
Executive summary

Scope

At request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands recommends health-based occupational exposure limits for the concentration of toxic substances in the air at the workplace. These recommendations are made by the Council's Dutch Expert Committee on Occupational Safety (DECOS).

The present advice on aluminium and aluminium compounds was prepared in cooperation with the Nordic Expert Group for Criteria Documents of Health Risks from Chemicals (NEG), an advisory body of the Nordic countries.

The conclusions in this advice are based on scientific publications which appeared before April 2009.

Physical and chemical properties

Aluminium (Al; CAS no. 7429-90-5) is the most abundant metal and the third most abundant element, after oxygen and silicon, in the earth's crust. Aluminium does not occur naturally in the metallic, elemental state, but found combined with other elements, such as oxygen, silicon, or fluoride, in soil, minerals, clays, and rocks (especially igneous rocks). Elementary aluminium is obtained from bauxite, which contains 40-60% aluminium oxide. It is a silvery, light, malleable, and ductile metal. In contact with air and water (moist), a thin layer of aluminium

oxide is formed, that protects from further oxidation. Aluminium metal is not water soluble.

Aluminium is used primarily for metallurgical purposes, especially in the production of aluminium-based alloy castings and wrought aluminium products. The major uses of aluminium and its alloys are in packaging, building and construction, transportation, and electrical applications. Aluminium compounds are found in consumer products such as antacids, astringents, buffered aspirin, food additives, and antiperspirants. Powdered aluminium metal is often used in explosives and fireworks.

Monitoring

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 spectroscopy (AMS) using radioactive ^{26}Al , and stringent precautions should be taken to produce accurate results.

Aluminium in air is usually associated with particulate matter and therefore standard methods involve collection of air samples on filters and acid extraction of the filters. Several methods for the determination of aluminium in occupational air are available. Recent methods as described by the Netherlands Normalisatie-instituut and the US National Institute for Occupational Safety and Health (NIOSH) use inductively coupled plasma-atomic emission spectroscopy (ICP-AES) for sample analysis. The methods cannot distinguish between aluminium and aluminium compounds.

Methods for the determination of aluminium in biological fluids (blood, urine) are available as well.

Limit values

In the Netherlands, there is no legally-binding occupational exposure limit (OEL) for aluminium or its compounds. There is currently no limit value for occupational exposures to aluminium and aluminium compounds at the European level.

In Germany, limit values for dust containing aluminium, aluminium oxide and aluminium hydroxide of 4 (inhalable fraction) or 1.5 mg/m^3 (respirable fraction) have been proposed.

The United Kingdom has set occupational exposure limit values for aluminium metal and aluminium oxide of 10 and 4 mg/m^3 , for the inhalable and respirable fraction, respectively, and for soluble aluminium salts of 2 mg/m^3 .

In Sweden, the OELs for aluminium soluble compounds and aluminium metal and oxide (total dust and respirable dust) of 1, 5, and 2 mg/m³, respectively. In addition, there are values for potassium aluminium tetrafluoride and aluminium stearate of 0.4 (inhalable dust) and 5 mg/m³ (total dust), respectively. Norway lists OELs for welding fumes of aluminium of 5 mg/m³, for aluminium oxide of 10 mg/m³ (total dust), for aluminium pyro powder of 5 mg/m³, and for soluble salts of 2 mg/m³. Denmark has set OELs for aluminium and aluminium oxide (powder and dust) of 5 and 2 mg/m³ (total and respirable dust, respectively), for aluminium metal fume of 5 mg/m³, and for soluble salts of 1 mg/m³. Finland has besides OELs for aluminium welding fume (1.5 mg/m³) and soluble compounds (2 mg/m³), limit values of 1 mg/m³ for both aluminium fluoride and aluminium sulphate. In Iceland, there are OELs for metallic aluminium powder and dust and aluminium oxide of 10 mg/m³ and for fume of 5 mg/m³.

The US American Conference of Governmental Industrial Hygienists (ACGIH) has replaced the several threshold limit values (TLV) for the various forms of insoluble aluminium by one value: 1 mg/m³ (respirable fraction).

Kinetics

Inhalation and dermal absorption have not been studied in detail; the percentage of aluminium absorbed following inhalation might be about 2%, the percentage for dermal exposure is not reported. Aluminium may directly enter the brain via the olfactory tract. Animal studies showed no significant increases in aluminium in tissues other than the lungs or serum after inhalation exposure to aluminium oxide and aluminium chlorohydrate, indicating that lung retention rather than absorption occurred.

After oral exposure, 0.1-1% of aluminium is absorbed (depending on the aluminium compound ingested and the diet composition).

When absorbed, aluminium binds to 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 were observed in the fetus, providing evidence of transplacental transfer of aluminium.

The kidney is the major route of excretion of absorbed aluminium. Several studies indicated that aluminium can be excreted in human milk.

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 strongly related to the current 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 mg 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.

Effects in humans

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

Despite its wide and extensive use in industries and cosmetics, the small number of reports on effects (mainly sensitisation) due to skin contact indicates that aluminium does not cause significant skin effects.

Numerous studies have examined the effects following occupational exposure to aluminium. These investigations mainly concerned the respiratory tract or the nervous system and included several occupational populations, such as workers in aluminium producing and processing industry and welders, exposed under various conditions (dust, fume, metal, oxide, etc.). Many studies addressing the respiratory tract show that exposure to aluminium can cause lung disorders, such as impaired lung function and pulmonary fibrosis, and the results of some of the neurotoxicity studies suggest that aluminium may induce subclinical effects, such as impaired performance in neurobehavioural tests on psychomotor and cognitive skills and changes in quantitative EEG. In none of these studies, exposure-response relationships could be established. Furthermore, there was frequently co-exposure to compounds that may induce similar effects.

Studies in workers in the aluminium production industry demonstrated increased mortality rates for especially lung and urinary bladder cancer. However, this is generally considered to be caused by co-exposure to carcinogenic compounds such as polycyclic aromatic hydrocarbons and not by aluminium.

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

Effects on laboratory animals

There are relatively little laboratory animal data on skin and eye effects of aluminium and aluminium compounds. Exposure to concentrations of 25 mg/m³ of aluminium chlorohydrate did not induce effects on the eyes of rats. Contrary to aluminium sulphate, chlorohydrate and hydroxide, 10% solutions of aluminium

chloride and nitrate were severely damaging to the skin. There were no data from relevant sensitisation tests.

Laboratory animal studies showed that mortality occurred at relatively high concentrations (>1000 mg aluminium/m³ as aluminium oxide) after acute inhalation exposure. Rats developed persistent microgranulomata in the lungs after exposure for four hours to concentrations of aluminium flakes of 200 and 1000 mg/m³, but not at exposures to 100 mg/m³. No data on acute dermal toxicity were available. Oral LD₅₀ values in rats and mice ranged from 261 to 980 mg/kg bw for several water-soluble aluminium compounds.

There were only a few, limited repeated animal inhalation studies. In the most relevant study, rats and guinea pigs were exposed to concentrations of aluminium chlorohydrate of 0.25, 2.5, and 25 mg/m³, six hours/day, five days/week, for six months. All animals exposed to 2.5 and 25 mg/m³ had multifocal granulomatous pneumonia and microgranulomas in the peribronchial lymph nodes. At 0.25 mg/m³, there were slightly increased alveolar macrophages in a few rats or guinea pigs and indications of granulomatous change in the peribronchial lymph node of one rat.

Apart from conflicting results in *S. typhimurium* strains TA98 and TA100, aluminium chloride was not mutagenic in other *S. typhimurium* strains, *E. coli*, or in mouse lymphoma cells. Aluminium fluoride was not mutagenic in *S. typhimurium* or *E. coli*. Aluminium chloride and sulphate induced increases in the frequency of micronuclei in human lymphocytes and fibroblasts by means of both clastogenic and aneuploidogenic mechanisms. Aluminium chloride caused other DNA damage. *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 sister chromatid exchanges in bone marrow cells of mice (not tested in rats). Several *in vitro* studies suggest that indirect mechanisms for which no-effect levels may exist underlie these effects.

There are limited data from carcinogenicity studies. No increase in tumour incidences was found in rats exposed to a refractory material consisting of 96% aluminium oxide and 4% silica at aluminium concentrations of ca. 2.3 mg/m³ 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.

There are no inhalation reproduction toxicity studies or studies on the effects of metallic aluminium on fertility or development, but there are studies in which

aluminium compounds were administered in the diet or drinking water. Daily doses of ca. 20 mg Al/kg bw/day (as aluminium chloride in the drinking water) did not affect reproductive capacity in male rats and in male or female mice. In prenatal developmental toxicity studies in which water-soluble aluminium compounds were orally administered to dams during gestation, effects on fetuses, viz., 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 post-natal studies, investigating (neuro)developmental and/or (neuro)behavioural effects in the offspring of dams treated with water-soluble 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 post-natal 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 23 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.

Evaluation and advice

DECOS considers the available human data insufficient to derive (a) health-based occupational exposure limit(s) for aluminium metal and aluminium compounds. With respect to animal data, DECOS is 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.* is considered relevant for the derivation of a health-based occupational exposure limit. In this study performed with aluminium chlorohydrate, a NOAEL could not be identified. At 0.25 mg/m³, the lowest level tested, there was an indication of granulomatous change in the peribron-

chial lymph node of only 1/10 rats. Since these changes were seen at higher incidences at 2.5 mg/m³, the next higher concentration tested, 0.25 mg/m³ is considered to be a lowest-observed-adverse-effect level.

The LOAEL of 0.25 mg/m³ is taken as a starting point for the derivation of a health-based recommended occupational exposure limit (HBROEL). For extrapolation to a HBROEL, the following aspects are taken into account: the absence of a NOAEL, the difference between experimental conditions and the exposure pattern of the worker (i.e., the exposure duration in the key experiment vs. exposure for 40 years), and interspecies and intraspecies variation. For the absence of a NOAEL, DECOS applies a factor of 2 because the effects observed in laboratory animals at 0.25 mg/m³ are considered to be minimal both with respect to incidence as severity. A factor for exposure duration is not deemed necessary, as the exposure time in the study of Steinhagen, six months, is considered sufficient for long-term exposure. No factor for interspecies differences is used as the animal data showed that granulomatous inflammation in rats, guinea pigs, and hamsters occurred at comparable concentrations. For intraspecies variation, a factor of 3 is taken.

Applying the total extrapolation factor of 6 results in a HBROEL for aluminium chlorohydrate of 0.05 mg/m³ (inhalable dust) (as an eight-hour time-weighted average).

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 result in precipitation of forms of aluminium hydroxide. DECOS infers 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. Since other aluminium compounds may behave in the lungs in a similar way, DECOS has considered the possibility to recommend a health-based occupational exposure limits for other aluminium compounds from the Steinhagen study. However, in DECOS's view, too little is known regarding the factors that determine the aluminium toxicity in the lungs to allow extrapolation to other aluminium compounds.

Therefore, DECOS concludes that, except for aluminium chlorohydrate, the data are insufficient to allow recommendation of (a) health-based occupational exposure limit(s) for aluminium metal or aluminium compounds.

Health-based recommended occupational exposure limit

The Dutch Expert Committee on Occupational Safety recommends a health-based occupational exposure limit for aluminium chlorohydrate of 0.05 mg/m³, as inhalable dust, as an eight-hour time-weighted average concentration.

No health-based occupational exposure limits could be recommended for aluminium metal or other aluminium compounds.

This report contains an additional consideration of DECOS about the use of the health-based occupational exposure limit for aluminium chlorohydrate for setting an occupational exposure limit for insoluble or poorly soluble forms of aluminium.