogenic potential was observed in male and female $B6C3F_1$ mice (n = 60/sex) given doses of 979 mg Al/kg/day as aluminium potassium sulphate (soluble) in the feed (base dietary aluminium not reported) for 20 months (Oneda *et al* 1994) and in male and female Long Evans rats and Swiss mice given 0.6 and 1.2 mg Al/kg/day as aluminium potassium sulphate (soluble) in drinking water (base dietary aluminium not reported), respectively, for 2–2.5 years (Schroeder and Mitchener 1975a, 1975b).

No increase in cancer was observed in male and female Wistar rats exposed via whole-body inhalation to refractory fibres consisting of 96 % aluminium oxide and about 4 % silica at concentrations of 2.18 or 2.45 mg/m^3 (as manufactured or aged fibres) for 86 weeks (Pigott *et al* 1981).

No studies were presented regarding cancer in animals after dermal exposure to various forms of aluminium.

Additional data
Female rats (SPF Wistar, n = 48/group) received doses of 6 mg ultrafine (nano)-particles of (insoluble) aluminium oxide or aluminium silicate (mean diameter: 0.013 and 0.015 µm, respectively) through intratracheal instillation once a week for 5 or 10 weeks. Of the animals treated with aluminium oxide for 5 or 10 times, 64 % (28/44) and 55 % (26/47) had one or more primary lung tumours. Of the animals treated with aluminium silicate, these figures were 49 % in each group (23/47 and 22/45, respectively). The incidence in control animals was 2 % (1/47). The period after first instillation in which 50 % of the animals died (excluding rats which died immediately after anaesthesia preceding instillation) was generally shorter in the treated groups (oxide: 111 and 97 weeks, respectively; silicate: 107 and 108 weeks, respectively) when compared to controls (111 weeks) (128, 156).

Lung tumour formation by intratracheal instillation of dusts is assumed to be caused by particle overload which may occur when the volume of particles in the lungs markedly impairs pulmonary clearance mechanisms (79, 95). Internationally, the relevance of intratracheal instillation is under debate and several investigators consider particle deposition by intratracheal instillation different from particle deposition by chronic inhalation. In addition, ultrafine particles were administered that have their own specific toxicological properties. Therefore, it is concluded that these experiments are of little relevance in assessing the potential carcinogenicity of aluminium (compounds) under occupational exposure conditions.

8.4 Genotoxicity

8.4.1 In vitro tests
ATSDR data
Aluminium was negative in an *in vitro* mutagenicity test in *S. typhimurium* (Marzin and Phi 1985). Results from a recombination repair (rec) assay in *B. subtilis* were negative as well (Kanematsu *et al* 1980).[1]

Additional data
Gene mutation assays
Aluminium fluoride (poorly soluble) was negative when tested in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 and in *E. coli* strain WP2uvrA at concentrations of 1–5 000 µg/plate with and without a metabolic activation system from induced male rat livers (S9) (175).

[1] According to IPCS/WHO 1997, the test in *S. typhimurium* was performed with aluminium chloride (soluble) in strain TA102 at concentrations of 10–100 nM per plate (i.e. ca. 1–10 µg/plate). In the rec assay, aluminium oxide (insoluble), chloride (soluble), sulphate (insoluble), and phosphate (soluble) were tested at concentrations of 1–10 mM (96).

Aluminium chloride (soluble) was not mutagenic when tested alone or combined with 9-aminoacridine in *S. typhimurium* strains TA98, TA100, TA102, TA1537 and TA2637 (concentration range tested: 1–5 000 µmoles/plate) (144). Other results from assays on aluminium chloride were listed in the Chemical Carcinogenesis Research Information System (CCRIS), published by the US National Library of Medicine (35). A pre-incubation assay in *S. typhimurium* strain TA98 without metabolic activation at concentrations of 0.3–3 ppm was reported to be negative (Ahn and Jeffery 1994). Pre-incubation assays in *S. typhimurium* strains TA98 and TA100, with and without induced rat liver S9 mix at concentrations of 20–5 000 µg/plate were positive, while testing under similar conditions in strains TA1535, TA1537 and TA1538 was negative (Japan Chemical Industry Ecotoxicology - Toxicology and Information Center 1996). A spot (without metabolic activation, concentration range: 0–0.8 M/disc) and a pre-incubation (with and without induced rat liver S9, concentration range: 20–5 000 µg/plate) assay in *E. coli* strain WP2uvra were both negative (Seo and Lee 1993, Japan Chemical Industry Ecotoxicology - Toxicology and Information Center 1996).

Aluminium chloride was found negative in the TK+/- L5178Y mouse lymphoma assay at concentrations of 570–625 µg/ml with and without S9. The mutation frequency was constant at about a 2-fold increase over control values, and total survival was not linearly related. Re-testing again resulted in non-linear cytotoxicity and little or no increase in mutation frequency (141).

Cytogenicity assays

Trippi *et al* performed a micronucleus test in cultures of lymphocytes and fibroblasts obtained from patients with sporadic or familial Alzheimer's disease and from healthy persons. In both groups of patients, the spontaneous frequencies of micronuclei in both cell cultures were statistically significantly higher than those in the respective control groups. In neither of the patient groups did incubation with 1 mM of aluminium sulphate (soluble) (for 72 hours) cause increases in the frequencies of micronuclei compared to spontaneous values. When lymphocytes and fibroblasts of healthy persons were treated with 1 mM aluminium sulphate, 1.8- to 2.7-fold increases in the micronucleus frequencies were found (194).

Migliore *et al* examined the induction of micronuclei in peripheral blood lymphocytes isolated from two young healthy non-smoking donors at concentrations of 0.5, 1, 2 and 4 mM aluminium sulphate (soluble) (treatment time: 72 hours). In donor A, there was a 1.9-fold ($p < 0.05$) and 2.5-fold ($p < 0.01$) increase in the frequency of micronuclei at 1 and 2 mM, respectively. In donor B, frequencies were increased about 2.3-fold ($p < 0.05$) at 0.5, 2 and 4 mM and 3.5-fold ($p < 0.01$) at 1 mM. Additional analysis with the fluorescence *in situ* hybridisation (FISH) technique of lymphocytes from donor B and treated with 0, 1 and 2 mM aluminium sulphate revealed increased frequency of centromere-positive and centromere-negative micronuclei. The concentrations tested did not show severe toxicity based on the relative amount of binucleated cells. Based on

these results, aluminium can act by means of clastogenic and aneuploidogenic mechanisms, showing the ability to interfere with chromosome segregation (125).

Human peripheral blood lymphocytes were treated with 1, 2, 5, 10 and 25 µg/ml aluminium chloride (soluble) in the G0/G1 phase, in the S/G2 phase, and during the whole cell cycle. The frequency of micronuclei increased initially, but decreased at high aluminium chloride concentrations. This drop of micronuclei frequency could be explained by a strong increase in the frequency of apoptosis. Aluminium chloride induced both micronuclei with and without centromeres (only studied at the concentration of 5 µg/ml). The G0/G1 phase of the cell cycle was found to be more sensitive than were the S and G2 phases. This points toward oxidative stress or liberation of DNase as the major source of DNA damage induced by aluminium (15).

Other tests

Aluminium chloride (soluble) and aluminium sulphate (soluble) were negative in the SOS chromotest in *E. coli* strains PQ37. The compounds were tested without adding S9 at concentrations up to 3 000 nM/ml, which were cytotoxic (145).

Valverde *et al* reported in an abstract that aluminium chloride (soluble) induced DNA single strand breaks only at the lowest concentration tested (0.1 µM) in an alkaline single cell gel electrophoresis assay. Aluminium chloride induced more damage in whole blood cells (leukocytes) than in isolated lymphocytes (197).

Lankoff *et al* investigated the level of DNA damage in human peripheral blood lymphocytes treated with aluminium and the impact of aluminium on the repair of DNA damage induced by ionising radiation. Cells were treated with different doses of aluminium chloride (soluble) (1, 2, 5, 10 and 25 µg/ml) for 72 hours. The level of DNA damage and of apoptosis was determined by the comet assay. The level of oxidative damage was determined by the application of endonuclease III and formamidopyrimidine DNA glycosylase. Based on the fluorescence intensity, cells were divided into cohorts of different relative DNA content that corresponds to G1, S and G2 phases of the cell cycle. The results revealed that aluminium induced DNA damage in a dose-dependent manner. However, at 25 µg/ml the level of damage declined. This decline was accompanied by a high level of apoptosis indicating selective elimination of damaged cells. Cells pre-treated with aluminium showed a decreased repair capacity indicating that aluminium inhibits DNA repair. It is assumed that the inhibition of proteins which contain so-called zinc finger domains or an impaired ligation step may be a possible mechanism of DNA repair inhibition (111).

Dominguez *et al* cultured primary human dermal fibroblasts from the outgrowth of skin biopsies from 10 persons. Cells were exposed for up to 5 days to a range of aluminium nitrate concentrations (1.85–74 µM) at physiological pH. Daily measurements were performed to assess the effect on cell DNA synthesis (using ^{3}H-thymidine incorporation measured by liquid scintillation counting) and cell proliferation (cell protein measurements). Culture conditions were in the absence of serum (quiescent cultures). A clear time- and concentration-related induction of

DNA synthesis was observed, although only a moderate induction of cell protein was determined. Furthermore, the mitogenic activity was found to be minimal, inconsistent, and not related to the induction of DNA synthesis. According to the authors, a second mitotic agent is probably required to let the cells pass to mitosis (53).

Latha *et al* showed that aluminium interacts with topological changes in (CCG)12 triplet repeats in blood samples of 10 fragile X syndrome patients. In the presence of 10 μM aluminium (maltolate), DNA induced stable Z-conformation in (CCG)12 repeats, inhibiting gene expression of the FMR1 gene in fragile X syndrome (112).

8.4.2 In vivo tests

ATSDR data

A significant increase in chromatid-type aberrations[2], with a non-random distribution over the chromosome complement, was found in the bone marrow of mice following intraperitoneal injections of 0.01, 0.05 or 0.1 molar of (soluble) aluminium chloride. No dose-response relationship could be demonstrated, although the highest dose of aluminium chloride did produce the greatest number of aberrations (Manna and Das 1972).

Aluminium chloride (soluble) caused cross-linking of chromosomal proteins and DNA in ascites hepatoma cells from Sprague Dawley rats (Wedrychowski *et al* 1986). Micromolar aluminium levels also reduced ^{3}H-thymidine incorporation in a transformed cell line (UMR 106-01), which indicates that aluminium may impede cell cycle progression (Blair *et al* 1989).

Furthermore, a negative transformation assay in Syrian hamster cells was reported (DiPaolo and Casto 1979).

Additional data

In a bone marrow chromosomal aberration test, Roy *et al* administered oral (gavage) doses of aluminium sulphate (soluble) of 0, 212, 265, 353, 530, 1 060 or 2 120 mg/kg bw/day (i.e. 0, 17, 22, 28, 43, 85, 172 mg Al/kg bw/day) or of aluminium potassium sulphate of 0, 503 or 764 mg/kg bw/day (i.e. 0, 28, 43 mg Al/kg bw/day) to groups of male rats (Rattus norvegicus, n = 5/group) for 7, 14 or 21 days. Administration of aluminium sulphate caused decreases in the mitotic index and increases in the frequency of abnormal cells and in the number of breaks per cell in all dose groups at all treatment periods. Most aberrations were chromatid breaks. Comparison of cytotoxic and clastogenic effects of aluminium sulphate and aluminium potassium sulphate (soluble) at doses having similar aluminium content did not show great differences (167).

In a bone marrow micronucleus test, Roy *et al* administered intraperitoneally doses of hydrated aluminium sulphate (soluble) of 250 or 500 mg/kg bw/day (i.e. ca. 20 and 40 mg Al/kg bw/day) for 2 days to groups of Swiss mice (n = 6/group, sex not reported). Additional groups received saline (vehicle control) or mito-

[2] According to IPCS/WHO, 1997, the aberrations included gaps, breaks, translocation and ring formations (96).

mycin C (positive control). Animals were killed 24 or 48 hours after the second dose. Per animal, 1 000 polychromatic erythrocytes (PCEs) were scored for determining the frequency of micronucleated cells and 1 000 normochromatic erythrocytes (NCEs) counted to evaluate cytotoxic effects. There was no effect on the NCE/PCE ratio. The frequency of micronucleated cells was increased by a factor of 2.2 (24 hours, not significant) and 2.5 (48 hours, not significant) at 250 mg/kg bw and by a factor of 5.3 (24 hours, $p < 0.05$) and 6.6 (48 hours, $p < 0.05$) at 500 mg/kg bw, when compared to vehicle controls. In both dose groups, a 7-day pre-treatment with a fruit extract or with comparable doses of ascorbic acid (the main extract component) induced frequencies similar to those seen in vehicle controls (166).

Dhir *et al* investigated the induction of SCEs in bone marrow cells of male Swiss mice ($n = 5$/group) obtained 24 hours after single intraperitoneal injections of doses of hydrated aluminium sulphate (soluble) of 100, 200 or 400 mg/kg bw (i.e. ca. 8, 16, 32 mg Al/kg bw). Per animal, 60 intact second division metaphases were scored for SCEs, and 100 metaphase cells were used to determine the proliferation rate index. Vehicle (saline) control and positive (mitomycin C) control groups were included. There was no effect on the proliferation rate index. The frequency of SCEs was dose-dependently (one-tailed trend test, $p < 0.001$) increased, by factors of 1.5, 2.1 and 2.8, respectively, when compared to vehicle control values. A 7-day pre-treatment with a fruit extract or with comparable doses of ascorbic acid (the main extract component) significantly reduced SCEs frequencies (48).

8.5 Reproduction toxicity

The effects of exposure to aluminium and aluminium compounds on reproduction have been reviewed and separately published by DECOS's Subcommittee on the Classification of Reproduction Toxic Substances. Data and conclusions presented by the subcommittee are summarised below. For detailed information on individual studies, it is referred to the subcommittee's report (84).

8.5.1 Fertility

The subcommittee did not present data on the effects of exposure to metallic aluminium on fertility.

In studies with water soluble compounds, administration of aluminium chloride (hexahydrate) via the drinking water did not affect fertility of mice or rats. In a poorly reported multi-generation study in mice, doses of 19.3 mg Al/kg bw/day (only dose tested) did not affect female or male reproductive capacity (146). In rats, concentrations up to ca. 500 mg Al/l (i.e. ca. 23 mg/kg bw/day, assuming a water intake of 10 ml/100 g bw and a rat body weight of 450 g (84)) did not cause changes in male reproductive capacity, changes in body or organ (including testis) weights, or (histo)pathological effects (19, 50). However, in another study, levels of ca. 11 mg Al/kg bw/day (calculated from a given body weight of 300 g, an assumed water intake of 10 ml/100 g bw and a drinking water concentration of

100 mg Al/l) suppressed sexual behaviour and induced decreases in absolute (but not in relative) testis and seminal vehicle weights, as well as in body weights. Male reproductive capacity was not affected (19).

Regarding compounds not soluble in water, dietary administration of basic sodium aluminium phosphate at doses of 75 mg Al/kg bw/day induced decreased absolute testis weights and histological changes (in 2/4) in male beagle dogs. No such effects were seen at a dose of 27 mg Al/kg bw (amounts included Al present in the basal diet) (154).

8.5.2 Developmental toxicity

The subcommittee did not present data on the effects of exposure to metallic aluminium on development.

The effects of water-soluble aluminium compounds were widely investigated in a series of prenatal and postnatal developmental toxicity studies. In the prenatal studies, no effects were observed in the foetuses of dams orally treated at dose levels that did not induce general toxic effects (124). In the foetuses of dams orally treated at dose levels inducing general toxicity (13 mg Al/kg bw/day in rats, 29 mg Al/kg bw/day in mice) decreased foetal weights and retarded ossification were seen (8, 23, 151). In the postnatal studies, (neuro)developmental and/or (neuro)-behavioural effects were investigated in the offspring of dams treated during gestation (5, 25, 26, 76, 126, 127, 130, 159, 170, 201) or during gestation and lactation (52, 54, 67-70, 72). No effects were observed on reproductive outcome parameters (pregnancy rate, absorptions, implantation sites, litter size, pup weight at birth). Aluminium doses that caused general toxic effects generally resulted in decreased pup weight gain, increased pup mortality, and neurodevelopmental and behavioural effects. However, after oral administration of doses not inducing general toxic effects, increased pup mortality and neurodevelopmental and behavioural effects were also observed (25, 54, 67, 69, 70, 126, 130). In mice, no effects were observed at daily dietary amounts of 10 mg Al/kg bw, while effects were observed at 50 mg Al/kg bw/day (67). In rats, no effects were seen at gavage doses of 18 mg Al/kg bw/day (effect level: 36 mg Al/kg bw/day) (126).

Regarding compounds not soluble in water, no effects on prenatal development in rats and mice were seen at the doses tested in the studies available. In all these studies, aluminium hydroxide was administered by gavage during gestational days 6–15. The highest levels tested were ca. 100 and 270 mg Al/kg bw in mice and rats, respectively (39, 40, 51, 74, 75). The subcommittee did not present data on effects on postnatal development.

8.6 Summary and evaluation

Rats exposed for 4 hours to 200 and 1 000 mg/m^3 aluminium flakes developed persistent microgranulomata in the respiratory tract at 14 days post-exposure. No effects were observed at levels of 100 mg/m^3 and below.

Solutions of 10 % of aluminium chloride (soluble) and aluminium nitrate (soluble) induced skin damage in mice, rabbits and pigs, while aluminium sulphate (soluble), chlorohydrate (soluble), and hydroxide (insoluble) did not.

Aluminium chloride (soluble) was negative in a mouse local lymph node assay, a test considered less appropriate for detecting sensitising capacity of metals.

Exposure to aluminium chlorohydrate (soluble) concentrations of 25 mg/m^3 (6.1 mg Al/m^3) did not induce (histological) effects on the eyes. No irritation studies following instillation of aluminium or its compounds into eyes of laboratory animals were available.

No mortality was induced in rats following 4-hour exposures to up to 1 000 mg Al/m^3 as aluminium oxide (insoluble).

No data on acute dermal toxicity were available.

Oral LD_{50} values in rats and mice ranging from 261 to 980 mg/kg bw were reported for several water-soluble aluminium compounds.

Following repeated inhalation exposure, mainly effects on the respiratory tract were observed. In a study with aerosolised aluminium chlorohydrate (soluble) in a silicone-ethanol vehicle, no effects were seen in rats concerning blood biochemistry endpoints or several organs/tissues including lungs and nose at exposure to 2.5 mg/m^3 (MMAD 4.28 ± 0.93 μm), 4 hours/day, 5 days/week for 22 days. However, in guinea pigs and rats exposed to 2.5 mg/m^3 aluminium chlorohydrate dust for 6 months, multifocal granulomatous pneumonia was observed. In addition, there were microgranulomas in the peribronchial lymph nodes. No effects were seen in the nasal cavities or the trachea. At 0.25 mg/m^3 (0.061 mg Al/m^3), there was an indication of granulomatous change in the peribronchial lymph node of one rat and slightly increased alveolar macrophages in a few rats and guinea pigs. In poorly reported studies, exposure to 1.3 and 1.8 mg/m^3 (0.37 and 0.41 mg Al/m^3) of respirable dusts of aluminium chloride or aluminium fluoride, respectively, for 5 months caused some changes in lung parameters indicative of alveolar macrophage damage. Similar effects as well as fibrosis and increased lung weights were seen in rats exposed to 2 mg/m^3 of an aqueous aerosol of aluminium sulphate, but not in concurrent experiments with sulphuric acid and potassium sulphate, suggesting the aluminium ion to be the toxic factor. No fibrosis was seen in rats examined 42 weeks after an 86-week exposure to a refractory material containing 96 % aluminium oxide and about 4 % silica at concentrations of 2.18 or 2.45 mg/m^3 (as manufactured or aged fibres). There were no data from neurotoxicity inhalation studies.

Oral studies in which an adequate range of endpoints was examined following repeated exposure of rats, mice or dogs to various aluminium compounds (sodium aluminium phosphate, aluminium hydroxide, aluminium nitrate) in the diet or drinking-water, showed only minimal effects (decreases in body weight gain generally associated with decreases in food consumption or mild histological effects) at the highest doses administered (70–300 mg Al/kg bw/day). In neurotoxicity studies in rats and mice, no significant histological changes in the brain were found, although neuromotor, behavioural and cognitive changes have been

observed consistently in these species. A LOAEL of 130 mg Al/kg bw/day was identified for decreased spontaneous motor activity in adult mice that were exposed to dietary aluminium lactate for 6 weeks. No decreased spontaneous motor activity was observed at 62 mg Al/kg bw/day.

No increase in tumour incidences was found in rats exposed to a refractory material consisting of 96 % aluminium oxide and 4 % silica at concentrations of 2.18 or 2.45 mg/m^3 for 86 weeks, with an additional exposure-free period of 42 weeks.

Aluminium potassium sulphate did not increase tumour incidences in mice given dietary doses as high as 979 mg Al/kg bw/day for 20 months or in rats (male) and mice (female) at drinking water doses of 0.6 and 1.2 mg Al/kg bw/day, respectively, for 2–2.5 years.

Intratracheal instillation of doses of 6 mg of ultrafine particles of aluminium oxide (mean diameter: 0.013 μm), once a week for 5 or 10 times, increased the number of animals having one or more primary tumours when compared to controls (64 % and 55 %, respectively, vs. 2 % in controls). Similar treatment with aluminium silicate (mean diameter: 0.015 μm) had similar results (49 % in both groups).

Aluminium chloride was not mutagenic in *S. typhimurium* strains TA102, TA1535, TA1537, TA1538 and TA2637, in *E. coli* strain WP2uvrA or in mouse lymphoma cells. Conflicting results were reported for *S. typhimurium* strains TA98 and TA100. Aluminium fluoride was not mutagenic in *S. typhimurium* or *E. coli*.

Aluminium chloride and aluminium sulphate induced increased frequencies of micronuclei in human lymphocytes and fibroblasts by means of clastogenic and aneuploidogenic mechanisms.

Aluminium (chloride) caused DNA damage and inhibited DNA repair. It induced DNA single strand breaks and cross-linked DNA and chromosomal proteins.

In vivo, levels ≥ 17 mg Al/kg bw, administered orally as its sulphate or potassium sulphate to rats or intraperitoneally as its sulphate to mice, increased the frequency of chromosomal aberrations in bone marrow cells of rats and mice, and of micronuclei and SCEs in bone marrow cells of mice (not tested in rats). Lower levels were not tested.

There were no inhalation reproduction toxicity studies or studies on the effects of metallic aluminium on fertility or development.

In studies with water-soluble compounds, doses of 19 mg Al/kg bw/day (as aluminium chloride) in the drinking water did not affect reproductive capacity in male or female mice. In rats, no effect was seen on male reproductive capacity at drinking water levels of ca. 23 mg Al/kg bw/day (as aluminium chloride). Regarding compounds not soluble in water, dietary administration of doses of 27 mg Al/kg bw/day did not result in testis weight or histological changes in male beagle dogs.

In prenatal developmental toxicity studies in which water-soluble aluminium compounds were orally administered to dams during gestation, no effects were observed in the foetuses at dose levels that did not induce general toxic effects. In the foetuses of dams treated at dose levels inducing general toxicity (13 mg Al /kg bw/day in rats, 29 mg Al/kg bw/day in mice) decreased foetal weights and retarded ossification were seen. In postnatal studies, investigating (neuro)developmental and/or (neuro)behavioural effects in the offspring of dams treated with water soluble aluminium compounds during gestation or during gestation and lactation, no effects were seen on reproductive parameters such as pregnancy rate, absorptions, implantation sites, litter size and pup weight at birth. Generally, effects on postnatal development such as pup weight gain, pup mortality and (neuro)behaviour were observed in the presence of general toxicity. However, increased pup mortality and neurodevelopmental and behavioural effects were also seen at doses not inducing general toxicity. In mice, dietary amounts of 10 mg Al/kg bw/day did not induce effects. In rats, there was impaired motor development at gavage doses of 36 mg Al/kg bw/day in one study, but not at doses of 18 mg/kg bw/day. Regarding compounds not soluble in water, no effects on prenatal development were seen following administration of aluminium hydroxide by gavage on gestational days 6-15 at the highest levels tested, i.e. ca. 100 mg Al/kg bw/day in mice and ca. 270 mg Al/kg bw/day in rats.

9. Existing guidelines, standards and evaluations

9.1 General population

No inhalation limit values for the general population could be located for aluminium and aluminium compounds.

9.2 Working population

Occupational exposure limits for aluminium and aluminium compounds in some European countries and the US, listed in the most recent publications available to the committees, are presented in Table 6. None of the countries or organisations attached a “skin notation” or considered aluminium or one of its compounds to have sensitising properties.

9.3 Evaluations

American Conference of Governmental Industrial Hygienists (ACGIH) Aluminium metal and insoluble compounds. In its threshold limit value (TLV) documentation of 2008, ACGIH stated that, generally, insoluble forms of aluminium are poorly absorbed and readily cleared from the lungs by mucociliary and bronchoalveolar clearance, but that there is evidence of aluminium accumulation in the body with long-term exposure. In workers exposed to high

Table 6. Occupational exposure limits (OELs) (as 8-hour TWAs) for aluminium and aluminium compounds in various countries.

Country - organisation	Aluminium compound	OEL (mg Al/m^3)	Ref.
Norway	Welding fume	5 [a]	(10)
	Oxide	10 [a] (total dust)	
	Pyro powder	5 [a]	
	Soluble salts	2	
Sweden	Metal, oxide	5 (total dust)	(191)
		2 (respirable dust)	
	Soluble compounds	1 (total dust)	
	Potassium aluminium tetrafluoride	0.4 [a] (inhalable dust)	
	Stearates	5 [a] (total dust)	
Denmark	Metal, oxide (powder, dust)	5 (total dust)	(11)
		2 (respirable dust)	
	Metal fume	5	
	Soluble salts	1	
Finland	Welding fume	1.5	(186)
	Soluble compounds	2	
	Fluoride	1 [a] (15-min value)	
	Sulphate	1	
Iceland	Metal (powder, dust)	10	(200)
	Oxide	10	
	Fume	5	
	Soluble compounds	2	
the Netherlands	- [b]	- [b]	(192)
United Kingdom - Health and Safety Executive	Metal, oxide	10 (inhalable dust)	(83)
		4 (respirable dust)	
	Soluble salts	2	
Germany - Deutsche Forschungs-gemeinschaft (MAK-Kommission)	Metal-, oxide-, hydroxide-containing dusts [c]	4 (inhalable fraction)	(47)
		1.5 (respirable fraction)	
- Arbeits- und Gesundheitsschutz (AGS)	-	-	(20)
United States			
- American Conference of Govern-mental Industrial Hygienists (ACGIH)	Metal, insoluble compounds	1 [d]	(3)
- Occupational Safety and Health Administration (OSHA)	Metal	15 (total dust)	(3)
		5 (respirable fraction)	
- National Institute for Occupational Safety and Health (NIOSH)	Metal	10 (total dust)	(3)
		5 (respirable dust)	
	Pyro powder	5	
	Soluble salts	2	
European Union	-	-	(58)

[a] Listed as mg/m^3.

[b] For inorganic fluorides, there is a 15-minutes time-weighted average (TWA) limit value of 2 mg F/m^3. For aluminium fluoride, this would be equivalent to 0.9 mg Al/m^3.

[c] Ultrafine particles and fibrous aluminium oxide are excepted. Aluminium oxide fibrous dust is classified in carcinogenicity category 2, i.e. listed among substances considered to be carcinogenic for man because sufficient data from long-term animal studies or limited evidence from animal studies substantiated by evidence from epidemiological studies indicate that they can make a significant contribution to cancer risk. Limited data from animal studies can be supported by evidence that the substance causes cancer by a mode of action that is relevant to man and by results of *in vitro* tests and short-term animal studies (see also Section 9.3).

[d] As respirable particulate matter. Aluminium metal and insoluble compounds are classified into carcinogenicity category A4, i.e. not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic to humans but which cannot be assessed conclusively because of lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.

levels of aluminium dust (100 mg/m^3-years, equivalent to 40 years of exposure at 2.5 mg/m^3), radiographic and mild pulmonary function changes have been observed. In animals, effects on the respiratory tract, including granulomatous reactions and biochemical alterations in bronchoalveolar lavage fluid, have been demonstrated after exposure to insoluble forms of aluminium at concentrations as low as 2.5 mg/m^3 of respirable particles. According to ACGIH, several studies suggest that long-term inhalation exposure to aluminium, resulting in body burdens corresponding to inhalation of 1.6 mg/m^3 for 40 years, can lead to subtle neurological deficits. Airborne concentrations in this range correspond to urinary aluminium levels of 100 µg/l, which appears to be a threshold for neurological effects. From these data, ACGIH concluded that a TLV-TWA of 1 mg/m^3, respirable particulate matter, should provide sufficient protection against potential adverse effects on the lungs and the nervous system. The recommended TLV-TWA applies to insoluble aluminium compounds (e.g. aluminium metal, aluminium oxide, stamped aluminium, aluminium in bauxite ore, emery).

ACGIH concluded further that the toxicological data were inadequate for the *soluble aluminium compounds, aluminium alkyl compounds, and for aluminium metal flakes and powder coated with oxidation inhibited oils* (2).

Deutsche Forschungsgemeinschaft (DFG)

Dusts containing aluminium metal, oxide or hydroxide. In 2007, an evaluation of the health effects of dusts containing aluminium, aluminium oxide and aluminium hydroxide was published. The Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area considered the lungs and the central nervous system to be the target organs in humans. High concentrations of aluminium in occupational air, which in the past often exceeded 6 mg/m^3 (respirable fraction) frequently induced lung fibrosis. Accompanying urinary levels of aluminium were higher than 200 µg/l (i.e. the biological limit value). However, dose-response relationships or no observed adverse effect levels (NOAELs) for lung fibrosis could not be established from the epidemiological studies. The exposure data were inadequate. Further, there was frequently co-exposure to other compounds and the aetiological role of aluminium could not be unequivocally identified. Similarly, effects on the central nervous system in occupationally exposed workers could not be evaluated. The DFG Commission temporarily maintains the current MAK-values of 1.5 and 4 mg/m^3 for respirable and inhalable aluminium dusts, respectively, but excludes ultrafine particles, which can among others occur during aluminium welding (as well as aluminium oxide fibres).

From developmental toxicity studies, the DFG Commission concluded that, especially for soluble aluminium compounds, effects on foetal and offspring body weights are the key developmental toxicity effects with a (subcutaneous) NOAEL of 2.7 mg Al/kg bw in rabbits and a (subcutaneous) LOAEL of 0.2 mg Al/kg bw in rats, respectively. Although the NOAEL in rabbits warrants a classification in pregnancy risk group C (i.e. “there is no reason to fear damage to the embryo or foetus when MAK and BAT values are observed”), the DFG Commission decided

to classify the aluminium dusts into pregnancy risk group D (i.e. among substances for which either there were no data for an assessment of damage to the embryo or foetus or the currently available data were not sufficient for classification in one of the groups A, B or C) based on the LOAEL in rats.

Based on the negative carcinogenicity study with potassium aluminium sulphate in mice, the DFG Commission did not classify aluminium into one of the carcinogenicity groups. The DFG Commission concluded that aluminium was not mutagenic in bacterial and mammalian cell systems. The induction of chromosomal aberrations and micronuclei was observed in *in vitro* systems, as well as *in vivo* in laboratory animals at high doses; however, low doses were not tested. Overall, these findings could be seen only as an indication of a genotoxic potential *in vivo*. The DFG Commission was further of the opinion that the genotoxic effects observed were indirect effects for which no-effect levels might exist but cannot be indicated from the data available.

Despite the extensive exposure to aluminium, aluminium oxide and aluminium salts, only a few cases of (contact) sensitisation have been reported. In several of these cases, sensitisation occurred following subcutaneous application of aluminium oxide-containing vaccines that was not considered relevant to workplace conditions. Experimental animal studies were negative. In several studies, allergic lung diseases were observed following massive inhalation exposure to aluminium or aluminium oxide. However, there was no firm evidence of respiratory tract sensitisation. Based on the available data, the commission considered aluminium not to be a sensitising agent (78).

Aluminium oxide fibrous dusts. In 1993, the DFG Commission evaluated and classified various types of fibrous dust with respect to their carcinogenic potential. In carcinogenicity studies in which aluminium oxide fibres were intrapleurally administered to rats, increased incidences of pleural sarcomas were observed. Although recognising that the intrapleural route is an unphysiological exposure route, the DFG Commission concluded that the data provided sufficient evidence of a carcinogenic potential of aluminium oxide fibres. Therefore, the DFG Commission stated that theses fibres should be handled like fibres classified in carcinogenicity category 2 (see also Table 6) (46).

Health and Safety Executive (HSE)

Aluminium metal. In 1991, HSE stated that the solubility of metallic aluminium is very low, although the exact extent of its bioavailability is not known and may depend on whether the particle surface is oxidised or covered by a stamping lubricant. Powders coated with mineral oil were associated with lung fibrosis. Since these were no longer produced in the UK, HSE excluded these powders – along with aluminium fume – from consideration of a limit. HSE concluded that there was no evidence that, when inhaled, aluminium is sufficiently absorbed to cause systemic effects and considered, for example, any link with Alzheimer's disease to be remote. Because of methodological problems, HSE doubted the validity and results of the neurotoxicity study in Canadian miners (see Rifat *et al* (160)) and regarded

this study as unconvincing and not a basis for firm conclusions. HSE found only little relevant information on the mutagenic or carcinogenic potential of aluminium. The excess cancer incidence among aluminium smelter workers was thought to be related to factors other than exposure of aluminium. HSE concluded that lung fibrosis was the critical health effect. Animal studies showed some lung effects, but not fibrosis, at 20–100 mg/m^3. Since, according to HSE, there was no evidence for effects in humans at levels below this range, HSE set occupational exposure limits at 4 mg/m^3 (respirable dust) and 10 mg/m^3 (inhalable dust), as 8-hour TWA (81).

Aluminium oxide. HSE stated that the solubility (and consequently bioavailability) of aluminium oxide was very low, and that there was no evidence that the slight absorption that might occur from inhaled dust is sufficient to cause any systemic effects. Any link between exposure and Alzheimer's disease was found to be remote. The neurotoxicity study in Canadian miners (see above) was found not convincing and not suitable for firm conclusions. HSE stated that there was no reliable evidence to suggest that significant health effects may arise from single exposures to aluminium or aluminium oxide dusts. It regarded the excess cancer incidence among aluminium smelter workers as probably related to factors other than aluminium or aluminium oxide. HSE found no evidence of genotoxicity and no information on reproduction toxicity. HSE concluded that, despite some case reports of effects on lungs in exposed workers, there was no evidence of such effects at the levels of 20–100 mg/m^3 used in animal studies (see above), and set occupational exposure levels at 4 mg/m^3 (respirable dust) and 10 mg/m^3 (inhalable dust) (81).

Finland

Aluminium fluoride. The occupational exposure limit for aluminium fluoride is based on increased incidences of bronchial hyperreactivity and asthma reported by Simonsson *et al* (1985) (177) and Hjortsberg *et al* (1994) (88). According to Simonsson *et al*, 6 and 7 cases of asthma occurred in 1975 and 1976, respectively, in a group of 35–40 workers of a Swedish aluminium fluoride-producing facility exposed to mean aluminium fluoride concentrations (personal air sampling) of 5.5 and 2.6 mg/m^3, respectively. During 1978–1980, when measures resulted in lower concentrations of 0.4–1.0 mg/m^3, 2 new cases appeared, while none occurred in 1981 and 1982 (no exposure levels reported) (177). Hjortsberg *et al* reported that exposure to potassium aluminium tetrafluoride used as a flux for soldering aluminium induced an increase of bronchial reactivity in small airways. Median exposure levels of respirable dust and of repirable particulate fluoride were 1.1 and 0.3 mg/m^3, respectively, while subsequent measures lowered levels to 0.7 and 0.1 mg/m^3, respectively (88).

Aluminium sulphate. The occupational exposure limit for aluminium sulphate is based on 4 cases of short-lasting asthma occurring during 1971–1980 in a group of 37 workers of a Swedish aluminium sulphate-producing facility exposed to average aluminium sulphate concentrations varying between 0.2 and 4 mg/m^3.

The induction of asthma was reported to be related to “heavy” dust exposure during rinsing or repair work (177).

World Health Organization (WHO)
The International Programme on Chemical Safety (IPCS), a joint venture of the United Nations Environmental Program (UNEP), the International Labour Organisation (ILO) and the World Health Organization (WHO), published an environmental health criteria document on aluminium in 1997. It was concluded that workers having long-term, high-level exposure to fine aluminium particulates might be at increased risk of adverse health effects. However, there were insufficient data from which occupational exposure limits with regards to the adverse effects of aluminium could be developed with any degree of certainty. It was stated that exposure to stamped pyrotechnic aluminium powder most often coated with mineral oil lubricants had caused pulmonary fibrosis, whereas exposure to other forms of aluminium had not been proven to cause pulmonary fibrosis. In most reported cases, there was exposure to other potentially fibrogenic agents. Further, it was said that irritant-induced asthma had been associated with inhalation of aluminium sulphate, aluminium fluoride or potassium aluminium tetrafluoride, and with the complex environment within the potrooms during aluminium production. IPCS was of the opinion that the data in support of the hypothesis that occupational exposure may be associated with non-specific impaired function were inadequate (96).

Agency for Toxic Substances and Disease Registry (ATSDR).
In its toxicological profile for aluminium, published in September 2008, ATSDR stated that the occupational exposure studies and animal studies suggested that the lungs and the nervous system might be the target organs of toxicity following inhalation exposure. Respiratory effects, in particular impaired lung function and fibrosis, have been found in numerous studies on a variety of aluminium workers. However, these effects have not been consistently seen across studies and interpretation of the data is also complicated by the lack of exposure assessment and the potential for concomitant exposure to other toxic compounds. Respiratory effects (granulomatous lesions) have also been observed in rats, hamsters and guinea pigs. According to ATSDR, it was unclear whether these effects were related to direct toxic effects of aluminium in lung tissue or on dust overload. Therefore, inhalation minimal risk levels (MRLs) for respiratory effects were not derived. Subtle neurological effects, including impaired performance on neurobehavioural tests and increased reporting of subjective neurological symptoms, have also been seen in workers chronically exposed to aluminium dust or fumes. Neurological examinations in experimental animal studies have been limited to measurement of brain weight and/or brain histopathology and no neurobehavioural tests were performed. In view of the poor characterisation of the exposure in the human studies, ATSDR did not derive inhalation minimal risk levels for aluminium (14).

International Agency for Research on Cancer (IARC).
In an evaluation of the carcinogenic effects of PAHs performed in 2005, IARC concluded that there was sufficient evidence in humans for the carcinogenicity of occupational exposures during aluminium production. This conclusion was based on several epidemiological studies on aluminium production workers in plants in Canada, France, Italy, Norway and the US. Several of these studies showed increased risks for cancer of the lungs and the urinary bladder. In a meta-analysis, a positive exposure-response relationship between cumulative exposure to benzo[a]-pyrene, as an index of exposure to PAHs, and both urinary bladder and lung cancer was found. In addition, in some of the studies, increased risks were found for lymphatic and haematopoietic as well as pancreatic cancer (94).

Health Council of the Netherlands: DECOS's Subcommittee on the Classification of Reproduction Toxic Substances
In its evaluation from 2009, the subcommittee concluded that two studies indicated that aluminium can be excreted in human milk at levels exceeding 710 µg/l, which is a level considered by the committee to be safe for breastfed babies. Based on this finding, the subcommittee recommended to label water-soluble aluminium compounds for effects during lactation with R64 (may cause harm to breastfed babies).

Further, based on prenatal development toxicity studies, the subcommittee recommended classifying water-soluble aluminium compounds (in accordance with the Directive 93/21/EEC of the EU) for developmental toxicity into Category 2 (substances which could be regarded as if they cause developmental toxicity in humans) and labelling water-soluble aluminium compounds with T; R61 (may cause harm to the unborn child). Due to a lack of appropriate data, the committee recommended neither classifying water-soluble aluminium compounds for effects on fertility nor metallic aluminium and insoluble aluminium compounds for effects on fertility or on developmental toxicity (84).

10. Hazard assessment

10.1 Assessment of the health risk

Inhalation and dermal absorption have not been studied in detail. The percentage of aluminium absorbed following inhalation of fumes might be about 2 % but is likely to depend on solubility and size. The percentage for dermal exposure is not reported.

Animal studies showed no significant increases in aluminium in tissues or serum after inhalation exposure to aluminium oxide (insoluble) and aluminium chlorohydrate (soluble), indicating that lung retention rather than absorption was taking place. After oral exposure, 0.1–1 % of aluminium is absorbed (depending on aluminium compound ingested and composition of the diet). Furthermore,

aluminium may directly enter the brain via the olfactory tract. The aluminium crosses the nasal epithelium and reaches the brain via axonal transport.

In animals, elevated levels of aluminium were observed in the foetus, providing evidence of transplacental transfer of aluminium. Several studies also indicated that aluminium can be excreted in human milk.

No human studies were found on local effects on the eyes and on the respiratory tract after acute exposure. Aluminium compounds are widely used in antiperspirants without harmful effects to the skin. In animal experiments, solutions of 10 % of aluminium chloride (soluble) and nitrate (soluble) were damaging to the skin, while aluminium sulphate (soluble), chlorohydrate (soluble) and hydroxide (insoluble) were not. Human data do not indicate that aluminium or its compounds are strongly sensitising. In laboratory animals – a mouse local lymph node assay –, aluminium chloride (soluble) was not sensitising. This test, however, is considered less appropriate for detecting sensitising capacity of metals.

No human studies were found regarding mortality or toxicologically relevant systemic health effects after acute exposure to aluminium and aluminium compounds.

Rats exposed for 4 hours to 200 and 1 000 mg/m^3 aluminium flakes developed persistent microgranulomata in the respiratory tract at 14 days post-exposure. No effects were observed at levels of 100 mg/m^3 and below. Exposure to aluminium chlorohydrate (soluble) concentrations of 25 mg/m^3 (6.1 mg Al/m^3) did not induce (histological) effects on the eyes. There were no irritation studies following instillation of aluminium or its compounds into the eyes of laboratory animals. No mortality was induced in rats following 4-hour exposures to up to 1 000 mg Al/m^3 as aluminium oxide. No data on acute dermal toxicity were available. Oral LD_{50} values in rats and mice ranged from 261 to 980 mg/kg bw for several water-soluble aluminium compounds.

Numerous studies have examined the effects following occupational exposure to aluminium. They included workers exposed to aluminium oxide, aluminium fluoride, and partially oxidised aluminium metal fumes in primary aluminium production (potrooms and foundries), workers exposed to aluminium dusts in plants producing or processing aluminium powder, miners inhaling the so-called McIntyre powder (15 % elemental aluminium and 85 % aluminium oxide) as a prophylactic agent against silicosis, and welders exposed to welding aerosols containing respirable aluminium-containing particles and aluminium oxide fumes. Generally, it was shown that under the varying working conditions, aluminium can cause effects on the respiratory tract, such as impaired lung function and pulmonary fibrosis, and, less consistently, mild effects on the nervous system, such as impaired performance in neurobehavioural tests on psychomotor and cognitive skills and changes in quantitative EEG.

However, in some cases, other compounds such as hydrogen fluoride and hydrogen chloride (in potrooms/foundries) or manganese and ozone (in welding) or smoking may have played a role. Further, exposure data, especially those from past exposure, are lacking. The data did not show a consistent relationship be-

tween neurotoxic effects and aluminium concentrations in blood or urine, which unfortunately cannot be recalculated to exposure concentrations. Therefore, the epidemiological studies are considered to be inappropriate to assess clear dose-response relationships and to identify critical effect levels.

There are only a few, limited repeated animal inhalation studies, in which mainly effects on the respiratory tract were examined and/or observed. In a study with aerosolised aluminium chlorohydrate (water soluble) in a silicone-ethanol vehicle, no effects were seen in rats (n = 15/sex/group) concerning blood biochemistry endpoints or several organs/tissues including lungs and nose at exposure to 2.5 mg/m^3, 4 hours/day, 5 days/week for 22 days. However, in guinea pigs and rats (n = 10/species/sex/group, gross and histological observations are from only 5 animals/species/sex/group) exposed to 2.5 mg/m^3 aluminium chlorohydrate (soluble) dusts for 6 months, multifocal granulomatous pneumonia was observed in all animals. In addition, there were microgranulomas in the peribronchial lymph nodes. No effects were seen in the nasal cavities or the trachea. At 0.25 mg/m^3, the lowest concentration tested (corresponding to 0.061 mg Al/m^3), there was an indication of granulomatous change in the peribronchial lymph node of one rat and slightly increased alveolar macrophages in a few rats and guinea pigs.

In two limited and poorly reported studies, exposure of rats to ca. 1.3–2 mg/m^3 of aluminium fluoride (poorly soluble) or aluminium chloride (soluble) dusts or of an aqueous aluminium sulphate aerosol affected the lungs as well (increased weights, stiff lungs, fibrosis, increased number of alveolar macrophages and of abnormal macrophages and granulocytes). No fibrosis was seen in rats examined 42 weeks after an 86-week exposure to a refractory material containing 96 % aluminium oxide and about 4 % silica at concentrations of ca. 2.3 mg/m^3. There are no data from neurotoxicity inhalation studies. However, aluminium compounds are neurotoxic in orally exposed animals at high doses (LOAEL of 130 mg Al/kg bw/day).

Both human and experimental animal data indicate that the effects on the respiratory tract are the key effects. The oral studies, in which an adequate range of endpoints was examined following repeated exposure of rats, mice or dogs to various aluminium compounds (sodium aluminium phosphate, aluminium hydroxide, aluminium nitrate, aluminium lactate) in the diet or drinking water and which showed only - minimal - effects at relatively high doses (> 60 mg Al/kg bw/day), are therefore not relevant for identifying critical effect levels.

In studies in workers in the aluminium production industry, where there was co-exposure to carcinogenic compounds such as PAHs, increased cancer mortality rates were reported. No studies were found on the (potential) carcinogenic effects in other groups of workers occupationally exposed to aluminium.

In rats exposed to a refractory material consisting of 96 % aluminium oxide and 4 % silica at aluminium concentrations of ca. 2.3 mg/m^3 for 86 weeks, with an additional exposure-free period of 42 weeks, no increase in tumour incidences was found.

Intratracheal instillation of doses of 6 mg of ultrafine particles of aluminium oxide (insoluble) (mean diameter 0.013 μm), once a week for 5 or 10 times, increased the number of animals having one or more primary tumours when compared to controls (64 % and 55 %, respectively vs. 2 % in controls). Similar treatment with aluminium silicate (mean diameter 0.015 μm) had similar results (49 % in both groups).

Aluminium potassium sulphate (soluble) did not increase tumour incidences in mice given dietary doses as high as 979 mg Al/kg bw/day for 20 months or in rats (male) and mice (female) at drinking water doses of 0.6 and 1.2 mg Al/kg bw/day, respectively, for 2–2.5 years.

These human and experimental animal data do not allow firm conclusions on the potential carcinogencity of aluminium or its compounds.

Apart from conflicting results in *S. typhimurium* strains TA98 and TA100, aluminium chloride (soluble) was not mutagenic in other *S. typhimurium* strains, *E. coli* or in mouse lymphoma cells. Aluminium fluoride (poorly soluble) was not mutagenic in *S. typhimurium* or *E. coli*.

Aluminium chloride (soluble) and aluminium sulphate (soluble) induced increases in the frequency of micronuclei in human lymphocytes and fibroblasts by means of both clastogenic and aneuploidogenic mechanisms.

Aluminium (chloride) caused DNA damage and inhibited DNA repair. It induced DNA single strand breaks and cross-linked DNA and chromosomal proteins.

In vivo, levels ≥17 mg Al/kg bw, administered orally as its sulphate or potassium sulphate to rats or intraperitoneally as its sulphate to mice, increased the frequency of chromosomal aberrations in bone marrow cells of rats and mice, and of micronuclei and SCEs in bone marrow cells of mice (not tested in rats). Lower levels were not tested.

These data indicate that aluminium is not mutagenic but that especially the water-soluble sulphate is clastogenic. *In vitro* experiments showed among others that aluminium interacts with DNA phosphate groups, which can result in changes in DNA structure, or with the microtubuli, which can cause aneuploidy. The clastogenic effects might therefore be indirect effects for which no-effect levels may exist. However, the *in vivo* experiments were performed at high-dose ranges that did not include no-effect levels.

There were no inhalation reproduction toxicity studies or studies on the effects of metallic aluminium on fertility or development.

In studies with water-soluble compounds, doses of 19 mg Al/kg bw/day (as aluminium chloride) in the drinking water did not affect female or male reproductive capacity in mice. In rats, no effect was seen on male reproductive capacity at drinking water levels of ca. 23 mg Al/kg bw/day (as soluble aluminium chloride). Regarding compounds not soluble in water, dietary administration of doses of 27 mg Al/kg bw/day (as basic sodium aluminium phosphate) did not result in testis weight or histological changes in male beagle dogs.

In prenatal developmental toxicity studies in which water-soluble aluminium compounds were orally administered to dams during gestation, effects on foetuses (decreased weights and retarded ossification) were only observed at dose levels inducing general toxicity effects (13 mg Al/kg bw/day in rats, 29 mg Al/kg bw/day in mice). In postnatal studies, investigating (neuro)developmental and/or (neuro)behavioural effects in the offspring of dams treated with water-soluble aluminium compounds during gestation or during gestation and lactation, no effects were seen on reproductive parameters such as pregnancy rate, absorptions, implantation sites, litter size and pup weight at birth. Generally, effects on postnatal development such as pup weight gain, pup mortality and (neuro)behaviour were observed in the presence of general toxicity. However, pup mortality and neurodevelopmental and behavioural effects were also seen at doses not inducing general toxicity. In mice, dietary amounts of 10 mg Al/kg bw/day did not induce effects. In rats, there was impaired motor development at gavage doses of 36 mg Al/kg bw/day, but not at doses of 18 mg/kg bw/day. Regarding compounds not soluble in water, no effects on prenatal development were seen following administration of aluminium hydroxide by gavage on gestational days 6–15 at the highest levels tested, i.e. ca. 100 mg Al/kg bw/day in mice and ca. 270 mg Al/kg bw/day in rats.

The available human data are considered insufficient to identify critical effect levels for aluminium metal and aluminium compounds. With respect to animal data, the committees are aware of the discussion on particle overload and effects in rats at high aluminium exposure, mostly about carcinogenic effects. There is also discussion whether non-neoplastic effects are relevant for humans or not. Especially in this case where the effects observed concern clearance mechanisms which differ between man and rat. However, the effects were seen at relatively low levels in rats as well as in guinea pigs and included infiltration of inflammatory cells and granuloma formation. Because pulmonary effects were also reported in occupationally exposed workers, the animal study of Steinhagen *et al* (190) is considered relevant to identify the critical effect level. In this study performed with aluminium chlorohydrate, a NOAEL could not be identified. At 0.25 mg/m^3, the lowest level tested (corresponding to 0.061 mg Al/m^3), there was an indication of granulomatous change in the peribronchial lymph node of 1/10 rats examined. Since these changes were seen at higher incidences at 2.5 mg/m^3 (the next higher concentration tested), 0.25 mg/m^3 is considered to be a minimal LOAEL, i.e. probably close to the NOAEL. The exposure duration of 6 months is considered sufficient for assessment of long-term exposure.

Aluminium chlorohydrate is regarded to be soluble. Commercially, it is, amongst others, available as solutions that remain clear and free of precipitate after years of storage at room temperature. However, aqueous dilution and/or an increase in pH to higher levels (pH 5–6) result in precipitation of forms of aluminium hydroxide (176). DECOS and NEG infer that a similar process may take place under the physiological conditions in the lung and that the effects seen in the study above are in fact likely to be caused by insoluble forms of aluminium hydroxide. Other

aluminium compounds may behave in the lungs in a similar way. However, too little is known regarding the factors that determine the aluminium toxicity in the lungs to allow extrapolation to other aluminium compounds. Therefore, the committees conclude that, except for aluminium chlorohydrate, the data are insufficient as a basis for occupational exposure limit(s) for aluminium metal or aluminium compounds. Still, NEG notes that workers exposed to aluminium oxide, 1-2 orders of magnitude above the minimal LOAEL for pulmonary toxicity of the chlorohydrate, exhibited similar lung effects. This indicates that aluminium oxide is less toxic than the chlorohydrate (1, 22, 115).

10.2 Groups at extra risk

Individuals with renal failure may be at extra risk for aluminium toxicity.

10.3 Scientific basis for an occupational exposure limit

The data are insufficient as a scientific basis for occupational exposure limits for aluminium metal or aluminium compounds other than aluminium chlorohydrate (soluble). For aluminium chlorohydrate, a minimal LOAEL for pulmonary effects in rats was indicated at 0.25 mg/m^3 (0.061 mg Al/m^3), the lowest level tested. Due to lack of data, no assessment can be made for other water soluble aluminium compounds.

The effects of aluminium chlorohydrate were probably caused by insoluble forms of precipitated aluminium hydroxide. The committees infer that insoluble or poorly soluble forms of aluminium might act similarly in the lungs and therefore might have similar effect levels as aluminium chlorohydrate. However, NEG notes that data on workers indicate that aluminium oxide is less toxic.

The scientific data do not suggest the need for a short-term exposure limit for aluminium and aluminium compounds.

11. Recommendation for research

No recommendations for research are made.

12. Summary

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Safety. 145. Aluminium and aluminium compounds. Arbete och Hälsa 2011;45(7):1-142.

Aluminium (Al) is silvery, light, malleable and ductile, and the most abundant metal in the earth's crust. Al is used primarily for metallurgical purposes, especially to produce Al-based alloy castings and wrought Al. Al compounds are found in consumer products such as antacids, astringents, buffered aspirin, food additives and antiperspirants. Powdered Al metal is often used in explosives and fireworks.

No human data were available on respiratory tract and eye irritation following acute/single exposure to Al or Al compounds. Despite the wide use of Al, the small number of reports on effects indicates that Al is not harmful to the skin.

Occupational high-level inhalatory exposure to Al can cause lung disorders such as impaired lung function and pulmonary fibrosis. In the most relevant repeated animal inhalation study, rats and guinea pigs were exposed to 0.25, 2.5 or 25 mg/m^3 Al chlorohydrate for 6 months. All animals in the two higher dose groups had multifocal granulomatomous pneumonia and microgranulomas in the peribronchial lymph nodes. At the lowest dose, these effects were regarded as minimal. Thus, 0.25 mg/m^3 (0.061 mg Al/m^3) is probably close to the no-effect level.

Some field studies suggest that Al induce subclinical neurotoxic effects, but no exposure-response relationships could be established and co-exposure to other compounds may have played a role. Al compounds are neurotoxic in orally exposed animals at high doses. There are no animal inhalation neurotoxicity studies.

Available data indicate that Al is not mutagenic, but that especially the water-soluble sulphate may cause chromosomal damage. Human and experimental animal data do not allow firm conclusions on the potential carcinogenicity of Al or its compounds. Increased cancer mortality rates in workers in the Al production industry especially for lung and urinary bladder is generally considered to be caused by co-exposure to carcinogenic compounds such as polycyclic aromatic hydrocarbons.

No studies were found on the effects of occupational exposure to Al or Al compounds on reproductive capacity, pregnancy outcome or postnatal development. In animals, there are studies in which Al compounds were administered in the diet or drinking water. Water-soluble Al compounds have induced postnatal development effects. No effects on prenatal development were reported.

Overall, the data are insufficient to identify a critical effect level except for Al chlorohydrate for which minimal pulmonary effects were seen in an animal study at 0.061 mg Al/m^3.

Keywords: aluminium, fibrosis, lung function, neurotoxicity, occupational exposure limit, pulmonary, review, risk assessment, toxicity

13. Summary in Swedish

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Safety. 145. Aluminium and aluminium compounds. Arbete och Hälsa 2011;45(7):1-142.

Aluminium (Al) är silverglänsande, lätt och formbart och den vanligaste metallen i jordskorpan. Al används främst inom metallurgi, i synnerhet för att tillverka Al-baserade gjutlegeringar och smidesaluminium. Al-föreningar finns i konsumentprodukter som vissa läkemedel, livsmedelstillsatser och antiperspiranter. Al-pulver används ofta i sprängämnen och fyrverkerier.

Det saknas humandata för ögon- och luftvägsirritation efter akut/enstaka exponering för Al eller dess föreningar. Den omfattande användningen i kombination med få rapporter om effekter tyder på att Al inte är skadligt för huden.

Hög yrkesmässig exponering för Al via inandning kan orsaka lungsjukdom som försämrad lungfunktion och lungfibros. I den mest relevanta djurstudien exponerades råttor och marsvin via inandning för 0,25, 2,5 och 25 mg/m^3 Al-klorhydrat i 6 månader. Vid de två högsta doserna hade alla djur multifokal granulomatös lunginflammation och mikrogranulom i peribronkiella lymfknutor. Vid den lägsta dosen bedömdes dessa effekter vara minimals, dvs. 0,25 mg/m^3 (0,061 mg Al/m^3) är troligen nära icke-effektnivån.

En del fältstudier antyder att Al ger upphov till subkliniska neurotoxiska effekter, men dos-responssamband har inte kunnat fastställas och samtidig exponering för andra ämnen kan ha haft betydelse. Al-föreningar i höga doser är neurotoxiska på djur vid oral tillförsel. Inhalationsstudier på djur saknas.

Tillgängliga data indikerar att Al inte är mutagent, men att särskilt den vattenlösliga sulfaten orsakar kromosomskador. Det går inte att dra några bestämda slutsatser om Al och dess föreningar är carcinogena utifrån studier på människa och djur. Den ökade dödligheten i cancer bland arbetare i Al-produktion, i synnerhet i lunga och urinblåsa, anses vara orsakad av samtidig exponering för cancerframkallande ämnen såsom polycykliska aromatiska kolväten.

Inga studier om effekter vid yrkesmässig exponering för Al eller dess föreningar har påträffats avseende reproduktionsförmåga, graviditetsutfall eller utvecklingen hos nyfödda. I djurförsök har Al-föreningar endast getts via födan eller dricksvattnet. Vattenlösliga Al-föreningar har då orsakat utvecklingsstörningar hos nyfödda. Inga effekter på fosterutveckling har rapporterats.

Sammanfattningsvis är data otillräckliga för att identifiera någon kritisk effektnivå utom för Al-klorhydrat för vilken minimala lungeffekter påvisats hos djur vid 0,061 mg Al/m^3.

Keywords: aluminium, fibros, hygieniskt gränsvärde, lungfunktion, neurotoxicitet, riskbedömning, toxicitet, översikt

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16. Data bases used in search of literature

This document has been based on publicly available scientific data. Except for sections related to reproduction toxicity, the evaluation of the toxicity of aluminium and aluminium compounds builds on the review by ATSDR from 1999 (13), which was superseded by an update in 2008 (14). The data on reproduction toxicity have been extracted from the evaluation by DECOS's Subcommittee on the Classification of Reproduction Toxic Substances, published in 2009 (84).

Additional data were obtained from the on-line databases Toxline, Medline, Chemical Abstracts, and TSCATS, covering the period January1998 to June 2005. The following chemical names and Chemical Abstracts Service (CAS) registry numbers were used:

alumin(i)um (7429-90-5),
alumin(i)um chloride (7446-70-0),
alumin(i)um chlorohydrate (1327-41-9, 11097-68-0, 84861-98-3),
alumin(i)um hydroxide (21645-51-2),
alumin(i)um lactate (18917-91-4),
alumin(i)um nitrate (13473-90-0),
alumin(i)um oxide (1344-28-1),
alumin(i)um phosphate (7784-30-7),
alumin(i)um fluoride (7784-18-1),
alumin(i)um sulphate (10043-01-3),
alumin(i)um carbonate (53547-27-6),
alumin(i)um potassium phosphate (10043-67-1),
alchlor (52231-93-3),
alumin(i)um pyro powder,
alumin(i)um flake powder, and
alumin(i)um welding fume

in combination with the following key words: expos*, kinetic*, toxic, animal, human, adverse effects.

This resulted in a very large amount of hits. Considering the scope of the present evaluation, literature references containing one of the following key terms were therefore excluded: transgenic; *in vitro*; alumin(i)um - pharmacology; therapeutic; dose-response relationship - drug; cells - cultured; drug effects; brain - drug effects; cell survival - drug effects; neurons - drug effects; cell division - drug effects; body weight - drug effects; plant roots - drug effects; vaccines - adverse effects; renal dialysis; renal dialysis - adverse effects; drug interactions; drug resistance - genetics; treatment outcome; ecology; crops - agricultural; soil; marine biology; adsorption; plant roots - growth and development; plant roots, metabolism; water; fresh water.

From June 2005 onwards, several updating searches were performed in PubMed. The final search was performed in April 2009.

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Appendix 1. Tables with human, *in vitro* and animal data

Effects of aluminium and aluminium compounds in humans, *in vitro* and in animal are summarised in Tables I-VII.

Table I. Human case reports.

Table II. Human studies on (non-carcinogenic) respiratory tract effects after long-term exposure.

Table III. Human studies on neurotoxic effects after long-term exposure.

Table IV. *In vitro* studies.

Table V. Animal studies on toxicity due to repeated exposure: inhalation studies.

Table VI. Animal studies on toxicity due to repeated exposure: oral studies.

Table VII. Animal studies on toxicity due to repeated exposure: parenteral studies.

Table I. Human case reports.

Human involved	Procedure	Effects	Remarks	Ref.
Inhalation				
46-year-old smoker (non-atopic)	Working as a caster of molten Al for 19 years in a rolling mill.	Occupational asthma: baseline spirometry showed airflow obstruction (FEV_1/FVC 2.56/4.72, predicted 3.53/4.32); moderate histamine reactivity (PC20 1.2 µmol); 2 hourly PEF measurements showed a significant occupational effect (software OASYS-2 score 2.67, positive > 2.51) with a diurnal variation of less than 20 %. Specific bronchial provocation testing showed a dual asthmatic reaction after a 3-min exposure to $AlCl_3$ (10 mg/ml), with a negative reaction to potassium chloride (10 mg/ml) at the same pH.	Subject was reassigned to work as a fork-lift truck driver outside the foundry. Non-specific reactivity returned to normal and serial PEF record showed no work-related effect, but asthmatic symptoms in relation to non-specific stimuli remained.	(31)
40-year-old worker	Working as a stamper for 14 years in a plant producing Al pyro powder. Exposure to high levels of Al: plasma: 41.0 µg/l (upper reference value: 10 µg/l) and urine: 407 µg/l (upper reference value: 15 µg/l).	Exercise-induced shortness of breath; reduction (57.5 %) of the vital capacity. Chest X-ray showed unspecific changes; small centrilobular, nodular opacities and slightly thickened interlobular septae.	Exposure to other fibrotic agents could be excluded.	(108)
2 co-workers, employed by the same Al shipbuilding facility	Chronic exposure to high unspecified concentrations of fumes during Al arc welding.	Severe pneumoconiosis characterised by diffuse pulmonary accumulation of Al metal and a corresponding reduction in lung function (Al fume-induced pneumoconiosis). Highest concentratio ns of Al particles in lung tissue (average of 9.26 billion Al particles per cm^3 of lung tissue) among 812 similar analyses in a pneumoconiosis database. One patient had an original clinical diagnosis of sarcoidosis but no evidence of granulomatous inflammation. Both patients died.	One subject smoked 4 cigarettes per day for 5 years. Other subject had a smoking history of 13–40 pack-years.	(91)

Table I. Human case reports.

Human involved	Procedure	Effects	Remarks	Ref.
Dermal exposure				
34-year-old man with a 2-year history of eczema of both hands and the right elbow flexure	At work, the man had used a compressor air pistol with his right hand to blow fillings out of newly milled narrow Al threads.	Erythema, hyperkeratosis, fissuring and partial desquamation on the hands. Patch testing was positive for Al.	-	(152)
43-year-old woman	Application of 1 g of a 20 % Al chlorohydrate-containing antiperspirant cream on each underarm, constituting a daily dose of 0.108 g of Al(III), which over a 4-year period amounted to 157 g Al.	Severe hyperaluminaemia (increase in plasma and urine Al concentrations), bone pain, extreme fatigue. Underarms, which were shaved regularly, did not have any rash or skin irritation.	-	(80)
8-year-old boy	Trauma of the hands in combination with exposure (hands) to Al dust.	Both hand palms had erythematous, oedematous, deep-seated, tender nodules and plaques over the thenar and hypothenar eminences, as well as over the palmar aspects of the metacarpophalangeal joints. Histopathology: a moderately heavy infiltration of neutrophils and some lymphocytes surrounding the eccrine structures in the dermis, with the most pronounced inflammation in the deep dermis around the eccrine coils. These findings were consistent with eccrine hidradenitis. Special staining was negative for bacterial and fungal microorganisms.	Patient had engaged in excessive physical activity at a baseball camp, primarily with overuse of his hands. Presumably this contributed to the sudden occurrence of skin lesions.	(174)
9-year-old boy	Patch test.	A single Finn Chamber was applied alone on Scanpor tape. A positive reaction as an infiltrated ring of papules at the area of most intense contact with the rim of the Al Finn Chambers at 48 and 96 hours indicated contact allergy to Al.	Al sensitivity attributed to exposure to Al-absorbed vaccines even though the patient had received his childhood vaccinations without any adverse effects.	(7)

Table I. Human case reports.

Human involved	Procedure	Effects	Remarks	Ref.
19-year-old woman with intermittent face dermatitis (flushes) and leg dermatitis	Patch test.	Patch testing with $AlCl_3$ in plastic chambers showed an allergic reaction by all three test concentrations.	-	(92)
Other routes (injections)				
26-year-old woman	Vaccination against hepatitis B with 2 intramuscular injections at monthly intervals.	Pruritic, sore, erythematous, subcutaneous nodules at the injection site which persisted for 8 months.	All the cases involved Al-absorbed vaccines.	(185)
33-year-old woman	Vaccination as described above.	Pruritic, painless papules and nodules at the injections site which resolved within 6 months. In the weeks following a booster 1 year later, papules, nodules and brown hyperpigmentation at the injection site which persisted for 8 months.		(185)
27-year-old woman	3 monthly intramuscular vaccinations against hepatitis B.	1 month after the 3rd vaccination, a painful erythematous nodule developed, which became a brown hyperpigmental plaque with hypertrichosis and subcutaneous granuloma, which persisted for over 1 year.		(185)
27-year-old woman	3 injections at monthly intervals.	2 weeks after the booster, pruritic, inflammatory infiltrated nodules appeared which increased pre-menstrually and persisted for 2 years. Patch tests showed 3 positives to 1 % aq. $AlCl_3$, 2 to 10 % aq. or pet. Al_2O_3, and 3 to blank Finn Chambers.		(185)
19-year-old and 37-year-old women	Immunisation with vaccines adsorbed on $Al(OH)_3$ for the treatment of extrinsic asthma and rhinitis for 4 and 10 years, resp.	Development of multiple itching nodules. Lesions were persistent and lasted for several years. Histopathological findings: foreign body reaction. Al was most probably involved in the pathogenesis of these lesions because its presence could be demonstrated in macrophages using energy-dispersive X-ray microanalysis.		(134)

FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, PC20: the histamine provocation concentration producing a 20 % fall in FEV_1, PEF: peak expiratory flow.

Table II. Human studies on (non-carcinogenic) respiratory tract effects after long-term exposure (in chronological order).

Study design/study population	Exposure assessment	Effects/Results	Remarks	Ref.
Cross-sectional study/ *Exposed:* 261 miners in Ontario, Canada. *Controls:* 346 unexposed miners.	Between 1944 and 1979, miners inhaled McIntyre powder (15 % elemental Al and 85 % Al_2O_3) as a prophylactic agent against silicotic disease for 10 or 20 min before each underground shift. The concentration of Al particles inhaled was estimated to be ca. 350 mg/m^3. For a 10-min exposure, the amount of Al retained in the lung was calculated to be about 20 mg assuming a tidal volume of 450 cm^3/breathe and 12 breaths/min. This corresponds to 2 mg/m^3 over an 8-hour workday assuming the conventional inhalation volume of 10 m^3.	With regard to respiratory effects, no adverse health effects on the lung observed.	-	(22, 160)
Cross-sectional study/ *Exposed:* 32 workers of an Al powder plant. Median exposure duration 12.6 (range 2–41.3) yrs and median age 41.5 (range 26–60) yrs. *Controls:* 30 workers of the same plant, not exposed to Al. Median age 42.5 (range 26–60) yrs.	*Al levels in workplace air, mean (range):* 12.1 (5–21) mg/m^3 (n = 11) *Al levels exposed, median (range):* plasma: 8.7 (5.1–25.9) µg/l urine: 109.9 (5.0–337) µg/l or 87.6 (4.6–605) µg/g creat. *Al levels controls, median (range):* plasma: 4.3 (1.6–25.9) µg/l urine: 7.6 (2.6–73.8) µg/l or 9.0 (1.9–51.8) µg/g creat.	Decreased FEV_1, MEF_{25}, MEF_{50}, and MEF_{75}. No diagnosis of lung fibrosis in any of the test persons.	Investigations included among others comprehensive anamnesis, whole body plethysmographic lung function test and X-ray thorax photography. Smoking contributed more to statistically significant difference in FEV_1 and MEF_{25} than exposure to Al.	(113)
Cross-sectional study/ *Exposed:* 55 male workers from an Al factory in Seydisehir, Turkey. *Controls:* 30 healthy male controls living and working far from the factory.	*Serum Al levels:* Al workers: 72.7 ± 9.9 µg/l Controls: 31.1 ± 3.9 µg/l	Spirometric parameters were significantly lower in workers than in controls ($p < 0.001$) and correlated negatively with both exposure time and serum Al levels.	Co-exposure to hydrogen fluoride, carbon monoxide, carbon dioxide, sulphur oxide and oxides of nitrogen.	(140)

Table II. Human studies on (non-carcinogenic) respiratory tract effects after long-term exposure (in chronological order).

Study design/study population	Exposure assessment	Effects/Results	Remarks	Ref.
Cross-sectional study/ *Exposed:* 147 workers of a modern German prebake Al plant (78 potroom workers, 24 foundry workers, 45 carbon-plant workers). *Controls:* 56 workers of the same plant (watchmen, craftsmen, office workers, laboratory employees).	No Al exposure assessment. Only urinary fluoride monitoring.	Potroom workers had significantly lower pre-shift results with regard to FVC (99.5 % vs. 107.2 % predicted, $p < 0.05$) and PEF (85.2 % vs. 98.4 % predicted, $p < 0.01$) as compared to controls. In a multiple regression model, a small but significant negative correlation was found between post-shift urinary fluoride concentrations and FVC, FEV_1 and PEF. Across-shift spirometric changes only in FVC among carbon-plant workers (103.0 ± 13.3 % predicted pre-shift value vs. 101.2 ± 13.6 % predicted post-shift value, $p < 0.05$).	Correction for smoking habits. Co-exposure to cryolite, fluorides, fumes, and gases (mainly hydrogen fluoride and sulphur dioxide).	(157)
Cross-sectional study/ *Exposed:* 75 potroom workers of a German prebake Al smelter (23 never-smokers, 38 current smokers, 14 ex-smokers). *Controls:* 56 workers of same smelter (watchmen, craftsmen, office workers, laboratory employees; 18 non-smokers, 21 current smokers, 17 ex-smokers).	No data presented.	No effects of potroom work on the prevalence of respiratory symptoms. Smokers in the potroom group had a lower prevalence of respiratory symptoms than never-smokers or ex-smokers, being significant for wheezing (2.6 % vs. 17.4 % and 28.6 %, resp., both $p < 0.01$), whereas respiratory symptoms in controls tended to be highest in smokers. Impairment of lung function found only in non-smokers, with lower results for FVC (98.8 % predicted), FEV_1 (96.1 % predicted) and PEF (80.2 % predicted) compared to controls (114.2, 109.9 and 105.9 % predicted, each $p < 0.001$). Effects of smoking on lung function only detectable in non-exposed controls (current smokers vs. non-smokers: FVC 98.8 % vs. 114.2 % predicted, $p < 0.01$; FEV_1 95.5 % vs. 109.9 % predicted, $p < 0.05$).	Effects of both smoking and occupational exposure on respiratory health may be masked in subjects with both risk factors, probably due to strong selection processes which result in least susceptible subjects continuing to smoke and working in an atmosphere with respiratory irritants (healthy worker effect). Co-exposure to cryolite, fluorides, fumes and gases (mainly hydrogen fluoride and sulphur dioxide).	(158)

Table II. Human studies on (non-carcinogenic) respiratory tract effects after long-term exposure (in chronological order).

Study design/study population	Exposure assessment	Effects/Results	Remarks	Ref.
Cross-sectional study/ *Exposed:* 2 964 current employees of 3 Al refineries in Western Australia. 2 388 males and 192 females provided complete data sets. 138 of the women worked in the administration process group, it was therefore decided to confine further analysis to men only. Median duration of employment 10 (range 0–33) yrs. *No controls*.	*Range of geometric means in different process groups (4-hour TWAs)* *Refinery 1:* Bauxite: 0.69–2.85 mg/m^3 Al: 1.56–2.18 mg/m^3 Caustic mist (NaOH): 0.34 mg/m^3 *Refinery 2:* Bauxite: 0.66–4.0 mg/m^3 Al: 0.98–1.37 mg/m^3 Caustic mist (NaOH): 0.34 mg/m^3 *Refinery 3:* Bauxite: 0.68–0.9 mg/m^3 Al: 1.2 mg/m^3 Caustic mist (NaOH): 0.09–0.4 mg/m^3 (15-min samples)	Work-related wheeze, chest tightness, shortness of breath and rhinitis reported by 5.0 %, 3.5 %, 2.5 % and 9.5 % of participants, resp. After adjustment for age, smoking and atopy, most groups of production workers reported a greater prevalence of work-related symptoms than did office employees. After adjustment for age, smoking, height and atopy, subjects reporting work-related wheeze, chest tightness and shortness of breath had significantly lower mean levels of FEV_1 (186, 162 and 272 ml, resp.) than subjects without these symptoms. Significant differences in FVC and FEV_1/FVC ratio, but not FEV_1, found between different process groups. Reduction in FEV_1/FVC was not related to any one of the particular exposures that had been estimated for the process groups.	Exposure to aluminium, bauxite and caustic mist (NaOH) was quantified. Smoking associated with an increased prevalence of work-related symptoms, and a deficit in the level of lung function among all employees. Atopic subjects were more likely to experience work-related symptoms than non-atopic subjects and had a lower FEV_1/FVC ratio. Uneven distribution of atopy between the various process groups and between refineries, suggesting selection factors before employment may account for some of the differences in symptom prevalence between groups.	(132)

Table II. Human studies on (non-carcinogenic) respiratory tract effects after long-term exposure (in chronological order).

Study design/study population	Exposure assessment	Effects/Results	Remarks	Ref.
Cross-sectional study/ *Exposed:* community of Ouro Preto, Brazil, located near an Al plant (hospital admissions in 1997 for selected respiratory diseases). *Controls:* communities far from any source of industrial air pollution: - Diamantina, Brazil, used for qualitative assessment of exposure to air pollution. - Vicosa, Minas Gerais, used for hospital admissions in 1997 for selected respiratory diseases.	Dust collected (n = 36 in each location) and analysed for Al, Mn, Mg and Ca content. Significantly different ($p < 0.05$) levels of Al in the 2 communities (21.7 ± 25.5 µg vs. 9.7 ± 6.4 µg on a filter over 30 days). The highest quantities were found near the Al plant. Furthermore, both 24-hour maximum values and annual mean concentrations of suspended particulate matter exceeded the average of international standards in Ouro Preto and fluorides exceeded standards by as much as 600 %.	Relative risk of hospital admissions for selected respiratory diseases: 4.11 (95 % CI 2.96–5.70). Risk was highest among individuals 30–39-years old (relative risk 11.70, 95 % CI 1.52–89.96). Admissions per thousand residents were highest for individuals younger than 10 years of age and for individuals older than 70 years.	2 control communities used for practical reasons. Co-exposure to other dust particulate matter and fluorides. Unability to determine whether Al was present in the more dangerous, inhalable particulate matter. Respiratory diseases often cause symptoms for which patients seek treatment outside a hospital. In Ouro Petro, less hospital beds were available.	(153)
Cross-sectional study/ *Exposed:* 50 male shipyard workers from Messina, Italy. Average age 31.82 ± 5.05 yrs and average occupational exposure 11.8 ± 3.71 yrs. *Controls:* 50 subjects not subject to exposure, homogenous in terms of age and gender.	*Range of Al air levels for 5 different shipyard areas:* 6.2–20.2 mg/m^3 (sampling time: 120 min) *Average Al blood levels:* exposed: 32.64 ± 8.69 µg/l unexposed: < 7.5 µg/l	No significant pathological conditions. Statistical comparison of the spirometric parameters (VC, FVC, FEV_1 and $FEF_{25–75}$ showed a significant decrease ($p < 0.01$) in the examined values in exposed workers. This decrease was found to be directly proportional to the blood Al level.	No information reported on co-exposure. Subjects with a history of allergic and/or respiratory disorders and those who smoked over 3 cigarettes per day were excluded.	(1)
Case-control study/ *Cases:* 13 males with potroom asthma from an Al smelter in Spokane, Washington, US (age 19–45 yrs). *Controls:* 38 males, 1 female without potroom asthma from the same smelter (age 19–45 yrs).	No data presented.	No differences observed in genotyping for the β2-adrenoreceptor, high-affinity immunoglobulin (Ig)E receptor and TNFα on potroom workers with an asthma-like condition and on individuals who did not develop respiratory problems.	Workers in potrooms are exposed to various air pollutants. Previous or current use of any tobacco product, including cigarettes, was common among the subjects (39 % of cases, 46 % of controls). A small number of subjects were studied.	(12)

Table II. Human studies on (non-carcinogenic) respiratory tract effects after long-term exposure (in chronological order).

Study design/study population	Exposure assessment	Effects/Results	Remarks	Ref.
Analysis of bronchial biopsy specimens from: *20 asthmatic Al potroom workers* (8 non-smokers, 12 smokers) *15 healthy Al potroom workers* (8 non-smokers, 7 smokers) *10 non-exposed controls* (all non-smokers)	Not estimated.	Median reticular basement membrane thickness significantly increased in both asthmatic workers (8.2 µm) and healthy workers (7.4 µm) compared to non-exposed controls (6.7 µm). Significantly increased median density of lamina propria CD45+ leukocytes (1 519 vs. 660 and 887 cells/mm^2) and eosinophils (27 vs. 10 and 3 cells/mm^2) and significantly increased concentrations of exhaled NO (18.1 vs. 6.5 and 5.1 ppb) in non-smoking asthmatic workers compared to non-smoking healthy workers and non-exposed controls. Significantly increased numbers of eosinophils in lamina propria in asthmatic smokers compared to non-exposed controls (10 vs. 3 cells/mm^2). Leukocyte counts and exhaled NO concentrations varied with smoking habits. Fewer leukocytes observed in asthmatic smokers than in non-smokers. Both eosinophilic and non-eosinophilic phenotypes of asthma recognised in potroom workers. Signs of airway inflammation also observed in healthy workers.	Potroom workers are exposed to a complex mixture of particulates and gases.	(178)

Table II. Human studies on (non-carcinogenic) respiratory tract effects after long-term exposure (in chronological order).

Study design/study population	Exposure assessment	Effects/Results	Remarks	Ref.
Cross-sectional study/ *Exposed:* 62 male workers of 2 Al powder-producing plants in Germany (20 non-smokers, 32 current smokers, 10 ex-smokers). Median exposure duration 123 (range 13–360) months, median age 41 (range 22–64) yrs and mean age 41.4 ± 9.9 yrs. *No controls.*	No workplace air monitoring. *Median (range) Al levels:* plasma: 12.5 (2.5–84.4) µg/l urine: 83.3 (3.7–630) µg/l or 104 (7.9–821) µg/g creat.	No clinically relevant findings from immunological tests. 15 (24 %) workers had chronic bronchitis, 4 (6.5 %) dyspnoea during exercise. 15 workers, among which 5 with chronic bronchitis and 4 with dyspnoea, had HRCT findings characterised by small rounded and ill-defined centrilobular nodular opacities, mainly in the upper lobes. With respect to lung function analysis, these workers showed only differences in VC (decrease, $p < 0.01$) when compared to workers without HRCT findings. Exposure years and Al plasma and urine concentrations appeared best predictors for HRCT findings. Age and decreased VC were of borderline significance.	Study aimed to investigate the possibility to detect HRCT findings in Al powder workers, which are consistent with early stages of lung fibrosis. Investigation included a standardised questionnaire, physical examination, lung function analysis (VC, FEV_1, Rtot, total lung capacity), chest X-ray, HRCT, immunological tests, and determination of Al in plasma and urine. All participants exposed to non-greased and at least barely greased powder. Affected workers were mainly workers exposed to barely or non-greased powders in the stamping workplace with highest Al dust levels (most of it with diameters < 5 µm).	(107)

Table II. Human studies on (non-carcinogenic) respiratory tract effects after long-term exposure.

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
Longitudinal study with 3 cross-sectional studies integrated within intervals of 2 years each. *Exposed:* 101 male Al welders of car-body construction industry with exposure duration 7–118 months, median age 35 (range 23–51) yrs, and 83 % smokers and ex-smokers (at study start). *Controls:* 50 male workers of same facility with median age 35 yrs (at study start).	*Median (range) workplace Al levels (as total dust with personal air sampler "Alpha 1" with a welding fume sampling head)* 1999: 0.47 (0.1–6.2) mg/m^3, n = 50 (start of the study) 2001: 0.67 (0.2–1.5) mg/m^3, n = 26 2003: 0.55 (0.15–0.96) mg/m^3, n = 26 *Median (range) pre-shift Al levels in exposed: plasma* 1999: 10.3 (2.3–20.7) µg/l, n = 101 2001: 4.3 (1.1–11.2) µg/l, n = 97 2003: 4.3 (1.7–11.4) µg/l, n = 93 *Median (range) pre-shift Al levels in exposed: urine* 1999: 71.8 (12.1–224) µg/l or 38.4 (12.9–112) µg/g creat., n = 101 2001: 58.3 (2.4–244.0) µg/l or 35.0 (5.1–195) µg/g creat., n = 96 2003: 21.7 (2.8–775) µg/l or 12.6 (1.9–646) µg/g creat., n = 99 *Median (range) post-shift Al levels in exposed: plasma* 1999: 8.3 (2.3–42.3) µg/l, n = 100 2001: 4.1 (0.7–11.7) µg/l, n = 78 2003: 4.3 (1.8–15.6) µg/l, n = 66 *Median (range) post-shift Al levels in exposed: urine* 1999: 47.6 (7.0–182) µg/l or 37.9 (7.0–120) µg/g creat., n = 101 2001: 39.8 (3.1–200) µg/l or 33.6 (9.0–230) µg/g creat., n = 79 2003: 16.1 (0.5–203) µg/l or 15.4 (0.7–94.9) µg/g creat., n = 69 *Median (range) post-shift Al levels in controls: plasma* 1999: 4.4 (2.3–20.7) µg/l, n = 50 2001: 2.3 (0.7–5.4) µg/l, n = 48 2003: 3.8 (1.6–10.0) µg/l, n = 47 *Median (range) post-shift Al levels in controls: urine* 1999: 9.0 (2.8–40.2) µg/l or 5.2 (1.7–30.3) µg/g creat., n = 50 2001: 7.3 (2.2–93.6) µg/l or 6.0 (1.6–60.9) µg/g creat., n = 47 2003: 9.3 (0.5–95.4) µg/l or 5.0 (0.2–40.3) µg/g creat., n = 49	Welders reported, partly significantly, more respiratory symptoms; in 2003, decrease in complaints. No evidence of an increased occurrence of restrictive pulmonary ventilation disorders, but in welders, worse results in the flow-volume curve, especially for the MEF_{25} and MEF_{50} at all investigations. No changes in FEV_1 and VC. HRCT revealed an increase in the incidence of emphysematous lung changes during the observation period (1999: 31.7 %; 2003: 58.8 %). In one welder, signs suspicious of an early stage of lung fibrosis.	Investigations included, amongst others, standardised medical history, physical examination, parameters of pulmonary function, HRCT of the lung of welders, determination of Al levels in urine and plasma. 98/101 welders completed first investigation. No relevant loss of test persons during the course of study but only 68/98 were still working as welders in 2003. Co-exposure to ozone (5-min TWAs (time weighted averages)): 1999: 38–75 mg/m^3, n = 3 2001: 32–126 mg/m^3, n = 6 2003: 16–68 mg/m^3, n = 6	(115)

Table II. Human studies on (non-carcinogenic) respiratory tract effects after long-term exposure.

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
Longitudinal study with 3 cross-sectional studies integrated within intervals of 2 years each. *Exposed:* 46 welders of 5 railway vehicle engineering and special vehicle production companies with median age 40 yrs (at study start). *Controls:* 37 workers of same companies with median age 38 yrs (at study start).	*Median (range) workplace air dust levels* 1999: 5.4 (0–31.5) mg/m^3, n = 37 (start of study) 2001: 5.4 (1.3–273) mg/m^3, n = 22 2003: 6.8 (1.9–29.7) mg/m^3, n = 19 *Median (range) pre-shift Al levels in exposed: plasma* 1999: 9.6 (4.1–31.0) µg/l, n = 32 2001: 10.6 (3.3–40.3) µg/l, n = 34 2003: 10.8 (4.0–39.3) µg/l, n = 28 *Median (range) pre-shift Al levels in exposed: urine* 1999: 137 (24.8–540) µg/l or 92.1 (17.9–292) µg/g creat., n = 33 2001: 153 (2.9–656) µg/l or 83.0 (5.2–421) µg/g creat., n = 34 2003: 97.7 (9.9–801) µg/l or 12.6 (1.9–646) µg/g creat., n = 31 *Median (range) post-shift Al levels in exposed: plasma* 1999: 11.6 (5.0–39.6) µg/l, n = 31 2001: 14.3 (3.8–51.0) µg/l, n = 22 2003: 13.2 (6.6–44.3) µg/l, n = 20 *Median (range) post-shift Al levels in exposed: urine* 1999: 130 (22.8–810 µg/l or 97.0 (17.9–399) µg/g creat., n = 31 2001: 146 (5.0–656) µg/l or 144 (8.9–423) µg/g creat., n = 25 2003: 93.7 (26.8–569) µg/l or 64.5 (23.9–560) µg/g creat., n = 22 *Median (range) post-shift Al levels in controls: plasma* 1999: 3.5 (1.0–8.2) µg/l, n = 27 2001: 2.8 (1.3–5.9) µg/l, n = 23 2003: 4.5 (3.3–5.9) µg/l, n = 17 *Median (range) post-shift Al levels in controls: urine* 1999: 5.8 (1.9–148) µg/l or 4.0 (1.6–78.9) µg/g creat., n = 27 2001: 6.0 (1.6–88.8) µg/l or 4.5 (1.6–86.2) µg/g creat., n = 24 2003: 8.3 (4.4–41.2) µg/l or 8.5 (1.8–37.5) µg/g creat., n = 17	Welders reported more symptoms than controls. Results of pulmonary function tests not consistent. Welders performed better in some tests (e.g. PEF in 2001) but worse in others (e.g. MEF_{25} in 2001). Generally, higher exposed welders had worse results than less exposed welders. HRCT revealed increased incidences of emphysematous lung changes during the observation period (1999: 37.2 %, 2003: 50 %). Signs suspicious of an early stage of lung fibrosis in 8 welders.	Investigations: see above: ref. (115). Decrease in study population during the study. Co-exposure to ozone (only exploratory measurements with test tubes; median: 0.16–0.42 ppm; maximum: 0.58–0.9 ppm). Inflammatory changes were found in the lungs of especially "high" exposed welders; changes observed in HRCT mainly concerned smokers and ex-smokers. [note: although pre-shift urine values seem to be higher than post-shift values, especially among car-body production workers, see above: ref (115), analysis of data from a subgroup of 62 workers surveyed annually from 1999–2003 did not show systematic differences between pre- and post-shift urinary Al concentrations, see Section 5.5 and Rossbach *et al* (165)].	(115)

FEF_{25-75}: forced expiratory flow between 25 and 75 % of FVC, FEV_1: forced expiratory volume in 1 second, FVC: forced vital capacity, HRCT: high-resolution computed tomography, MEF_x: maximal expiratory flow at x % VC, PEF: peak expiratory flow, Rtot: total resistance, TNFα: tumour necrosis factor alpha, VC: vital capacity.

Table III. Human studies on neurotoxic effects after long-term exposure (in chronological order).

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
Cross-sectional study/ *Exposed:* 261 miners in Ontario, Canada. *Controls:* 346 unexposed miners.	Between 1944 and 1979, miners inhaled McIntyre powder (15 % elemental Al and 85 % Al_2O_3) as a prophylactic agent against silicotic disease for 10 or 20 min before each underground shift. This corresponds to 2 mg/m^3 over an 8-hour workday (see Table II, references (22, 160).	No significant differences between exposed and non-exposed miners in reported diagnoses of neurological disorder. Exposed miners performed less well than did unexposed workers on cognitive state examinations: impaired cognitive functions in 4 % of the unexposed miners, 10 % of the miners with 0.5–9.9 yrs of exposure, 15 % of the miners with 10.0–19.9 yrs of exposure, and 20 % of miners with > 20 yrs of exposure.	-	(22, 160)
Cross-sectional study/ *Exposed:* 38 Al welders. Mean age 39.0 (range 26–56) yrs and no. of welding yrs 17.1. *Controls:* 39 railway track (mild steel) welders. Mean age 40.1 (range 23–59) yrs and no. of welding yrs 13.8.	No workplace air monitoring *Median (range) Al levels:* Exposed: blood: 3 (< 1–27) µg/l urine: 22 (4–255) µg/l or 24 (4.5–162) µg/g creat. Controls: blood: 1 (< 1–11) µg/l urine: 3 (< 1–26) µg/l or 4.7 (< 1–25) µg/g creat.	Regarding the symptoms questionnaires, Al welders reported statistically significantly more symptoms from the nervous system (especially fatigue) at the time of test (as well as fewer symptoms of pain during the past 6 months) than the controls. Compared to controls, Al welders scored significantly lower in 4 out of 20 psychological tests (non-dominant hand tapping speed, Luria-Nebraska motor scale task No. 3 and No. 4, dominant hand pegboard) and had significantly higher amplitude of the dominant hand in the diadochokinesis test. Of the varying variables, "acute symptoms from the central nervous system", "symptoms (6 months) pains and aches", "tapping (speed) non-dominant hand" and "Luria-Nebraska motor scale task No. 4" showed a statistically significant dose-effect relation according to the analysis of variance. Similar dose-effect relation also found adjusting urinary concentrations to µg/g creat; 75th percentile was 24.5 µg/g creat. Dose-effect relation also calculated between the number of hours exposed to Al and blood concentrations. An Al exposure > 7 028 hours	Investigations included 4 different questionnaires on symptoms, psychological methods (simple reaction time, finger tapping speed and endurance, digit span, vocabulary, tracking, symbol digit, cylinders, olfactory threshold, Luria-Nebraska motor scale), neurophysiological methods (electroencephalography, event-related auditory evoked potential (P300), brainstem auditory evoked potential and diadochokinesometry), determination of Al levels in urine and blood. Al welders and controls merged and subdivided into 3 groups based on urinary Al levels: 8 µg/l (50th percentile, n = 39), > 8–24 µg/l (50th–75th percentile, n = 19) and > 24 µg/l (> 75th percentile, n = 19) for further analysis of possible dose-effect relationships; in the 3rd group, the median urinary Al level was 59 µg/l while levels were > 100 µg/l in 5 welders. Groups comparable as to education	(182), see also (98)

Table III. Human studies on neurotoxic effects after long-term exposure (in chronological order).

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
		had the same effect as a urinary Al concentration > 24 µg/l. Concentration of Al in blood did not relate to symptoms or performance. Re-analysing these data (together with 2 other Al-exposed groups-see below: ref. (98)) controlling for age and multiple comparisons (Bonferroni), observed differences disappeared.	and social background. No effect of adjustment for age or alcohol consumption on any of the results. Some co-exposure to solvents during leisure activities in 2 controls. The only subject who had ingested Al-containing antacids daily during the past 10 years was a control welder (highest urinary Al concentration among the controls of 26 µg/l).	
Cross-sectional study/ *Exposed:* 41 workers from an Al reclamation plant in South eastern US. *Controls:* 32 local and 66 regional referents.	No workplace air or biological monitoring.	Compared to referents, exposed subjects had slower simple and choice reaction times (i.e. 77 milliseconds (ms) vs. 137 ms, resp., $p < 0.0001$); faster balance, measured as sway speed (with eyes closed) by 0.32 cm/s ($p < 0.005$); less acute colour discrimination ($p < 0.0001$); lower cognitive function scores by a factor of 8.3 ($p < 0.0001$); longer Trail Making A and Trail Making B (dexterity, coordination, decision making, peripheral sensation and discrimination) scores by 10 s ($p < 0.001$) and 50 s ($p < 0.0001$), resp.; longer peg placement scores by an additional 9 s ($p < 0.008$); 4-fold higher POMS (tension, depression, anger, vigour, fatigue and confusion) scores ($p < 0.0001$); more neurobehavioural, rheumatic, and respiratory symptoms.	Exposed subjects motivated by health concern (selection bias). Exposure to Al, Mn, vinyl chloride monomer and other chemicals. Correction for age. Alveolar carbon monoxide levels which provided evidence of cigarette smoking lower in the exposed than in the referent subjects	(103)
Case-control study/ *Cases:* 89 subjects diagnosed with probable Alzheimer's disease from a large health maintenance organisation in Seattle, Washington, US. *Controls:* 89 controls	No workplace air or biological monitoring. Occupational history obtained from spouses of cases and controls as well as from controls themselves. After the interview, an industrial hygienist, blinded to case-control status, rated exposures	Non-significant association found between Alzheimer's disease and ever having been occupationally exposed to Al (OR 1.46, 95 % CI 0.62–3.42). Dose-response analyses not significant for duration of exposure in years, intensity of exposure, and age at which half the cumulative life-time exposure was achieved.	Alcohol consumption neither a confounder nor an effect modifier with regard to Alzheimer's disease, initially, dietary intake of Al thought to be the route of exposure, however, because Al is poorly absorbed from the gastro-intestinal tract, this theory has met with controversy and scepticism. Alternative proposals have focussed on inhalation of Al as a	(77)

Table III. Human studies on neurotoxic effects after long-term exposure (in chronological order).

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
matched by age, sex, and type of informant.	per job: 0, 1, 2.5 and 5 (representing no, low, moderate and high exposure, resp.).		possible route of exposure. Olfactory neurons are in contact with both the nasal lumen and the olfactory bulbs, making them nearly the first tissue accessible to inhaled toxicants and potentially providing a direct single-cell pathway to the central nervous system (49).	
Cross-sectional study/ *Exposed:* 51 male Al welders from 10 Finnish companies *Controls:* 28 male mild steel welders.	Based on mean serum and urinary Al levels, 3 groups defined: High-exposure group (n = 24): 14.3 and 269 µg/l, resp. Low-exposure group (n = 27): 4.6 and 60 µg/l, resp. Controls: 2.4 and 12 µg/l, resp.	No impairment on the finger tapping, Santa Ana dexterity, simple visual reaction times, any of the verbal memory tasks, the similarities subtest of Wechsler adult intelligence scale, or the Stroop task. The low-exposed group performed poorer on the memory for designs and on more difficult block design items demanding preliminary visuospatial analysis. The time limited synonym task, embedded figures, digit symbol speed, and the backward counting component of the divided attention task showed exposure-response relations.	Investigations included interviews to obtain details on education, occupational history, past and present exposure to neurotoxic agents, general health, past and present diseases, injuries, clinical symptoms, medication (incl. Al-containing antacids), smoking habits, alcohol consumption; neuropsychological tests assessing the main cognitive domains (psychomotor function, attention, verbal abilities, visuospatial skills, memory and learning); and determination of Al levels in serum and urine and of blood Pb. Exclusion criteria: neurological illness, exposure to other neurotoxic agents, possible primary learning disabilities, native language other than Finnish or Swedish. No heavy drinkers or psychotropic drug users. No difference in social consumption of alcohol between groups. No use of Al-containing antacids. No data on possible co-exposure (to e.g. Mn), but site visits did not reveal potentially confounding exposures. Blood Pb levels were within normal range (0.2–0.4 µmol/l).	(6)

Table III. Human studies on neurotoxic effects after long-term exposure (in chronological order).

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
Cross-sectional study/ *Exposed:* 62 male and 3 female Al welders from 10 Finnish companies. *Controls:* 25 male mild steel welders.	No workplace air monitoring. Based on median serum and urinary Al levels, 3 groups defined: High-exposure group (n = 30): 12.4 and 192 µg/l, resp. Low-exposure group (n = 29): 3.8 and 49 µg/l, resp. Controls (n = 25): 2.2 and 11 µg/l, resp.	Comparison by covariance analysis, with age as a covariate, revealed significant differences between high-exposure group and controls: in *symptom scales*: fatigue ($p = 0.027$), emotional lability depression ($p = 0.045$), memory and concentration problems ($p = 0.004$); in *neuropsychological tests*: Bourbon-Wiersma dot cancellation accuracy ($p = 0.0497$), counting backwards ($p = 0.042$), dual-task cancellation speed ($p = 0.047$), dual-task counting speed ($p = 0.021$), synonyms ($p = 0.011$), memory for designs ($p = 0.021$) (performance of digit span forward tended to improve with exposure); in *neurophysiological tests*: visual EEG analysis showed mild diffuse abnormalities in 17 % of the low-exposure group and 27 % of the high-exposure group, and mild to moderate epileptiform abnormalities in 7 and 17 %, resp. (both with a significant exposure-related linear trend).	Same study population (differing in numbers) as in ref. (6) above. Investigations: mood and symptoms questionnaires and neurophysiological tests (quantitative and visual EEG analysis, P3 ERP), see ref. (6) above. Potential confounder age was controlled in the statistical analyses. Study population was homogenous in terms of ethnic/cultural background, education, social status, occupation, and the main job characteristics; see further ref. (6).	(161)
Longitudinal study with 2 cross-sectional studies integrated with a 5-yr interval 1st study: *Exposed:* 32 workers of a German Al powder plant. Median exposure duration 12.6 (range 2–41.3) yrs and median age 41.5 (range 26–60) yrs. *Controls:* 30 unexposed workers from the same plant. Median employ-	No workplace air monitoring. *Median (range) Al levels*: Exposed: plasma: 8.7 (5.1–25) µg/l urine: 110 (5.0–337) µg/l or 87.6 (4.6–605) µg/g creat. Controls: plasma: 4.3 (1.6–7.1) µg/l urine: 7.6 (2.6–73.8) µg/l or 9.0 (1.9–51.8) µg/g creat.	In the 2 cross-sectional studies, no significant exposure-related differences between the 2 study groups found for the psychometric tests and P300 parameters. Longitudinal comparison of the 2 evaluations revealed statistically significantly improved performances in the exposed subjects for 4 of the psychometric tests and a significantly poorer performance in one other test. Similarly, controls performed better in some tests and poorer in other ones. No dose-effect relationship for length of exposure or plasma or urinary Al concentrations and any of the primary neurological variables.	Investigations included standardised medical history, neuropsychological tests, evaluation of P300 potentials (not in 2nd study), determination of plasma and urinary Al levels. Groups were matched for age, gender, professional training and education level. No information reported on co-exposure. No evidence found that medication containing Al was taken. High alcohol consumption reported in some workers in the 2 groups could mask mild Al-induced central nervous system changes. Shift in age between the exposed and control groups (self-selection). No evidence that persons with a below-	(116)

Table III. Human studies on neurotoxic effects after long-term exposure (in chronological order).

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
ment duration 15.7 (range 2.8–37.4) yrs and median age 42.5 (range 26–60) yrs. 2nd study: *Exposed:* 21 Al powder workers. Median exposure duration 16 (range 2–41.2) yrs and median age 46 (range 31–65) yrs. *Controls:* 15 unexposed workers from the same plant. Median employment duration 17.2 (range 6.1–35.1) yrs and median age 41 (range 30–57) yrs.	*Median (range) Al levels:* Exposed: plasma: 6.7 (1.6–20.6) µg/l urine: 24.1 (3.4–218.9) µg/l or 19.8 (3–202.7) µg/g creat. Controls: plasma: 4.3 (1.9–12.9) µg/l urine: 6.5 (2–25.4) µg/l or 4.5 (2.2–15.9) µg/g creat.		average test performance or high or long exposure to Al did not participate in the follow-up examination. Tendency for persons who admitted to high alcohol consumption in the first evaluation not to participate in the follow-up evaluation.	
Cross-sectional study/ *Exposed:* 20 Al welders of a railroad wagon production facility. Median exposure duration 7 (range 2–21) yrs and median age 28.0 (range 21–52) yrs. *Controls:* 20 construction workers. Median age 30.5 (range 22–53) yrs.	*Median Al levels in workplace air - measured inside respiratory protection:* 0.9 (0.6–3.8) mg/m^3. *Median Al urinary level:* 41 (19–130) µg/l or 36 (14–110) µg/g creat.	Welders had more subjective neuropsychiatric symptoms than referents (median 2 vs. 1, $p = 0.047$). Welders as a group performed better than referents on a tremor test (hand steadiness), but years of exposure, not age, was predictive of poorer performance. Welders' reaction times rapid by clinical standards (mean simple reaction time (SRT): 221 ms; mean continuous performance test (CPT): 364 ms). However, there was a statistically significant relation between longer reaction times and Al in air.	Investigations included a questionnaire (related to neurological symptoms and to memory and concentration difficulties) and neuropsychological tests. The welding aerosol contained mainly respirable Al-containing particles; nitrogen oxides and ozone were also emitted. Inclusion criteria: at least one year of employment and being currently at work. Exclusion criteria: exposure to solvents, disease which could affect the CNS, including cancer, cerebrovascular diseases, neurological diseases and diabetes. Alcohol consumption slightly (not significantly) higher among controls. The possibility of	(18)

Table III. Human studies on neurotoxic effects after long-term exposure (in chronological order).

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
			selection of workers with high manual skills into welding work and a possible job-related training effect might partly explain the good performance among welders. Performance on reaction time tasks may be sensitive to motivational factors; exposed welders could have been more motivated to perform well, since they were more concerned about an effect of welding on the nervous system.	
Cross-sectional study/ *Exposed:* 119 male smelters (33 potroom, 86 male foundry workers) Exposure duration ≥ 5 yrs and median age 46.1 (range 24–63) yrs. 16 Al flake powder production workers. Median age 34.7 (range 22–48) yrs. 38 Al welders. Mean age 39.0 (range 26–56) yrs and no. of welding yrs 17.1. *Controls:* 39 mild steel welders. Median age 39.0 (range 23–59) yrs.	No workplace air monitoring. *Median (range) blood and urinary Al levels:* Smelters: 1.0 (< 1–18) µg/l and 4.0 (< 1–34) µg/l or 4.2 (< 1–23) µg/g creat. Flake powder production workers: 9.0 (< 1–21) µg/l and 83.0 (12–282) µg/l or 59.0 (12–139) µg/g creat. Al welders: 3 (1–27) µg/l and 22 (4–255) µg/l or 24 (4.5–162) µg/g creat. Mild steel welders: 1.0 (< 1–11) µg/l and 3.0 (< 1–26) µg/l or 4.7 (< 1–25) µg/g creat.	Smelters showed very low Al uptake as their Al blood and urinary levels were close to normal. No effects on the nervous system detected. The group of workers exposed to flake powder had high concentrations of Al in blood and urine, even higher than those of the Al welders. However, Al has not been shown to affect the functioning of the nervous system in flake powder producers. Contrary to a previous analysis (see above: ref. (182)), no significant differences found for the Al welders.	Investigations included a symptom and mood questionnaire, psychological and neurophysiological tests, determination of Al in urine and of Al, Pb and Mn in blood. Workers exposed to Al flake powder were also exposed to white spirit vapours (mean 76, range 24–99 mg/m^3). There could have been a slight effect from shift work in the potroom and foundry workers as they more often than steel welders reported sleep disturbances. No confounding by alcohol. The flake powder production workers had lower Pb blood levels than the other groups. Mn blood levels did not differ between groups. There was a negative correlation between Al blood levels and seniority among the flake powder producers.	(98), see also (182)

Table III. Human studies on neurotoxic effects after long-term exposure (in chronological order).

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
Cross-sectional case-control study conducted in northern Italy/ *Exposed:* 64 former Al dust-exposed workers fr. an Al-remelting plant. Mean age 67.8 ± 0.9 yrs. *Controls:* 32 unexposed demographically similar blue collar workers. Mean age 66.9 ± 1.1 yrs.	Significantly higher internal doses of aluminium in serum (14.1 ± 3.5 vs. 8.2 ± 1.17 µg/l) and iron in blood (408.6 ± 100.6 vs. 277.3 ± 84.20 mg/l) in the ex-employees compared to the control group.	Concerning blood/serum metal levels, only levels of Al and Fe were significantly different (i.e. higher in exposed) between groups. Neuropsychological and -physiological tests showed a significant difference in the latency of P300, MMSE score, MMSE-time, CDT score and CDT-time between exposed and controls. P300 latency was found to correlate positively with Al in serum and MMSE-time. Al in serum affected on all tests: a negative relationship observed between internal concentrations, MMSE score, and CDT score; a positive relationship found between internal concentrations, MMSE-time and CDT-time.	Groups matched for age, professional training, economic status, educational and clinical features. Investigations included clinical and neuropsychological and neurophysiological tests, and determination of levels of Al, Cu and Zn in serum, and of Mn, Pb and Fe in blood. Potential confounders such as age, height, weight, blood pressure, schooling years, alcohol, coffee consumption and smoking habit taken into account.	(155)
Longitudinal study with 3 cross-sectional studies integrated within intervals of 2 yrs each/ *Exposed:* 101 male Al welders of car-body construction industry with exposure duration 7–118 months, median age 35 (range 23–51) yrs and 83 % smokers and ex-smokers (at study start). *Controls:* 50 male workers of same facility with median age 35 yrs (at study start).	Levels of Al in workplace air and in plasma and urine: see Table II: ref. (115).	Compared to controls: no more symptoms in the modified Q16 questionnaire. No statistically significant differences in psychomotor performance and other behavioural tasks. Some small changes in reaction time when comparing data from 1999 and 2001, but since they were not seen in 2003, they are not considered to be relevant.	Investigations included, amongst others, standardised medical history, physical examination including the neurological status, and neurobehavioural testing among which a symptom questionnaire, modified Q16, and computerised and non-computerised tests: psychomotor performance (steadiness, line tracing, aiming, tapping), verbal intelligence (WST), simple reaction time, block design (HAWIE), digit span, symbol-digit substitution, switching attention (EURO-NES), and standard progressive matrices and determination of Al levels in urine and plasma. 98 of 101 welders completed first investigation. No relevant decrease in study population during course of study but only 68/98 still working as welders in 2003. No mixed exposure to possible neurotoxic substances such as solvents, Mn and other welding fumes.	(28, 101, 115)

Table III. Human studies on neurotoxic effects after long-term exposure (in chronological order).

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
Longitudinal study with 3 cross-sectional studies integrated within intervals of 2 yrs each/ *Exposed:* 46 welders of 5 railway vehicle engineering and special vehicle production companies with median age 40 yrs (at study start). *Controls:* 37 workers of same companies with median age 38 yrs (at study start).	Levels of Al in workplace air and in plasma and urine: see Table II, ref. (115) (differences are noticed between some data presented by Letzel and those by Kiesswetter, probably because of differences in sample sizes).	Final analysis concerned 20 welders (mean age 43.3 ± 7.4 yrs, mean education index 1.4 ± 0.4, mean plasma carbohydrate-deficient transferrin: 4.3 ± 4.2 U/l, mean Al-welding yrs 14.8 ± 4.1) and 12 controls (mean age 42.9 ± 5.7, mean education index 1.2 ± 0.4, mean carbohydrate-deficient transferrin 2.9 ± 5.5 U/l). Course of total dust levels had U-shape with minimum of 5.5 mg/m^3 at 2nd examination and maximum of 8.1 mg/m^3 at 3rd examination (n.s.). Biomonitoring data showed inverse u-shape trend: pre-shift urinary Al levels had maximum at 2nd examination and minimum at 3rd (140 and 88 µg/g creat., resp.; $p < 0.001$); plasma Al levels rose from about 13 µg/l at 1st examination to about 16 mg/l at both others (n.s.). Post-shift urine and plasma values were higher than pre-shift values by 30 µg/g creat. and 3.5 µg/l, resp. Statistical analysis of the biomonitoring data showed high long-term stability and sensitivity to acute shift-dependent exposure changes. No significantly increased symptom levels in welders. No significant differences in performance courses during the 4-year period. No correlation between biomonitoring and performance variables. Structure of neurobehavioural outcomes determined by possible indicators of "a priori" intelligence differences between subjects, not by their exposure information.	Investigations: see above. Due to economic problems (close-down, lay-offs) significant decrease in study population during the study, leaving 75 % (n = 33) of the exposed and 70 % (n = 26) of the controls in 2001, and 45 (n = 20) and 32 % (n = 12), resp., in 2003. Only "pure" Al welders with at least 2 years of Al exposure and no current or former exposure to other potential neurotoxic exposures at work included. Controls had no known neurotoxic exposures at work. Courses of neurobehavioural changes analysed with MANCOVA considering the covariates age, indicators of "a priori" intelligence differences (education or "premorbid" intelligence), and alcohol consumption (plasma carbohydrate-deficient transferrin).	(102), see also (29, 115)

Table III. Human studies on neurotoxic effects after long-term exposure (in chronological order).

Study design/population	Exposure assessment	Effects/Results	Remarks	Ref.
Oral exposure				
Case-control study/ *Cases:* 23 subjects with newly-diagnosed Alzheimer's disease from the Loretto Geriatric Center, Syracuse, NewYork, US. *Controls:* 23 subjects without newly-diagnosed Alzheimer's disease matched to cases on age, gender and date of admission to the centre.	Next-of-kin asked to complete information on the resident's medical history, lifestyle behaviour and dietary intake before admission to the centre. An expanded form of the Health Habits and History Questionnaire was used to determine dietary intake.	The crude OR for daily intake of foods containing high levels of Al was 2.0 and, when adjusted for covariates, 8.6 ($p = 0.19$). Intake of pancakes, waffles, biscuits, muffins, cornbread and/or corn tortillas differed significantly ($p = 0.025$) between cases and controls. Adjusted odds ratios were also elevated for grain product desserts, American cheese, chocolate pudding or beverages, salt and chewing gum. However, the odds ratio was not elevated for tea consumption.	According to the authors, larger studies warranted to corroborate or refute these preliminary findings.	(163)

CDT: clock drawing test, EURO-NES: European neurobehavioural evaluation system, HAWIE: Hamburg-Wechsler-Intelligenztest für Erwachsene, MANCOVA: multiple analysis of covariance, MMSE: mini-mental state examination, n.s.: non-significant, OR: odds ratio, POMS: profile of mood states, WST: Wortshatztest (vocabulary test).

Table IV. *In vitro* studies (in chronological order).

Cell type	Concentrations tested	Remarks/results	Reference
Calvaria cell cultures from foetuses of timed-pregnant Wistar rats	0, 3, 10, 30, 100 and 3 000 μM $AlCl_3$ (the total Al content, determined by AAS, in the medium was the equivalent of 0.98, 6.07, 16.82, 40.19, 88.45 and 284.52 μM, resp., and the corresponding free Al^{3+} concentrations (assessed after ultrafiltration) were 1.11, 1.75, 3.40, 6.22, 5.38 and 12.11 μM).	Examination of the effects of $AlCl_3$ on osteoprogenitor proliferation and differentiation, cell survival, and bone formation. A dose-dependent increase in the number of bone nodules present at early times (day 11) but no significant effect on nodule numbers at later times (day 17). From time course experiments, increased nodule number beginning from day 7. Alkaline phosphatase activity stimulated. Decreased colony formation, inhibited cell growth in late log phase, and decreased saturation density of the treated cultures. At concentrations of > 30 μM: degeneration of the cell layer and an increasing fibrillar appearance of the matrix present in between or adjacent to nodules when cultures were maintained for more than 15 days; significantly decreased viability of cells obtained from 13–17 days cultures; cellular toxicity frequently observed in cultures containing 300 μM Al, and by days 17–19, cells, nodules and matrix were disintegrating in these cultures.	(24)
Rat glioma (C-6) and murine neuroblastoma (NBP2) cells	0.5 mM $Al_2(SO_4)_3$	Assessment of early changes in oxidative parameters consequent to a 48-hour exposure to $Al_2(SO_4)_3$. Significant increase in reactive oxygen species (ROS) production. Significant decrease in glutathione (GSH) content in glioma cells. No significant changes in the neuroblastoma cells. Mitochondrial respiratory activity in glioma cells also significantly higher in the treated cells. As judged by morin-metal complex formation, Al can enter glioma cells much more readily than neuroblastoma cells.	(33)
Brain, liver, kidney homogenates of adult mice	0, 0.5, 1.0, 2.5, 4.0, 5.0 mM $Al_2(SO_4)_3$	Examination of effect of $Al_2(SO_4)_3$ on δ-aminolevulinate dehydratase (ALA-D); $Al_2(SO_4)_3$ concentration needed to inhibit the enzyme activity: 0.5–5.0 mM (n = 3) in brain, 4.0–5.0 mM (n = 3) in liver, 1.0–5.0 mM (n = 3) in kidney.	(172)

Table IV. *In vitro* studies (in chronological order).

Cell type	Concentrations tested	Remarks/results	Reference
Organotypic cultures of 2–4 day-old newborn Wistar rat hippocampus	50 µM glutamate and 0.4 mM $AlCl_3$ in the growth medium separately or in combination	Examination of the effect of Al on the development of glutamate-mediated neurotoxicity. Exposure to glutamate in the presence of Al^{3+} ions for up to 24 hours resulted in the development of typical excito-toxic neuronal changes, whereas separate glutamate treatment or single Al application did not. The neuronal lesions consisted of pronounced mitochondrial abnormalities, which are characteristic for early excito-toxic events. Severe swelling of the mitochondria led to disruption of their internal structure and resulted in an apparent microvacuolisation of the perikaryal cytoplasm of some pyramidal neurons.	(123)
Synaptosomes from a specific mouse strain, heterozygous for a GDNF and the corresponding wildtype mouse cerebral tissue.	0, 0.3, 0.9, 1.5, 2.0, 2.8 mM Al lactate	Examination of effect of 1-hour exposure at 37 ^{o}C of Al on the activity of the neural membrane integral protein, ATPase (total ATPase activity and Mg^{2+}-ATPase activity). Decreased synaptosomal total ATPase and Mg^{2+}-ATPase activities from 0.9 mM. GDNF+/- synaptosomas less sensitive than wildtype cerebral synaptosomes.	(105)
SH-SY5Y neuroblastoma cells	0, 0.3, 0.9, 1.5, 2.0, 2.8 mM Al lactate	Acute 24-hour cell toxicity test. Dose-dependent decrease in cellular ATP content observed from 0.3 mM. These concentrations also caused a decreased ATPase activity of synaptosomal membranes.	(105)

ATP: adenosine triphosphate, GDNF: glial cell line-derived neurotrophic factor.

Table V. Animal studies on toxicity due to repeated exposure: inhalation studies.

Species, strain/ no. per group	Exposure conditions	Remarks/results	Reference
Rat, Fischer 344 and guinea pig, Hartley/ n = 10/sex/species/group	0.25, 2.5, 25 mg/m^3 Al chlorohydrate, 6 h/day, 5 days/wk, 6 months	The chlorohydrate used contained 24.5 % Al. Actual concentrations: 0.245 (± 0.46), 2.63 (± 0.92), and 21.18 (± 2.75) mg/m^3. Median MMAD: 1.6, 1.20 and 1.53 µm, respecttively; 84 % MMAD: 6.20, 5.78 and 5.34 µm, respectively (geometric SD: 3.88, 4.82, and 3.49, respectively). Body weights regularly recorded during study. At study termination, 5 animals/sex/ group sacrificed for pathological evaluation, remaining 5 animals/sex/ group for haematology and Al tissue level determinations. No effect on haematological parameters. Decreased body weights in rats exposed to 25 mg/m^3. Markedly increased lung weights and significantly increased relative lung weights in rats and guinea pigs exposed to 25 mg/m^3. Lungs of all rats and guinea pigs showed significant dose-related increases in Al accumulation when exposed to 0.25, 2.5 or 25 mg/m^3. Upon pathological evaluation, only effects on respiratory tract: at 0.25 mg/m^3: slight exposure-related changes in 3/10 guinea pigs, characterised by an increase in alveolar macrophages which were more diffusively distributed when compared to control animals. Also in rats, slightly increased alveolar macrophages and an indication of granulomatous change in the peribronchial lymph node of one rat. At 2.5 or 25 mg/m^3: multifocal granulomatous pneumonia in all (n = 10) rats and (n = 10) guinea pigs, characterised by proliferation and/or infiltration of mononuclear inflammatory cells and large macrophages in alveoli around the termination of air passage ways. Also, in the peribronchial lymph nodes, microgranulomas composed of large cells with eosinophilic cytoplasm but not containing vacuoles or other evidence of phagocytised material. At 25 mg/m^3: increased number of goblet cells in the nasal cavities. No lesions in the trachea.	(190)
Rat, Sprague Dawley/ n = 15/sex/group	0, 0.34 (± 0.22), 2.50 (± 0.37) mg/m^3 aerosolised Al chlorohydrate (in a silicone-ethanol vehicle), 4 h/day, 5 days/wk, 22 days	Mean MMAD: 1.57 (± 0.45) and 4.28 (± 0.93) µm, resp. Sham- and vehicle-control group included. No behaviour suggesting eye irritation. No mortality in any of the groups. No effect on final mean body weights. No effect on "normalised" wet tissue/ organ weights. No effect on serum analyses data. No consistent relationship between Al tissue concentrations of the liver, gastric mucosa and parathyroid glands and exposure conditions and measured Al concentrations. No remarkable abnormalities upon gross post-mortem examinations. No remarkable abnormalities upon histological examination of the livers, kidneys, adrenals and parathyroids of 6 animals/sex/group.	(193)

Table V. Animal studies on toxicity due to repeated exposure: inhalation studies.

Species, strain/ no. per group	Exposure conditions	Remarks/results	Reference
Rat (no more data)	2 mg/m^3 $Al_2(SO_4)_3$ as an aqueous aerosol	No data on exposure conditions and particle size. Increases in the number of pulmonary alveolar macrophages and of distorted oversized pulmonary alveolar macrophages and granulocytes, and in the permeability of the alveolar wall; increased lung weights, stiffer lungs, fibrosis (at the level of the terminal and respiratory bronchioles); decreases in copper, zinc, and iron levels.	(64)
Rat, Sprague Dawley/ n = 50 males/group	0, 1.83 (± 0.7) mg/m^3 $AlCl_3$ or 1.28 (± 0.3) mg/m^3 AlF_3, 6 h/day, 5 days/wk, 5 months	Particle size < 10 µm. Rats (n = 10/group) killed at (approximately) monthly intervals. Aimed at physiological and biochemical parameters as early adverse effect indicators (lysozome level; glucose-6-phosphate dehydrogenase, alkaline phosphatase activity in lung lavage fluid; leakage of iv-injected ^{125}I-serum albumin into alveolar fluids, amount of tracer retained in circulatory system; lavage fluid protein; pulmonary alveolar macrophage number and viability; body weight; liver, kidney, brain, lung weight). No effect on body weight. Authors summarised that *$AlCl_3$* induced increases proportional to exposure time in lysozyme levels and alkaline phosphatase activities, total protein, and relative kidney and liver weights; that *AlF_3* increased relative liver weights and alkaline phosphatase activity; that *Al* affected pulmonary alveolar macrophage integrity and the kidney, but that the effects on the liver and on Type II cells of the alveoli were antagonised by fluoride. [note of committees: poor and inconsistent reporting hampers proper evaluation].	(64)
Rabbit, New Zealand white/ n = 8 males/group	0, 212 mg/m^3 alchlor [a], 4 h/day, 5 days	Increased absolute lung weights ($p < 0.01$). Acute bronchopneumonia and moderate thickening of alveolar walls seen at histological examination of 3 animals.	(55)
Hamster, Syrian golden/ n = 10 males/group	0, 16, 35, 53, 168 mg/m^3 alchlor [a], 4 h/day, 3 days	Aimed at establishing a dose-response relationship for changes in absolute lung weight. Decreased body weight ($p < 0.01$) (not further specified). Increased absolute lung weights at 16 mg/m^3 ($0.05 < p < 0.1$) and at 35, 53 and 168 mg/m^3 ($p < 0.01$).	(55)
Hamster, Syrian golden/ n = 30 males/group	0, 49 mg/m^3 alchlor [a], 4 h/day, 3 days	Groups of animals killed at post-exposure days 1, 2, 3, 4 and 7. Decreased body weight ($p \leq 0.01$). Increased absolute lung weights at day 1 ($p \leq 0.01$) and at days 2, 3 and 4 ($p \leq 0.025$) (lung weight data were from 10 animals/group which would imply that 50 animals were exposed and not 30).	(55)

Table V. Animal studies on toxicity due to repeated exposure: inhalation studies.

Species, strain/ no. per group	Exposure conditions	Remarks/results	Reference
Hamster, Syrian golden/ n = 20 males/group	0, 164 mg/m^3 alchlor [a], 6 h/day on day 1 and 4 h/day on days 2 and 3.	Animals (n = 4/group) killed at post-exposure days 1, 3, 6, 10 and 27. Markedly decreased body weights with apparently complete recovery within 2 wks. Acute bronchopneumonia. Moderate to marked thickening of alveolar walls due to neutrophil and macrophage infiltration. Small granulomatous foci at bronchioloalveolar junction. Decrease in severity of these changes with time. No microscopic changes in liver, heart, kidneys.	(55)
Hamster, Syrian golden/ n = 24 males/group	0, 52 mg/m^3 alchlor [a], 6 h/day, 10, 20 or 30 exposures	Animals (n = 4/group) killed after 10, 20 and 30 exposures and after 2, 4 and 6 post-exposure weeks. After 10 exposures: microscopic changes in lungs characterised by a few foci of macrophages and heterophils. After 20 and 30 exposures: these changes were more marked; numerous foci of macrophages and heterophils in parenchymatous tissue especially at the bronchioloalveolar junction; fine bluish dark granules in macrophages in the granulomatous nodules. 2 weeks after 30 exposures: thickened alveolar walls due to infiltration of macrophages and heterophils. Lung changes still present 4 and 6 weeks post-exposure.	(55)

[a] A propylene glycol complex of Al-chloride hydroxide.
MMAD: mass median aerodynamic diameter, SD: standard deviation.

Table VI. Animal studies on toxicity due to repeated exposure: oral studies.

Species, strain, no./group	Exposure conditions	Remarks/results	Reference
Rat, Sprague Dawley exposed: n = 4 males controls: n = 10 males	0, 1 000 mg $AlCl_3$/l in drinking water for 12 wks	Abolished aggression: suppression of lateralisations, boxing bouts, fight with stud male, ventral presenting postures.	(19)
Rat, Wistar n = 3 males/group	0, 25 mg Al/rat/day (i.e. ca. 85 mg Al/kg bw/day) as $Al_2(SO_4)_3$ in drinking water for 3–5 wks	Rats maintained on the diet remained healthy and their body weight was 86 ± 5 % of control rats. Reduction of NMDA-induced increase of extracellular cGMP by 50 %; the increase in extracellular cGMP induced by the nitric oxide-generating agent *S*-nitroso-*N*-acetylpenicillamine higher (240 %) in rats treated with Al. Immunoblotting showed that Al reduced the cerebellar content of calmodulin and nitric oxide synthase by 34 and 15 %, resp. Basal activity of soluble guanylate cyclase decreased by 66 % in Al-treated rats. Activity after stimulation with *S*-nitroso-*N*-acetylpenicillamine similar to controls. Basal cGMP in the cerebellar extracellular space decreased by 50 % in aluminium-treated rats.	(87)
Rat, Wistar n = 6–7 males/group	0 (< 50 µg Al/l), 270 mg Al/l as $Al(OH)_3$, 270 mg Al/l as $AlCl_3$ and citric acid (molar ratio 1:2) (n = 6) in drinking water for 7 wks	Study aimed at Al accumulation in the brain. No statistically significantly increased Al levels in plasma and brain.	(143)
Rat, Sprague Dawley n = 7 males/group	34 mg $AlCl_3$/kg bw/day (i.e. ca. 7 mg Al/kg bw/day), every other day for 30 days	Study aimed at biochemical parameters, free radicals, and enzyme activities in plasma and different tissues of male rats. Significant ($p < 0.05$) induction of free radicals (thiobarbituric acid-reactive substances). Decreased activity of glutathione *S*-transferase and levels of sulphydryl groups in rat plasma, liver, brain, testes, kidney. Significantly decreased aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, acid phosphatase, and phosphorylase activities in liver and testes. Significantly increased activities of these enzymes in plasma. Significantly increased lactate dehydrogenase activities in plasma, liver, testes, brain. Significantly decreased acetylcholinesterase activities in brain and plasma. Significantly decreased plasma total protein, albumin, total lipids. Significantly increased glucose, urea, creatinine, bilirubin, cholesterol levels.	(56)

Table VI. Animal studies on toxicity due to repeated exposure: oral studies.

Species, strain, no./group	Exposure conditions	Remarks/results	Reference
Rat, Wistar n = 12 males/group	2 g/l $AlCl_3 \times 6\ H_2O$ in the drinking water (ad libitum), for 6 months	Examination of the potential role of Al accumulation in the brain of aged (i.e. 22-month-old) rats on the development of neurodegenerative features observed in Alzheimer's disease. Measurement of levels of Al, Zn, Cu, Mn in brain sections (prosencephalon + mesencephalon, cerebellum, pons-medulla) in n = 6/group. Measurement of area covered by mossy fibres in about 25 consecutive hippocampal sections (by computer-assisted morphometric methods following Timm's preferential staining). No data given on actual Al exposure from diet and drinking water. During exposure, aggressiveness evident. Increase ($p < 0.05$) in Al level in prosencephalon + mesencephalon, pons-medulla (not in cerebelllum). Increase in Cu level in pons-medulla only ($p < 0.05$). Increase in Zn level in cerebellum only ($p < 0.01$). No changes in Mn levels. Significant increase (+ 32 %) in the area occupied by the mossy fibres in the hippocampal CA3 field. The authors stated that since Cu, Zn and Mn are essential components of the cytosolic and mitochondrial superoxide dismutases, it is possible that the increased content of these ions in the rats represents an increased amount of genetic expression of these antioxidant enzymes. Considering that the positivity to Timm's reaction is based on the presence of free or loosely bound Zn^{2+} ions within synaptic terminals and that Zn^{2+} ions are reported to be accumulated by hippocampal neurons when tissue injury occurs, the increased area of the mossy fibres in CA3 field of treated rats could indicate increased hippocampal damage. The ageing CNS might be particular susceptible to Al toxic effects which may increase the cell load of oxidative stress and may contribute, as an aggravating factor, to the development of neurodegenerative events as observed in Alzheimer's disease.	(63)
Mouse, Swiss Webster n = 3/sex/group	0.007 (control), 1 mg Al/g diet (i.e. probably ca. 1 and 152 mg Al/kg bw/day; see (71)) as Al lactate, from conception to maturity	Abstract. Diffuse decreased thickness of myelin sheaths; mean myelin sheath widths 16 % smaller ($p = 0.04$); axon perimeters also smaller on the average (not significant).	(73)

Table VI. Animal studies on toxicity due to repeated exposure: oral studies.

Species, strain, no./group	Exposure conditions	Remarks/results	Reference
Mouse, CD-1 n = 25 males/group	0, 300, 600 mg Al/kg bw/day, as $Al(NO_3)_3 \times 9\ H_2O$ in drinking water for 2 wks.	One-half of the animals in each group were concurrently subjected to restraint stress during 1 hour/day throughout the study. No remarkable effects on open-field activity or on the number of avoidances in an automatic reflex conditioner. Lower motor resistance and coordination in a rotarod at 600 mg Al/kg bw/day, restraint stress alone or concurrent administration of Al (300 and 600 mg/kg bw/day) plus restraint stress. Significantly increased Al levels in whole brain and cerebellum after exposure to Al plus restraint stress.	(41)
Mouse, Swiss n = 8/sex/group	0, 1 g % (34 mM) sodium citrate and 1 g % (34 mM) sodium citrate + 3.3 g % (49.5 mM) $Al_2(SO_4)_3$ in drinking water, for 1 month.	Study aimed to investigate the *in vitro* and *in vivo* effects of $Al_2(SO_4)_3$ on δ-amino-levulinic acid dehydratase (ALA-D) activity in the brain, liver and kidney of adult mice. $Al_2(SO_4)_3$ significantly inhibited ALA-D activity in kidney (23.3 ± 3.7 % (mean ± SE)), but significantly enhanced it in liver (31.2 ± 15.0 %). Significant increase in Al levels in the liver (527 ± 3.9 %), kidney (283 ± 1.7 %), not in the brain. Hepatic Al concentrations increased in animals treated only with 1 g % sodium citrate (34 mM) (217 ± 1.5 %).	(172)
Mouse, BALB/c n = 5 males/group	0, 0.95, 4.3, 21.3 mg Al/kg bw/day, as $AlNH_4(SO_4)_2$ in drinking water, for 1 month (Al taken from basal diet calculated to be ca. 22 mg/kg bw/day).	No treatment related differences in final body weight, in relative organ weights, in body weight gain. No signs of gross behavioural alterations. Expression of TNFα mRNA in cerebrum significantly increased among Al-treated groups in a dose-dependent manner. No Al-related effects on other cytokines. No significant differences in cytokine mRNA expressions in peripheral cells (splenic macrophages and lymphocytes).	(196)
Mouse, BALB/c n = 5 males/group	0, 0.9, 4.6, 23 mg Al/kg bw/day, as $AlNH_4(SO_4)_2$ in drinking water, for 4 wks (Al taken from basal diet calculated to be 25 mg/kg bw/day).	Lower levels of dopamine, dihydroxyphenylacetic acid, homovanillic acid in the hypothalamus of Al-treated mice, most notably in the low-dose group. No marked alterations in norepinephrine, serotonin, 5-hydroxyindoleacetic acid levels in any brain region.	(195)
Mouse, Swiss Webster (45-days old; beginning at puberty) exposed: n = 10–11 males/group, controls: n = 22 males	1 (control), 17, 78, 122, 152 mg Al/kg bw/day, as Al lactate in diet, for 4 wks; 1 (control), 12, 69, 98, 137 mg Al/kg bw/day, as Al lactate in diet, for 8 wks (with or without 3.2 % citrate to promote Al absorption).	Dose-response effect on brain weight, brain Al and Mn levels, and grip strength at the end of the 4-wk exposure. Increased brain Al levels at the end of the 8-wk exposure, but no dose-response effects on other variables. Neither exposure influenced auditory startle amplitude.	(71)

Table VII. Animal studies on toxicity due to repeated exposure: parenteral studies.

Species, strain/no. per group	Exposure conditions	Remarks/results	Reference
Rat, Sprague Dawley n = 8 males/group	3 mg Al/rat (i.e. ca. 21–33 mg Al/kg bw/day), as Al gluconate. Intraperitoneal injection every 3rd day for 3 wks.	Increased cortical levels of glutathione and rates of generation of reactive oxygen species. Increased glutamine synthetase activity in the cortex. Increased levels of creatine kinase (another enzyme susceptible to oxidative stress) in cortices of treated rats. Treatment had very minor effects on hepatic parameters of oxidative events.	(27)
Rat, Wistar n = 12 males/group	5.4 mg Al/kg bw/day, as Al-L-glutamate suspension (294 mg/kg), Na-L-glutamate suspension (294 mg/kg), or 0.9 % NaCl. Subcutaneous injection 6 days/wk for 10 wks.	Decreased Fe plasma level. Al accumulation in, especially, the striatum where Fe levels were decreased and in the hippocampus where thiobarbituric acid-reactive substances were increased without polyunsaturated fatty acid modifications.	(24)
Rat, Wistar n = 3 males/group	2.0 mg Al/kg bw, as Al chloride in saline. Single intravenous injection, with or without either citric acid or maltol.	Study aimed at Al accumulation in brain. No statistically significant increase in brain Al levels after 48 hours.	(143)
Rat, Wistar n = 5 males/group	8 mg Al/kg bw/day, as $AlCl_3$ in saline. Intraperitoneal injection 6 days/wk for 2 wks, with or without either citric acid or maltol.	Study aimed at Al accumulation in brain. Injections of $AlCl_3$ and an equimolar amount of maltol enhanced accumulation of Al in the brain. No significant increases in groups receiving Al chloride alone or with citric acid.	(143)
Rabbits, New Zealand White n = 8 males/group	2.7 mg Al/kg bw/day, as Al lactate. Intravenous injection 5 days/wk for 4 wks (control group: 0.3 mmol/kg sodium lactate).	Distended mesangial cells in the glomerular tufts in 6/8 rabbits with greyish blue granular material, which was identified as an Al compound. Other consistent findings in the glomeruli: microaneurysm and segmental sclerosis in 6/8 rabbits. Less frequently observed glomerular changes: crescent formation, necrosis with calcification, fibrosis of the Bowman's capsule, cystic dilation of the Bowman's space, exudation of erythrocytes into the Bowman's space.	(89)

CNS: central nervous system, cGMP: cyclic guanosine monophosphate, NMDA: *N*-methyl-D-aspartate, TNFα: tumour necrosis factor alpha.

Appendix 2. The committees

Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG)

Gunnar Johanson, *chairman*	Institute of Environmental Medicine, Karolinska Institutet, Sweden
Kristina Kjærheim	Cancer Registry of Norway
Anne Thoustrup Saber	National Research Centre for the Working Environment, Denmark
Tiina Santonen	Finnish Institute of Occupational Health
Vidar Skaug	National Institute of Occupational Health, Norway
Mattias Öberg	Institute of Environmental Medicine, Karolinska Institutet, Sweden
Jill Järnberg and Anna-Karin Alexandrie, *scientific secretaries*	Swedish Work Environment Authority

Dutch Expert Committee on Occupational Safety (DECOS)

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TM Pal	Netherlands Center for Occupational Diseases
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RA Woutersen	TNO Quality of Life and Wageningen University and Research Centre
PB Wulp	Labour Inspectorate
JHJ Stouten, *scientific secretary*	Health Council of the Netherlands

Appendix 3. Previous NEG criteria documents

NEG criteria documents published in the scientific serial Arbete och Hälsa (Work and Health):

Substance/Agent	Arbete och Hälsa issue
Acetonitrile	1989:22, 1989:37*
Acid aerosols, inorganic	1992:33, 1993:1*
Acrylonitrile	1985:4
Allyl alcohol	1986:8
Aluminium	1992:45, 1993:1*
Ammonia	1986:31, 2005:13*
Antimony	1998:11*
Arsenic, inorganic	1981:22, 1991:9, 1991:50*
Arsine	1986:41
Asbestos	1982:29
Benomyl	1984:28
Benzene	1981:11
1,2,3-Benzotriazole	2000:24*D
Boric acid, Borax	1980:13
1,3-Butadiene	1994:36*, 1994:42
1-Butanol	1980:20
γ-Butyrolactone	2004:7*D
Cadmium	1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	1990:2*D
Carbon monoxide	1980:8
Ceramic Fibres, Refractory	1996:30*, 1998:20
Chlorine, Chlorine dioxide	1980:6
Chloromequat chloride	1984:36
4-Chloro-2-methylphenoxy acetic acid	1981:14
Chlorophenols	1984:46
Chlorotrimethylsilane	2002:2
Chromium	1979:33
Cobalt	1982:16, 1994:39*, 1994:42
Copper	1980:21
Creosote	1988:13, 1988:33*
Cyanoacrylates	1995:25*, 1995:27
Cyclic acid anhydrides	2004:15*D
Cyclohexanone, Cyclopentanone	1985:42
n-Decane	1987:25, 1987:40*
Deodorized kerosene	1985:24
Diacetone alcohol	1989:4, 1989:37*
Dichlorobenzenes	1998:4*, 1998:20
Diesel exhaust	1993:34, 1993:35*
Diethylamine	1994:23*, 1994:42
2-Diethylaminoethanol	1994:25*N
Diethylenetriamine	1994:23*, 1994:42
Diisocyanates	1979:34, 1985:19
Dimethylamine	1994:23*, 1994:42
Dimethyldithiocarbamates	1990:26, 1991:2*
Dimethylethylamine	1991:26, 1991:50*
Dimethylformamide	1983:28
Dimethylsulfoxide	1991:37, 1991:50*
Dioxane	1982:6
Endotoxins	2011;45(4)*D

Substance/Agent	Arbete och Hälsa issue
Enzymes, industrial	1994:28*, 1994:42
Epichlorohydrin	1981:10
Ethyl acetate	1990:35*
Ethylbenzene	1986:19
Ethylenediamine	1994:23*, 1994:42
Ethylenebisdithiocarbamates and Ethylenethiourea	1993:24, 1993:35*
Ethylene glycol	1980:14
Ethylene glycol monoalkyl ethers	1985:34
Ethylene oxide	1982:7
Ethyl ether	1992:30* N
2-Ethylhexanoic acid	1994:31*, 1994:42
Flour dust	1996:27*, 1998:20
Formaldehyde	1978:21, 1982:27, 2003:11*D
Fungal spores	2006:21*
Furfuryl alcohol	1984:24
Gasoline	1984:7
Glutaraldehyde	1997:20*D, 1998:20
Glyoxal	1995:2*, 1995:27
Halothane	1984:17
n-Hexane	1980:19, 1986:20
Hydrazine, Hydrazine salts	1985:6
Hydrogen fluoride	1983:7
Hydrogen sulphide	1982:31, 2001:14*D
Hydroquinone	1989:15, 1989:37*
Industrial enzymes	1994:28*
Isoflurane, sevoflurane and desflurane	2009;43(9)*
Isophorone	1991:14, 1991:50*
Isopropanol	1980:18
Lead, inorganic	1979:24, 1992:43, 1993:1*
Limonene	1993:14, 1993:35*
Lithium and lithium compounds	2002:16*
Manganese	1982:10
Mercury, inorganic	1985:20
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Methanol	1984:41
Methyl bromide	1987:18, 1987:40*
Methyl chloride	1992:27*D
Methyl chloroform	1981:12
Methylcyclopentadienyl manganese tricarbonyl	1982:10
Methylene chloride	1979:15, 1987:29, 1987:40*
Methyl ethyl ketone	1983:25
Methyl formate	1989:29, 1989:37*
Methyl isobutyl ketone	1988:20, 1988:33*
Methyl methacrylate	1991:36*D
N-Methyl-2-pyrrolidone	1994:40*, 1994:42
Methyl-tert-butyl ether	1994:22*D
Microbial volatile organic compounds (MVOCs)	2006:13*
Microorganisms	1991:44, 1991:50*
Mineral fibers	1981:26
Nickel	1981:28, 1995:26*, 1995:27
Nitrilotriacetic acid	1989:16, 1989:37*
Nitroalkanes	1988:29, 1988:33*
Nitrogen oxides	1983:28
N-Nitroso compounds	1990:33, 1991:2*

Substance/Agent	Arbete och Hälsa issue
Nitrous oxide	1982:20
Occupational exposure to chemicals and hearing impairment	2010;44(4)*
Oil mist	1985:13
Organic acid anhydrides	1990:48, 1991:2*
Ozone	1986:28
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Penicillins	2004:6*
Permethrin	1982:22
Petrol	1984:7
Phenol	1984:33
Phosphate triesters with flame retardant properties	2010;44(6)*
Phthalate esters	1982:12
Platinum	1997:14*D, 1998:20
Polyethylene,	1998:12*
Polypropylene, Thermal degradation products in the processing of plastics	1998:12*
Polystyrene, Thermal degradation products in the processing of plastics	1998:12*
Polyvinylchloride, Thermal degradation products in the processing of plastics	1998:12*
Polytetrafluoroethylene, Thermal degradation products in the processing of plastics	1998:12*
Propene	1995:7*, 1995:27
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Propylene glycol ethers and their acetates	1990:32*N
Propylene oxide	1985:23
Refined petroleum solvents	1982:21
Refractory Ceramic Fibres	1996:30*
Selenium	1992:35, 1993:1*
Silica, crystalline	1993:2, 1993:35*
Styrene	1979:14, 1990:49*, 1991:2
Sulphur dioxide	1984:18
Sulphuric, hydrochloric, nitric and phosphoric acids	2009;43(7)*
Synthetic pyretroids	1982:22
Tetrachloroethane	1996:28*D
Tetrachloroethylene	1979:25, 2003:14*D
Thermal degradation products of plastics	1998:12*
Thiurams	1990:26, 1991:2*
Tin and inorganic tin compounds	2002:10*D
Toluene	1979:5, 1989:3, 1989:37*, 2000:19*
1,1,1-Trichloroethane	1981:12
Trichloroethylene	1979:13, 1991:43, 1991:50*
Triglycidyl isocyanurate	2001:18*
n-Undecane	1987:25, 1987:40*
Vanadium	1982:18
Vinyl acetate	1988:26, 1988:33*
Vinyl chloride	1986:17
Welding gases and fumes	1990:28, 1991:2*
White spirit	1986:1
Wood dust	1987:36
Xylene	1979:35
Zinc	1981:13

* in English, remaining documents are in a Scandinavian language.
D = collaboration with the Dutch Expert Committee on Occupational Safety (DECOS).
N = collaboration with the US National Institute for Occupational Safety and Health (NIOSH).

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