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Addendum to Aluminium

Assessment Values in Biological Material – Translation of the German version from 2018

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BAT value documentation

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Abstract

In 2017, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the biological tolerance value (BAT value) for aluminium [7429-90-5]. Available publications are described in detail.

The BAT value of 60 µg aluminium/g creatinine evaluated in 2009 was based on the linear correlation between external and internal exposure. The aim of this re-evaluation was the derivation of a health-based BAT value considering the most sensitive critical effect of aluminium, the neurotoxicity. For this purpose, the available studies of aluminium-exposed workers were taken into account, when the internal aluminium exposure as well as the occurrence of subclinical neurotoxic effects were determined. The effects had been measured with standardised neuropsychological test procedures. From these studies, a no observed adverse effect level (NOAEL) of 50 µg/g creatinine for the occurrence of subtle neurotoxic effects of humans was estimated. Therefore, a BAT value of 50 µg aluminium/g creatinine was evaluated. Sampling time for long-term exposures is at the end of the shift after several shifts.

Keywords

aluminium; occupational exposure; biological tolerance value; BAT value; toxicity

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BAT (2017)	**50 µg aluminium/g creatinine** Sampling time: for long-term exposures: at the end of the shift after several shifts
MAK value	1.5 mg/m³ A (1997)
	4 mg/m³ E (2006)
Absorption through the skin	–
Carcinogenicity	–

11 Re-evaluation

In 1989, a BAT value of 200 µg aluminium/L urine was derived (Bauer and Schaller 1990) based on a correlation between external exposure and internal exposure to aluminium at the then valid MAK value of 6 mg/m³ (measured as fine dust). After lowering the MAK values for aluminium to 1.5 mg/m³ (respirable fraction, 1997) and 4 mg/m³ (inhalable fraction, 2006), the BAT value was lowered to 60 µg/g creatinine on the basis of the relationship between external and internal exposure (Letzel 2009).

This evaluation is based on the aluminium-specific effects.

11.1 Metabolism and Toxicokinetics

There are the following routes of entry for aluminium and its compounds into the body: inhalation, ingestion and, to a limited extent, also absorption through the skin. The daily dietary intake is estimated to be 1.6 to 13 mg. The oral bioavailability of aluminium after dietary exposure is approximately 0.1% (EFSA 2008). There are only few studies on the dermal absorption of aluminium compounds investigating the absorption of aluminium chlorohydrate from antiperspirants. In these studies, penetration rates of 0.01% in vivo (Flarend et al. 2001) and up to 0.06% in vitro (Pineau et al. 2012) were reported.

Occupational exposure to dust or fumes containing aluminium can lead to increased respiratory absorption of aluminium, influenced by factors such as the solubility of the relevant substances or particle size. Krewski et al. (2007) estimate that inhalation of aluminium dust and fume at the workplace by refinery workers and welders leads to a daily intake of approximately 21 mg/day (300 µg/kg body weight/day), 1–2% of which are bioavailable.

After absorption into the body, aluminium in plasma is bound to the protein transferrin (~ 90%) or to citrate, phosphate or as citrate-phosphate complex (7–8%) (Yokel and McNamara 2001) and then distributed in the organism. Evidence of aluminium nanoparticles found in the human brain and results from animal experiments show that certain aluminium species are able to cross the blood-brain barrier (Exley and House 2011; House et al. 2012; Sethi et al. 2008).

Due to the strong protein binding, aluminium accumulates in the brain and there in particular in the hippocampus, where the concentration was 6 times higher than in the cerebral cortex (Kaur et al. 2006). In addition to the redistribution of aluminium into the brain upon entry into the systemic circulation, the transport of aluminium into the brain via the olfactory epithelium and the olfactory nerve fibres is also discussed (Perl and Good 1987).

High aluminium concentrations are found especially in the skeleton. Whereas aluminium is released relatively rapidly from most tissues and excreted in the urine, elimination from the bones proceeds very slowly with a half-life of several years. After chronic exposure, aluminium may therefore accumulate in this compartment (EFSA 2008; Hellström et al. 2005). Data on the elimination of aluminium from the human body vary considerably. Elimination half-lives have been published, ranging from a few hours (Pierre et al. 1995; Sjögren et al. 1985) to several weeks, months or years (Elinder et al. 1991; Letzel et al. 1999; Ljunggren et al. 1991; Sjögren et al. 1988, 1996). Besides, major inter-individual differences in half-lives of 13 to 215 days are observed. The biological half-life of urinary aluminium excretion seems to depend on individual factors as well as largely on cumulative pre-exposure (Letzel et al. 1999; Sjögren et al. 1988). The urinary excretion kinetics depend on aluminium storage in at least two functional compartments of the organism with different elimination behaviour. In particular bones and lungs are the subject of discussion (Sjögren et al. 1988).

Despite the relatively high daily intake of aluminium, only relatively small amounts of aluminium can normally be detected in blood and organs. The data on background exposure of the general population show major fluctuations in serum or plasma levels. According to the German Federal Environment Agency, the reference range for aluminium in serum is < 5 µg/L (UBA 1998). According to clinical practice guidelines (National Kidney Foundation 2003), serum aluminium levels in dialysis patients should be below 20 µg/L.

The German Federal Environment Agency set a provisional reference value of 15 µg/L for urinary aluminium excretion levels in the general population (UBA 1998).

The toxicokinetics of aluminium after controlled exposure of 12 subjects to the emissions of a metal inert gas welding process were investigated in a study by Bertram et al. (2015) (total dust mass concentration of 2.5 mg/m^3, aluminium 1.29 mg/m^3 for 6 hours, biomonitoring using high-resolution atomic absorption spectrometry). After the end of exposure, urinary aluminium concentrations had increased significantly from 13.5 µg aluminium/L to 23.5 µg aluminium/L urine on average. No significant increase in plasma aluminium concentrations was observed. Elimination kinetics were biphasic, with urinary aluminium having returned to baseline concentrations after about seven days.

11.2 Toxicology

The various physical and chemical forms of aluminium differ with regard to their substance-specific bioavailability and their distribution in the body after exposure. They therefore also have a different potential effect and probably a different mechanism of action. At the workplace, exposure to sparingly soluble aluminium compounds is particularly prevalent. Nonetheless, a certain proportion of these are

bioavailable, since biomonitoring of workers yielded increased aluminium levels in plasma/serum and increased urinary excretions compared to the general population (see Section 11.3). Consequently, not only the particle properties but also the aluminium-specific effects have to be taken into account for evaluation.

While the Al^{3+} ion is the entity responsible for tissue damage with soluble aluminium compounds, the inhalation toxicity of sparingly soluble aluminium oxides is mainly determined by the particle properties, irrespective of Al^{3+} (Willhite et al. 2014).

A consistently high particle load leads to an accumulation of particles containing aluminium in the **lungs** and lymph nodes. It impairs pulmonary clearance and causes chronic inflammation and ultimately pulmonary fibrosis ("**aluminosis**", see Bauer and Schaller 1990; Greim 2007).

Soluble aluminium occurs as a highly positively charged Al^{3+} ion with a high affinity for phosphate groups (ATP) and metal-binding amino acids such as histidine, tyrosine and arginine. This can affect iron and calcium homoeostasis. The binding of Al^{3+} to phosphate groups of DNA and RNA affects DNA topology and influences the expression of various genes essential for brain functions in the CNS (Kawahara and Kato-Negishi 2011). The **CNS toxicity** of aluminium was observed in dialysis patients treated with dialysis fluids containing aluminium (dialysis encephalopathy) (see Bauer and Schaller 1990; Greim 2007). Various in vivo and in vitro studies show that aluminium can influence more than 200 biologically important reactions in the nervous system (Kawahara and Kato-Negishi 2011). Numerous neuropsychological tests, aiming to assess various cognitive and motor functions, are used to objectify behavioural toxic effects. Some of the neurotoxic mechanisms affect important neurobiological processes underlying these functions. Aluminium damages in particular cholinergic neurons by affecting acetyl-CoA (citric acid cycle; formation and release of acetylcholine) and influences neuronal signalling pathways associated with the N-methyl-D-aspartate (NMDA) receptor (Nday et al. 2010). These processes are closely linked to motor skills, learning and memory. There is currently no evidence of a link between exposure to aluminium and Alzheimer's disease (Kawahara and Kato-Negishi 2011; Walton 2014). Individuals suffering from Alzheimer's disease were found to have elevated brain aluminium levels (Bhattacharjee et al. 2013; Candy et al. 1986). To date, however, it remains unclear whether this is a cause or an effect of Alzheimer's disease.

No consistent data from epidemiological studies are currently available regarding the influence of aluminium salts used in antiperspirants on the development of **breast cancer**. Various working groups found no evidence that the use of antiperspirants increases the risk of breast cancer (Fakri et al. 2006; Mirick et al. 2002; Namer et al. 2008). An association is described in the studies by McGrath (2003) and by the working group of Darbre et al. (Darbre 2005, 2016; Darbre et al. 2011; Farasani und Darbre 2015). In animal studies, the oral administration of a carcinogenic non-aluminium-containing substance (2,7-dimethylbenz[a]anthracene) induced mammary gland tumours in which significantly elevated aluminium concentrations were measured (Ogoshi et al. 1994). According to these results, aluminium does not seem to trigger the tumours, but is stored to a greater extent in tissue during tumour development.

Aluminium and its compounds are currently not classified as carcinogens both nationally and internationally. A peripheral neurotoxic effect (polyneuropathy) has not been scientifically proven. Other toxic effects (e.g. on **bones** and **blood**) as well **developmental toxicity** are described in the MAK Value Documentation (Greim 2007).

11.3 Relationship between Internal Exposure and Effects

Occupational exposure to dust containing aluminium, aluminium oxide or aluminium hydroxide occurs in the metal industry (during welding, grinding, polishing, aluminium powder production or processing), in foundries (during melting, casting, cleaning or blasting) and in plants processing or working such materials (e.g. blasting of metal parts or corundum blasting or with surface coatings). This may result in inhalation exposure to respirable dust and fumes containing aluminium (Greim 2007).

Pulmonary Toxicity

In humans, aluminium has been reported to have pathogenic effects on the lungs. Aluminosis occurs at aluminium concentrations of more than 200 µg/L urine (see Bauer and Schaller 1990; Greim 2007; Kraus et al. 2006).

Neurotoxicity

Epidemiological studies were conducted to investigate neurotoxic effects by identifying the two major functional areas involved in motor and cognitive functions using different test methods. The tests in the individual areas are not completely independent of each other, but nevertheless cover totally different functions, e.g. attention, learning, memory, reasoning or executive functions in the cognitive domain. These functions are further subdivided into various sub-functions, e.g. short-term and long-term memory, or – depending on the type of information to be memorized – semantic and episodic memory. With regard to motor skills, functions such as motor speed, dexterity or tremor are investigated. In tracking tasks in particular, there is a clear overlap between motor and cognitive performance. It is important to note that not all functions or sub-functions have to be impaired at the same time in the case of a disorder. Table 1 and Table 2 give an overview of the available occupational studies in which individuals exposed to aluminium were examined with regard to their internal exposure and possible neurotoxic effects, specifying the neuropsychological tests used and the parameters of significantly impaired performance. A study by Hartwig (2011) delivers a compilation of individual tests with explanations. In the occupational studies, various internationally recognized neuropsychological test batteries were applied, e.g. tests of the WHO-NCTB (Neurobehavioral Core Test Battery) and of the EURO-NES (European Neurobehavioral Evaluation System). Studies are evaluated in which the excretion of aluminium was quantified as a parameter of internal exposure.

Cross-sectional studies of workers after exposure to aluminium

Table 1 summarizes the available cross-sectional studies which published both biomonitoring data and results from neuropsychological examinations for workers

exposed to aluminium. In a Finnish study, low- and high-exposure aluminium welders as well as a reference group of mild steel welders were examined (Akila et al. 1999 as well as Riihimäki et al. 2000). Based on an aggregated measure of aluminium body burden, the subjects were classified into a high-exposure, low-exposure and reference group (Riihimäki et al. 2000). Even the low-exposure group performed poorer in the memory for designs test as well as visuospatial and constructive task (block test) at mean urinary aluminium concentrations of 61 µg/L (range 30–108 µg/L). Exposure-response relationships could be established for the synonyms, embedded figures, digit symbol substitution and dual-task tests (Akila et al. 1999). The high-exposure group showed a significant increase in fatigue, emotional instability and concentration difficulties compared to the reference group. Subsidiary aspects of these symptoms also showed significant trends in the reference, high- and low-exposure group. Neuropsychological tests in the analysis by Riihimäki et al. (2000) revealed effects in the Bourdon-Wiersma dot cancellation test, in a dual task that demanded complex attention and processing of information in the working memory system, in backward counting as well as in synonyms and memory for designs tests. Dose-response relationships occurred in these test and in the forward digit span task. The EEG analysis revealed pathological findings only for aluminium welders. Mild, diffuse abnormalities were found in 17% of the low-exposure group and 27% of the high-exposure group, and mild to moderate epileptiform abnormalities in 7% and 17%, respectively. The authors concluded that neurophysiological and neuropsychological measurements as well as subjective symptomatology indicated mild but unequivocal findings dose-dependently associated with increasing aluminium body burden. According to the authors, the body burden threshold for adverse effect approximates a value of 4–6 µmol aluminium/L urine (108–162 µg/L urine) and 0.25–0.35 µmol aluminium/L serum (7–9 µg/L serum) among aluminium welders (Riihimäki et al. 2000).

Bast-Pettersen et al. (2000) observed an excretion of 40.5 (18.9–129.5) µg aluminium/L urine and 35.8 (14.3–109.7) µg aluminium/g creatinine in 20 aluminium welders who had been exposed to aluminium for an average of 8 years. The biomonitoring results for the 20 construction workers without aluminium exposure who served as referents were not published. The welders reported more symptoms, but as a group they performed better than the referents on a tremor test (hand steadiness). Years of exposure, but not age, was predictive of poorer performance. The welders' reaction times were rapid by clinical standards. Although the welders as a group performed better than the referents, there was a significant relation between longer reaction times and aluminium concentrations in the air. The authors saw the relations between hand steadiness and years of exposure, as well as between reaction time and airborne aluminium concentration as an indication of slight effects from exposure to aluminium. The welders' better performance was explained by a selection bias, since workers with high manual skills and a possible job-related training effect were examined.

In an earlier study by this working group, elderly workers (aged 61–66 years) at a Norwegian aluminium plant who had been exposed to aluminium in the foundry or in the potroom over a long period of at least 10, on average 19 years, were examined (Bast-Pettersen et al. 1994). The subjects showed differences in the intelligence quotient (higher for foundry workers than for potroom workers and controls). The

biomonitoring studies were conducted after or shortly before retirement. The aluminium concentrations in the urine of the workers were 12.6 ± 7.1 µg/L (potroom) and 9.9 ± 8.8 µg/L (foundry) and in the urine of the controls 7.8 ± 5.2 µg/L. There was a significant difference in the tremor test and a tendency towards impaired visuospatial organisation (block design test) among the potroom workers. The average urinary aluminium concentration in younger colleagues working in the same company, however, was 54 µg/L for potroom workers and 32 µg/L for foundry workers. This may indicate that the elderly workers examined in this study had been exposed to significantly lower aluminium levels than their younger colleagues some time before the study. Due to the long exposure period, it is possible that long-term effects have been observed despite the fact that the urinary aluminium concentration at the time of measurement was in the range of the background exposure of the general population.

Guo et al. (1999) examined 101 workers from an aluminium production plant and 64 controls. With 29.9 (7.9–105.3) µg/L, the urinary aluminium concentration in the exposed workers was significantly higher than in the controls with 15.1 (4.7–26.7) µg/L. The creatinine-adjusted values were unusually high with 41.8 (14.9–111.1) µg/g creatinine and 17.7 (3.5–42.8) µg/g creatinine (in each case mean value (range)) compared to the concentrations per liter urine, which suggests a high dilution of the urine samples. The workers were exposed to airborne aluminium concentrations of 5.31 mg/m^3 on average. With regard to neuropsychological tests, the scores achieved by younger exposed workers on the digit span test, by middle-aged exposed workers on the digit symbol substitution test, and by older exposed workers on the pursuit aiming test were found to be markedly lower in all exposed groups compared to the control groups of the same age ranges. Affective disturbances were observed in older workers exposed to aluminium, but not in younger workers. Exposure to aluminium seems to have an age-dependent influence on the behaviour. In the multiple comparisons, only some differences were found depending on the different age groups, while there was no consistency in the generally weak effects. Younger workers were more likely to suffer from impaired memory, while in older workers the mood and attention tended to be affected.

He et al. (2003) examined 32 controls and 33 potroom workers who had been exposed to aluminium for 15 ± 6 years. The airborne aluminium concentration was 6.4 (2.9–11.4) mg/m^3. The urinary aluminium concentration was specified as 40.1 ± 9.4 µg/g* creatinine for the group of exposed workers and 26.8 ± 8.9 µg/g* creatinine for the control group (*obviously wrongly specified as µg/mg creatinine in the publication). Neuropsychological tests yielded significantly lower scores for information processing speed (digit symbol substitution test) and pursuit aiming in potroom workers compared to the control group. This study, too, showed certain inconsistencies in the different test performances. For example, the exposed workers performed significantly better on the simple reaction time test.

Hosovski et al. (1990) analysed blood and urine samples from 87 workers who had been exposed to aluminium fumes and dust in an aluminium foundry for at least 6 years, as well as 60 controls. Deferoxamine was then administered to the subjects to release aluminium from the storage depots in their bodies. Afterwards, aluminium was again determined in biological material. Prior to the deferoxamine treatment, urinary aluminium concentrations were 45 ± 55 µg/L in the exposed

workers and 7 ± 8 µg/L in the controls, as well as 103 ± 116 µg/L (exposed workers) and 11 ± 13 µg/L (controls) after the deferoxamine treatment. Neuropsychological tests yielded lower scores for choice reaction time, oculomotor coordination, psychomotor performance, short-time memory (digit span), information processing speed, visuoconstruction (object assembly) and reasoning (picture completion) in the exposed workers. According to the authors, these changes could be a consequence of the long-term effects of aluminium.

Sjögren et al. (1996) examined 38 aluminium welders having been exposed to aluminium for at least 5 years and 39 controls. The concentrations of 24.0 (4.5–162) µg aluminium/g creatinine determined for the exposed workers and 4.7 (< 1–24.9) µg/g creatinine for the controls are probably 25% too low, as estimated by the authors by comparison with values from external control samples. Some samples were taken up to 150 days after exposure. In the questionnaire, welders reported more symptoms than controls. Neuropsychological tests such as the Luria-Nebraska neuropsychological battery, the finger tapping test and the pegboard test revealed some motor impairments. After dividing the welders into three groups with varying levels of exposure, the authors observed impaired motor performance in the tapping test and in one of the Luria-Nebraska tests in the workers with highest level of exposure (> 24 µg/L, median 59 µg aluminium/L urine). A significant dose-response relationship was found for the tapping test. The authors conclude that subtle motor disturbances can be observed at concentrations from about 50 µg aluminium/L urine upwards.

The 17 aluminium welders from a shipyard examined in the study by Hänninen et al. (1994) showed median concentrations of 64.8 (24.3–164.6) µg aluminium/L urine as well as median concentrations of 4.9 (0.8–17.3) µg aluminium/L serum after approximately four years of exposure to aluminium. The time of sampling was inconsistent with a variable distance to exposure (partly during the summer holidays) and to neuropsychological testing. In the neuropsychological tests, the authors observed effects on memory (digit span, memory for designs) and learning. Quantitative electroencephalography (EEG) revealed an exposure-response relationship for alpha activity in the frontal area using correlation analysis. A control group was not examined.

The studies by Polizzi et al. (2002), Zawilla et al. (2014), Giorgianni et al. (2014) and Yang et al. (2015) did not measure aluminium concentrations in urine, but in serum or plasma (see Table 1).

Longitudinal studies of workers subjected to continued exposure to aluminium

Table 2 gives an overview of the available longitudinal studies of workers exposed to aluminium, who were subjected to both biomonitoring studies and neuropsychological tests.

In the longitudinal studies by Buchta et al. and Kiesswetter et al., two groups of aluminium welders were examined who differed in their range of work activities and the resulting exposure. One group consisted of serial automotive production workers employed at a major automobile manufacturer (Buchta et al. 2003; Kiesswetter et al. 2009). The second group consisted of welders from five different companies of the train body and truck trailer construction industry (Buchta et al. 2005; Kiesswetter et al. 2007). Both studies were conducted as longitudinal studies based on a re-

peated measurement design over a period of four years with three measurements (cross-sectional studies) at two-year intervals.

At the beginning of the study (1999), cohort I from the automotive industry comprised 101 aluminium welders (mean age in 1999: 35 years) and a demographically similar control group of 50 subjects of the same industry, who were not exposed to aluminium. In the third examination (2003), 99 exposed workers and 50 controls were available for investigation. In cohort II from the train body and truck trailer construction industry, 44 aluminium welders (mean age in 1999: 40 years) and 37 controls were examined in 1999. In the third examination (2003), only 20 exposed workers and 12 controls were available for investigation. The examination programme included a standardised medical history interview, a physical examination, a pulmonary function test, high-resolution computed tomography (HRCT) of the lungs (only aluminium welders), biomonitoring (aluminium in urine and in plasma) and ambient air monitoring as well as selected psychometric tests. The subtests of the EURO-NES test battery were evaluated using multivariate analysis of covariance (MANCOVA) for repeated measurements. Age, education and CDT (carbon hydrate-deficient transferrin = marker for alcohol consumption) were considered as covariates. Any relevant exposure to other neurotoxic substances such as solvents or lead was excluded on the basis of occupational history. In addition to the cross-sectional studies, exposure monitoring (air monitoring and biomonitoring) of the welders was performed at annual intervals. The monitoring was carried out before and after each shift. Table 2 shows the results of urinary aluminium concentrations. The welders in the train and truck construction industry had higher aluminium concentrations of 59–144 µg/g creatinine than the welders in the automobile industry (13–38 µg/g creatinine), while median aluminium concentrations of 4–9 µg/g creatinine were measured in the controls.

The exposed workers in the **train and truck construction industry** (cohort II) showed significantly poorer neuropsychological test performance on the symbol-digit substitution test and the attention switching task (Buchta et al. 2005). After another 2 years, the exposed workers performed significantly worse than the controls in the block design test (Kiesswetter et al. 2007). Kiesswetter et al. concluded that despite high exposure (maximum value of up to 560 µg/g creatinine), the aluminium welders who had been exposed for an average of 15 years showed no significantly increased symptom levels compared to control groups. As no correlation was found between performance parameters and exposure markers (e.g. aluminium in urine) in terms of a dose-response relationship, the authors considered it rather unlikely that exposure to aluminium had an effect on cognitive performance. Differences in performance between the two groups were therefore considered to be due to selection rather than exposure.

The authors discussed the possibility of a "healthy worker/survivor effect", since the mean exposure time was > 11 years and the inclusion criterion for the study was a minimum exposure of > 2 years. Some workers who had developed symptoms might have left the plant. Due to the small sample size, the authors also assumed that the study had limited statistical power (Buchta et al. 2005).

In the longitudinal study conducted in the **automobile industry** (cohort I), a significant effect was observed for the simple reaction time, which, however, did not increase with the duration of exposure. In the authors' opinion, it could be a random

result (just one positive result given a large number of tests performed) or a result describing possible pre-exposure group differences (Buchta et al. 2003). Exposed workers' simple reaction time was also found to be significantly increased in the third examination (cross-sectional study). Kiesswetter et al. (2009) see no evidence of adverse neuropsychological effects attributable to aluminium welding. The authors stressed that possible selection effects had to be taken into account in the interpretation of differences in performance in cross-sectional studies to be able to reliable prove the impact of exposure. With regard to the long-term exposure of the subjects investigated, it should be noted that higher exposure levels are to be assumed for the pre-1999 period. Retrospective analysis of the biomonitoring data available in the plant concerned since 1991 indicates mean exposure of up to about 60 µg/g creatinine in the mid-1990s (Roßbach et al. 2007).

In another longitudinal study with two cross-sectional studies, Letzel et al. (2000) examined workers from the field of aluminium powder production at 5-year intervals, determining aluminium in urine and in plasma as well as event-related potentials and performing neuropsychological tests. The rather small number of participants and the significant decline in the number of participants in the longitudinal study must be taken into account. While 32 workers participated in the first examination, only 15 currently exposed and 6 formerly exposed workers participated in the second one. As a result of the first examination, occupational hygiene was improved, which led to a significant decrease in the mean internal exposure (range) of the exposed workers (n = 21) from 77.1 (4.6–321.4) µg/g creatinine to 19.8 (3–202.7) µg/g creatinine in the second examination. The aluminium concentrations measured in the controls were 9.0 (1.9–51.8) µg/g creatinine and 4.5 (2.2–15.9) µg/g creatinine, respectively. Longitudinal comparison of the first and second examination revealed significantly improved test performance in the control group for 5 out of 9 neuropsychological tests. Corresponding improvements were found in the group of exposed workers only for 2 out of the 5 tests in question (in total for 3 out of 9). This group's performance in the "object assembly" test was found to have deteriorated significantly over time. At the same time, a significant decrease in performance in terms of sustained attention was observed in the control group.

Meta-analysis

A meta-analysis by Meyer-Baron et al. (2007) took into account the studies by Akila et al. (1999), Bast-Pettersen et al. (1994, 2000), Buchta et al. (2003, 2005), Guo et al. (1999), He et al. (2003), Hosovski et al. (1990) as well as Sjögren et al. (1996), so that a total of 449 exposed and 315 control subjects were examined. In the 6 neuropsychological tests with 10 performance variables, exposed subjects performed significantly worse in the digit symbol substitution test than the controls. The authors concluded that even urinary aluminium concentrations below 135 µg/L have an impact on cognitive performance.

Critical aspects of the occupational studies available

Many cross-sectional studies suggest that that the measured urinary aluminium levels reflect the subjects' actual long-term exposure to aluminium only to a limited extent. Reasons for this include the unfavorable timing of the sampling or measurement problems. Cross-sectional studies based on one-time measurements can

therefore hardly be used to determine the dosage of a chronic cumulative toxic effect, unless it can be reasonably assumed that the exposure conditions have not changed over the years, i.e. are representative of the examined subjects' working lives.

Another critical aspect is the selection of the investigated groups, in particular of the control groups. Individual performance in neuropsychological tests is affected by numerous parameters (i. a. age, premorbid intelligence, trainable motor skills). It is therefore difficult to find groups that differ in their exposure to aluminium but are comparable with regard to as many potential influencing factors as possible. If exposed subjects and controls of a company are investigated, there is the challenge of assigning them correctly to the control group or the group of exposed workers. In the case of cross-sectional comparisons between different groups of workers, like for example welders and construction workers, it is questionable whether these studies can produce meaningful results, for example with regard to the effects of aluminium on motor activity. The problems associated with different activities being carried out by exposed subjects and controls also affect longitudinal studies. Ideally, however, this impact is mitigated in the case of longitudinal studies by the possibility of examining the development of differences in performance between the two groups over time. Another advantage of longitudinal studies is the use of repeated exposure assessment. In this way, long-term exposure can be determined more reliably than with one-time cross-sectional studies.

The risk of systematic bias of the studies used was assessed in a standardized manner. The following criteria were applied:

1. Selection of participants
2. Assignment to group of exposed subjects and control group
3. Exclusion criteria
4. Information status of the investigators
5. Consideration of covariates
6. Completeness of results (any missing values explained?)
7. Selective presentation of results
8. Conflict of interest faced by the authors, and
9. Sufficient statistical power

to be able to detect at least medium effects (effect size ≥ 0.50). Major problems were encountered as regards statistical power. Several studies were not able to detect medium effect sizes due to sample sizes. It is not possible to detect or statistically cover minor impairments, which are to be avoided using a BAT value, on the basis of studies with insufficient sample sizes. Some occasional difficulties were also encountered in relation to the exclusion criteria and the group assignment or in relation to a selective or incomplete presentation of results. A further critical aspect is the decrease in sensitivity and specificity of the test batteries in some studies due to summarizing evaluation. Besides, it often remains unclear whether the impact of circadian rhythms on performance, which could be significant in the case of shift work, was taken into account.

Based on corresponding risk of bias assessments, the quality and strength of evidence were rated as moderate according to the recommendations of Johnson et al. (2014).

11.4 Evaluation of the BAT Value

The most sensitive endpoint for the derivation of a health-based BAT value for aluminium is the occurrence of preclinical neurotoxic effects after exposure. These effects can be objectified with standardized neuropsychological tests and are used in occupational studies as an indirect method of assessing neurotoxic effects. These are early signs of possible structural or functional damage to the central nervous system.

The type of exposure (e.g. welding, powder production) affects the systemic exposure to aluminium and thus the occurrence of possible effects. As aluminium-related neurotoxic effects are not acute, but chronic, cumulative long-term exposure is important for the assessment of adverse effects. Ultimately, an exposure parameter would have to be generated based on the level and duration of exposure. For cumulative exposure assessment, however, multiple measurements would be required to allow for a reliable estimation. Such measurements are not available for the study collectives in question or in practice. Therefore, this procedure cannot be used for the evaluation of a BAT value.

As a first step, the evaluation of a BAT value on the basis of the available occupational studies is carried out in relation to the available longitudinal studies. In these studies, possible selection effects are of minor importance due to the investigation of effects in the course of time. Any changes in long-term exposure can be detected quantitatively by repeated exposure assessment. The one-time exposure assessment in cross-sectional studies is considered too unreliable to provide a quantitative assessment of the effects of chronic long-term exposure.

In the studies by Buchta et al. (2005) and Kiesswetter et al. (2007), welders exposed to aluminium in the **train and truck construction industry** were examined and medians (ranges; year) of 97.0 (17.9–399.0; 1999), 143.9 (8.9–431.8; 2001) and 64.5 (23.9–560.0; 2003) µg aluminium/g creatinine were measured in the post-shift urine. At a median aluminium concentration of approx. 100 µg/g creatinine in post-shift urine measured over a period of 5 years, welders exposed to aluminium performed worse in most of the repeatedly performed neuropsychological tests compared to controls with 4.0 (1.6–78.9; 1999), 4.5 (1.6–86.2; 2001) and 8.5 (1.8–37.5; 2003) µg/g creatinine (Buchta et al. 2005; Kiesswetter et al. 2007). After long-term exposure to high levels of aluminium in the train and truck construction industry, effects were increasingly observed, which, however, could not be reliably statistically verified due to the small number of subjects (20 exposed, 12 controls). The median internal exposure of the welders of approx. 100 µg/g creatinine is therefore interpreted as the LOAEL (Lowest Observed Adverse Effect Level).

With a significantly larger sample size (92 exposed, 50 controls), the only effect observed in a second study in **automotive engineering** was a significant prolongation of simple reaction time. As this effect did not increase with exposure time, it is not considered to be caused by exposure to aluminium. The lower exposure range covered in this study with median urinary concentrations in welders of up to 38 µg aluminium/g creatinine is considered to be the NOAEL (No Observed Adverse Effect Level) (post-shift urine levels of 37.9 (7.0–120.5; 1999, in the previous years rather higher), 33.6 (9.0–230.1; 2001) and 15.4 (0.7–94.9; 2003) µg/g creatinine) (Buchta et al. 2003; Kiesswetter et al. 2009).

In a study by Letzel (2000) conducted at an **aluminium powder plant**, no significant aluminium-induced effects were observed in exposed workers at urinary aluminium concentrations of 77.1 and 19.1 µg/g creatinine (median concentrations each), respectively, compared to controls. Longitudinal comparison yielded similar results. In the course of the study, there was a significant decrease both in exposure (presumably due to subjects who were no longer exposed) and in the number of subjects (decrease in number of exposed subjects from 32 to 21). The results of this study are thus less suitable for estimating a NOAEL. If only the available longitudinal studies are taken into account, a BAT value of 50 µg/g creatinine can be derived based on the NOAEL of 38 µg/creatinine from the studies by Buchta et al. (2003) and Kiesswetter et al. (2009) (post-shift median 1999, mean value of 43 µg/g, in the previous years rather higher (Roßbach et al. 2007)) and a LOAEL of 100 µg/g taking into account the small sample size from the studies by Buchta et al. (2005) and Kiesswetter et al. (2007).

In a second step, all the data available are analysed. Figure 1 shows the results obtained in the individual studies in their **entirety**. Each triangle corresponds to an effect size estimate related to the exposure concentration of the study. The effect size estimates are standardized mean differences, i.e. the difference between the mean test results of the exposed subject group and the control group is divided by the variance of the control group.

They thus represent standardized mean differences. If the median of the exposure concentration was known, the effects were related to it, while in all other cases the mean value was used. The area highlighted in grey depicts effect size estimates between 0.2 and –0.2 (by definition smaller than "small effects" (Cohen 1988)).

While numerous effects with positive effect sizes can (still) be detected at low concentrations, their proportion decreases as exposure increases, and the negative effects are increasing. As there are significant differences in exposure within the studies and medians provide a more robust estimate of exposure, all estimates used for the derivation of the BAT value that refer to **cognitive** effects are plotted against the respective median of the internal exposure in Figure 2. Studies without median data were not taken into account.

The studies used for evaluation reveal a trend towards poorer cognitive performance as internal exposure increases. Above a value of about 50 µg/g creatinine, cognitive effects can thus be expected that go beyond the measure of negligible effects (negative effect size > 0.2) and can therefore be considered to be adverse.

There was no such clear correlation for motor effects.

For the derivation of the BAT value, the criteria established by the DFG ad hoc working group "Behavioural Toxicology" were applied, which were published by the Commission (DFG 1997). Accordingly, only those exposure-related changes are considered adverse effects that, in terms of magnitude, number, size and type, can no longer be regarded as tolerable performance deficits or tolerable deterioration of the well-being. Basically, the following criteria must be taken into account:

- Magnitude of the exposure effect
- Number of exposure effects
- Type of effects

- Consistency of effects in various studies
- Size of exposure effects
- Lack of reversibility of exposure effects

After applying these criteria to the results of the aforementioned occupational studies, in particular magnitude, type and size of the effects as well as consistency in various studies – the question of reversibility cannot be assessed due to lack of data – a urinary aluminium level of 50 µg/g creatinine is suggested as the BAT value for aluminium. This value corresponds to the NOAEL and confirms the finding that adverse cognitive effects are not to be expected even after chronic exposure if concentrations fall below this value.

It should be noted that this value is subject to uncertainties. For most of the studies it can be assumed that previous aluminium exposure levels were considerably higher. To date, however, there are no occupational studies investigating exposure over the entire working life.

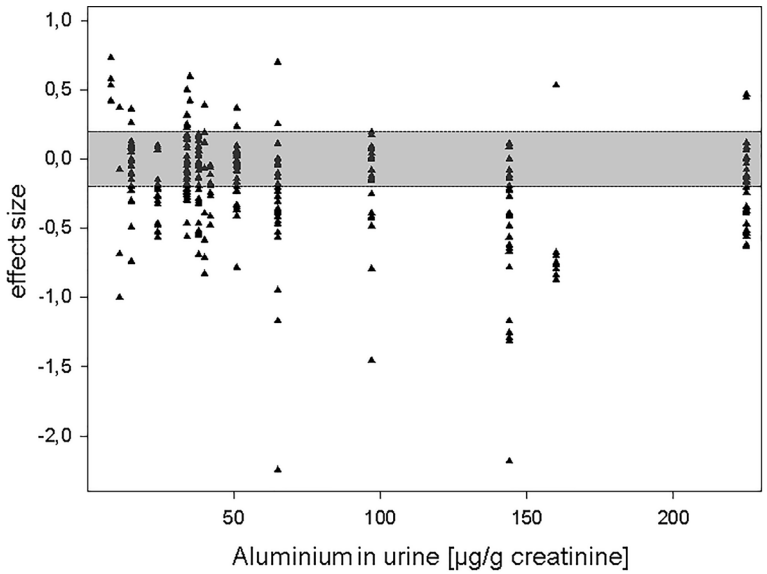

Figure 1 Cognitive and motor effects in their entirety identified in all studies, related to medians (if available) or mean values of urinary aluminium concentrations

The grey area depicts effect sizes that are still below small effect sizes (d = 0.2–0.5) (Cohen 1988).

Studies from left to right:

Bast-Pettersen et al. 1994: low-exposure group
Bast-Pettersen et al. 1994: high exposure group
Kiesswetter et al. 2009
Sjögren et al. 1996
Buchta et al. 2003: time of investigation 2; Riihimäki et al. 2000: low-exposure group
Bast-Pettersen et al. 2000
Buchta et al. 2003: time of investigation 1; Hosovski et al. 1990
He et al. 2003
Guo et al. 1999
Kiesswetter et al. 2007
Buchta et al. 2005: time of investigation 1
Buchta et al. 2005: time of investigation 2
Riihimäki et al. 2000: high exposure group
Akila et al. 1999

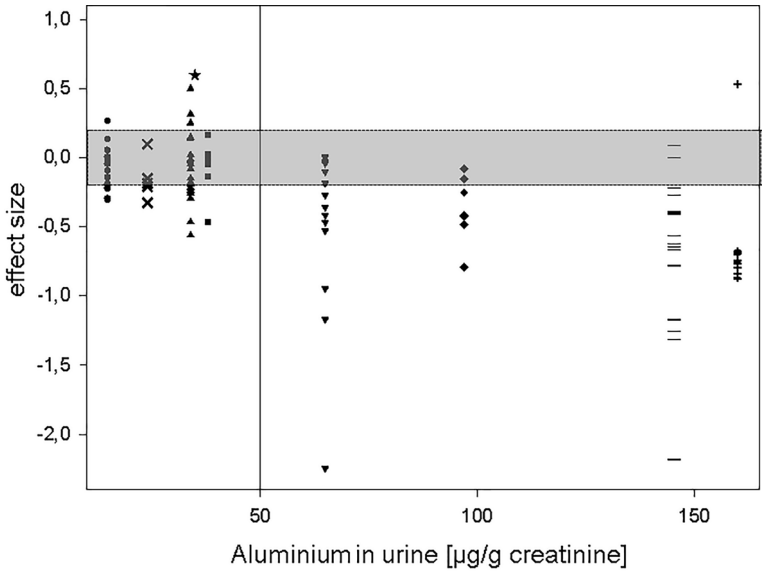

Figure 2 Cognitive effects in their entirety identified in the studies, related to the medians of urinary aluminium concentrations

Effect sizes highlighted in grey are below the small effect sizes (d = 0.2–0.5) (Cohen 1988). The vertical line separates effects observed at aluminium concentrations of above 50 µg/g creatinine.

Studies from left to right:

- ● Kiesswetter et al. 2009
- × Sjögren et al. 1996
- ▲ Buchta et al. 2003: time of investigation 2; Riihimäki et al. 2000: low-exposure group
- ★ Bast-Pettersen et al. 2000
- ■ Buchta et al. 2003: time of investigation 1
- ▼ Kiesswetter et al. 2007
- ◆ Buchta et al. 2005: time of investigation 1
- + Buchta et al. 2005: time of investigation 2
- – Riihimäki et al. 2000: high exposure group

The overall picture is consistent. The assessment of both the longitudinal studies and all studies in their entirety leads to the conclusion that for aluminium a NOAEL of 50 µg/g creatinine can be derived for the occurrence of preclinical neurotoxic effects in humans. Thus, a BAT value of

50 µg aluminium/g creatinine

In the case of long-term exposure, sampling shall be carried out at the end of the shift after several previous shifts.

11.5 Interpretation

The BAT value is evaluated in relation to creatinine in order to compensate for possible diuretic dilution effects (Roßbach et al. 2006).

The BAT value refers to normally concentrated urine, in which the creatinine level ranges from 0.3–3 g/L (Bader and Ochsmann 2010; WHO 1996). As a rule, it is advisable to repeat the measurement in normally hydrated subjects for urine samples outside the limits specified above.

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Approved by the Working Group: 23 January 2018

Table 1 Cross-sectional studies of individuals occupationally exposed to aluminium, showing the internal exposure, the neuropsychological tests used and the significant effects in terms of a decline in performance mentioned in the publication.

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine [µg/g crea]	Al in blood [µg/L]	Al in air [mg/m³]		
Akila et al. 1999	aluminium welders and controls (steel welders) 38.4 y* (22–58)	control group (< 1 µmol/L) n = 28	12.4* µg/L			tapping, Santa Ana dexterity test, simple reaction time, digit span, digit symbol substitution test, Stroop colour and word test, dual task, similarities, synonyms, paired associates, memory for designs, interference recall, similarities recall, digit symbol recall	low exposure group performed poorer than control group on: • memory for designs • block design test (some items) high exposure group performed poorer than low exposure group and control group on: • synonyms (no difference between low exposure group and control group) • digit symbol substitution test • dose-response relationships: • digit symbol substitution test • embedded figures • synonyms • dual task (some items)
		low exposure (1.1–4.0 µmol/L) n = 27	60.7* (29.7–107.9) µg/L				
		high exposure (> 4.1 µmol/L) n = 24	269.3* µg/L				

Table 1 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine [µg/g crea]	Al in blood [µg/L]	Al in air [mg/m³]		
Riihimäki et al. 2000	aluminium welders (1/3 had been exposed for > 10 y) control group (steel welders) 38.1 y* (29–48)	control group (< 1 µmol/L) n = 25	10.8# µg/L	2.2# S		tapping, Santa Ana dexterity test, simple reaction time, digit span, digit symbol substitution test, Stroop colour and word test, Bourdon-Wiersma dot cancellation accuracy, dual task, similarities, synonyms, embedded figures, block design test, associative learning, similarities recall, digit symbol recall, homogeneous interference, memory for designs	high exposure group performed poorer than control group on: • Bourdon-Wiersma dot cancellation accuracy • dual task • counting backwards • synonyms • memory for designs • dose-response relationships: • digit span forward • digit symbol substitution test • Bourdon Wiersma dot cancellation accuracy (some items) • counting backwards • dual task • synonyms
	low exposure 36.1 y* (24–54)	low exposure (1.1–4.0 µmol/L) n = 29	48.6# µg/L	3.8# S			
	high exposure 42 y* (22–58)	high exposure (> 4.1 µmol/L) n = 30	191.6# µg/L	12.4# S			

Table 1 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine [µg/g crea]	Al in blood [µg/L]	Al in air [mg/m³]		
Bast-Pettersen et al. 2000	aluminium welders (exposed for 8 y* (2–21)) 33 y* (21–52)	exposed group n = 20	40.5# (18.9–129.5) µg/L		0.9 (range 0.6–3.8)[1)]	static steadiness simple reaction time	dose-response relationships: • static steadiness • simple reaction time
	construction workers as a matched control group 34 y* (22–53)	control group n = 20	35.8# (14.3–109.7)				
Bast-Pettersen et al. 1994	aluminium production, (exposed for 19 y* (at least 10 y))					static steadiness, grooved pegboard test, simple reaction time, digit symbol substitution test, trail making test A, trail making test B, Benton visual retention, digit span, 12 words/learning and retention, 15 word pairs/learning and retention, information, similarities, vocabulary, picture completion, block design test	high exposure group performed poorer than control group on: • static steadiness (some items) • block design test
	potroom: 63 y*	n = 14 potroom workers	12.6* ± 7.1 µg/L	3.6* ± 1.6 S			
	foundry: 64 y*	n = 8 foundry workers	9.9* ± 8.8 µg/L	4.1* ± 2.2 S			
	control: 63 y*	n = 16 controls	7.8* ± 5.2 µg/L	2.9* ± 1.5 S			

Table 1 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure Al in urine [µg/g crea]	Al in blood [µg/L]	Al in air [mg/m³]	Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
Guo et al. 1999	aluminium production (founding, smelting, welding, exposed for at least 5 y) 37 y* ± 9	exposed group n = 101	exposed group 29.9* (7.9–105.3) µg/L control group 15.1* (4.7–26.7) µg/L		5.31* (0.67–10.76) µg/m³	simple reaction time, digit span, Santa Ana dexterity test, digit symbol substitution test, Benton visual retention, pursuit aiming	exposed group performed poorer than control group (in different age groups) on: • digit span forward • digit symbol substitution test • pursuit aiming
	controls 40 y* ± 9	control group n = 64	exposed group 41.8* (14.9–111.2) control group 17.7* (3.5–42.8)				
He et al. 2003	aluminium electrolysis (exposed for 15* ± 6 y) 35 y* ± 3	exposed group n = 32	exposed group 40.1* ± 9.4 µg/mg crea		6.36* (2.90–11.38)	simple reaction time, digit span, Santa Ana dexterity test, digit symbol substitution test, Benton visual retention, pursuit aiming	exposed group performed poorer than control group on: • digit symbol substitution test • pursuit aiming exposed group performed better than control group on: • simple reaction time
	matched control group	control group n = 34	control group 26.8* ± 8.9 µg/mg crea[2)]				

Table 1 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine [µg/g crea]	Al in blood [µg/L]	Al in air [mg/m³]		
Hosovski et al. 1990	aluminium foundry exposed to aluminium fumes and dust for at least 6 y (19 ± 7) 41 y* ± 7	exposed group n = 87	exposed group 45.4* ± 55.0 µg/L	exposed group 136.9* ± 103.2	4.6–11.5	simple reaction time complex reaction time Wechsler intelligence scale Bender Visual Motor Gestalt test	exposed group performed poorer than control group on: • complex reaction time • oculomotor coordination • sum of psychomotor tests • digit span • digit symbol substitution test • picture completion • object assembling
	control group 42 y* ± 9 5-day hospitalisation and treatment with deferoxamine	control group n = 60	control group 7.3* ± 7.8 µg/L	control group 58.1* ± 74.7			
Sjögren et al. 1996	aluminium welders (exposed to Al and Mn for at least 5 y) 39 y* (26–56)	exposed group n = 38	exposed group 22.0# (4–255) µg/L control group 3.0# (< 1–26) µg/L	exposed group 3.0# (< 1–27)		simple reaction time finger tapping digit span vocabulary, tracking digit symbol substitution test cylinders, Luria-Nebraska motor scale diadochokinesis	exposed group performed poorer than control group on: • Luria-Nebraska motor scale, subtests 3 and 4 • tapping • pegboard • dose-response relationships: • tapping
	controls (railroad welders) 40.1 y* (23–59)	control group n = 39	exposed group 24.0# (4.5–162) control group 4.7# (< 1–24.9)	control group 1.0# (< 1–11)			

Table 1 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine [µg/g crea]	Al in blood [µg/L]	Al in air [mg/m³]		
Hänninen et al. 1994	aluminium welders (shipyard, exposed for approx. 4 y, mostly used respiratory protection) 37 y* (24–48)	exposed group n = 17	64.8# (24.3–164.6) µg/L	4.9# (0.8–17.3) S		simple reaction time, tapping, Santa Ana dexterity test, digit symbol substitution test, block design test, embedded figures, symbol learning, memory for designs, digit span, associative learning, similarities, synonyms	dose-response relationships: • memory for designs • symbol learning • digit span • unexpected dose-response relationships: • simple reaction time
	no controls						
Polizzi et al. 2002	aluminium workers (retired for at least 10 y, formerly exposed to aluminium dust) 68 y* ± 1	formerly exposed group n = 64		exposed group 14.1* ± 3.5 S		mini-mental state examination (MMSE) clock drawing test	formerly exposed group performed poorer than control group on: • MMSE • clock drawing test
	controls 67 y* ± 1	control group n = 32		control group 8.2* ± 1.2 S			

Table 1 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine [µg/g crea]	Al in blood [µg/L]	Al in air [mg/m³]		
Zawilla et al. 2014	aluminium dust (aluminium factory in Egypt) 46 y* ± 10	high exposure group n = 23		26.5* ± 8.9 S	10.3* ± 2.4 (Al total dust)	Addenbrooke's cognitive examination-revised (ACE-R)	high exposure group performed poorer than low exposure group on: • memory (4 subtests) • language (2 subtests) • verbal fluency (2 subtests) • visuospatial and perceptual abilities (3 subtests) • dose-response relationships: • total score of cognitive performance
		intermediate exposure group n = 31		15.6* ± 4.3 S	6.5* ± 1.5 (Al total dust)		
	controls 46 y* ± 12	control group n = 51		4.4* ± 2.1 S			
Giorgianni et al. 2014	aluminium welders (shipyard, exposed for 15.8 ± 6.5 y) 38 y* ± 7	exposed group n = 86		exposed group 24.2* ± 10.0 S	19,5*	Wechsler memory scale (WMS), Stroop colour and word test, attention matrices test	exposed group performed poorer than control group on: • Wechsler memory scale (total score) • Stroop colour and word test (total score) • attention matrices test (total score) • dose-response relationships: • total score
		control group n = 90		control group 6.9* ± 2.0 S			

Table 1 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine [µg/g crea]	Al in blood [µg/L]	Al in air [mg/m³]		
Yang et al. 2015	Aluminium workers (potroom, exposed for at least 10 y; 21.2 y* ± 6.5) 45 y* ± 4	exposed group n = 366		48.99# (6.63–158.8) S		mini-mental state examination (MMSE)	medium exposure group performed poorer than low exposure group on: • MMSE high exposure group performed poorer than medium exposure group on: • MMSE • dose-response relationships: • mild cognitive impairment

Aluminium: 1 µmol/L = 26.98 µg/L
Abbreviations: PRE = pre-shift; POST = post-shift; U = urine; P = plasma; S = serum; y = years; MV = mean value; SD = standard deviation; creatinine = crea
* mean
# median
1) inside the respiratory protection
2) The Commission assumes that this is a unit error and that the values given in µg/g crea are correct.

Table 2 Longitudinal studies of individuals occupationally exposed to aluminium, showing the internal exposure, the neuropsychological tests used and the significant effects in terms of a decline in performance.

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine	Al in plasma [µg/L]	Al in air [mg/m³]		
Buchta et al. 2005	aluminium welders (train body and truck trailer construction industry, exposed for 11 y* ± 6) 43 y* ± 9	1999 PRE n = 33 POST n = 31	[µg/L]: PRE 136.6# (24.8–540.4); POST 130.0# (22.8–810.0) [µg/g crea]: PRE 92.1# (17.9–292.2); POST 97.0# (17.9–399.0)	PRE 9.6# (4.1–31.0); POST 11.6# (5.0–39.6)	5.6# (0–31.5) (median respirable dust-air) n = 36	vocabulary, recall of digits, block design, static steadiness, line tracing, aiming, tapping, pegboard, simple reaction time, standard progressive matrices, trail making, symbol-digit substitution, digit span, switching attention	exposed group performed poorer than control group in the second examination on: • symbol-digit substitution test • attention switching test (some items)
	control group (production workers from the same enterprise, published in Kiesswetter (2007) 40 y* ± 7	2001 PRE n = 34 POST n = 25 PRE n = 32 POST n = 25	[µg/L]: PRE 152,7# (2.9–656.3); POST 145.5# (5.0–656.3) [µg/g crea]: PRE 90.1# (7.6–420.6); POST 143.9# (8.9–431.8)	PRE 10.6# (3.3–40.3); POST 14.3# (3.8–51.0)	4.5# (1.3–15.6) (median respirable dust-air) n = 21		

Table 2 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine	Al in plasma [µg/L]	Al in air [mg/m³]		
Kiesswetter et al. 2007	aluminium welders (train body and truck trailer construction industry, exposed for 15 y* ± 4) 43 y* ± 7	exposed group 2003 PRE n = 31 POST n = 22 PRE n = 31 POST n = 22	[µg/L]: PRE 97.7# (9.9–801.4); POST 93.7# (26.8–568.6) [µg/g crea]: PRE 58.8# (10.7–276.4); POST 64.5# (23.9–560.0)	PRE 10.8# (4.0–39.3); POST 13.2# (6.6–44.3)	6.8# (1,9–29.7) (total dust-air)	vocabulary, recall of digits, block design, static steadiness, line tracing, aiming, tapping, pegboard, simple reaction time, standard progressive matrices, trail making, symbol-digit substitution, digit span, attention switching	exposed group performed poorer than control group on: • block design test
	control group (production workers from the same enterprise) 43 y* ± 6)	control group 1999 n = 27 2001 n = 24 2003 n = 17	[µg/L]: 5.8# (1.9–148.3); 6.0# (1.6–88.8); 8.3# (4.4–41.2) [µg/g crea]: 4.0# (1.6–78.9); 4.5# (1.6–86.2); 8.5# (1.8–37.5)	3.5# (1.0–8.2); 2.8# (1.3–5.9); 4.5# (3.3–5.9)			

Table 2 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine	Al in plasma [µg/L]	Al in air [mg/m³]		
Buchta et al. 2003	aluminium welders (automobile industry, exposed for 4.7 y* ± 1.6) 37* ± 7 control group (n = 38, from the same enterprise, published in Kiesswetter et al. 2009) 36* ± 8	exposed group 1999 n = 98	[µg/L]: PRE 71.8# (12.1–223.7); POST 47.6# (7.0–181.8) [µg/g crea]: PRE 38.4# (12.9–112.2); POST 37.9# (7.0–120.5)	PRE 10.3# (2.3–20.7); POST 8.3# (2.3–42.3)	0.47# (0.1–6.17) (median respirable air dust)	vocabulary, recall of digits, block design, static steadiness, line tracing, aiming, tapping, pegboard, simple reaction time, standard progressive matrices, trail making, symbol-digit substitution, digit span, attention switching	exposed group performed poorer than control group on: • simple reaction time
		exposed group 2001 n = 97	[µg/L]: PRE 58.3# (2.4–244); POST 39.8# (3.1–200.2) [µg/g crea]: PRE 35.4# (5.1–194.5); POST 33.6# (9.0–230.1)	PRE 4.3# (1.1–11.2); POST 4.1# (0.72–11.7)	0.67# (0.2–1.5)		

Table 2 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine	Al in plasma [µg/L]	Al in air [mg/m³]		
Kiesswetter et al. 2009	aluminium welders (automobile industry, exposed for 9 y* ± 2) 39 y* ± 7	exposed group 2003 PRE n = 99 POST n = 69	[µg/L]: PRE 21.7# (2.8–775.0); POST 16.1# (0.5–203.2) [µg/g crea]: PRE 12.6# (1.9–645.8); POST 15.4# (0.7–94.9)	PRE 4.3# (1.7–11.4); POST 4.3# (1.8–15.6)	0.7# (0.2–1.5)	vocabulary, recall of digits, block design, static steadiness, line tracing, aiming, tapping, pegboard, simple reaction time, standard progressive matrices, trail making, symbol-digit substitution, digit span, attention switching	exposed group performed poorer than control group on: • simple reaction time
	control group (from the same enterprise) 38 y* ± 8	control group 1999 n = 50 2001 n = 48 2003 n = 49	[µg/L]: 9.0# (2.8–40.2); 7.4# (2.2–93.6); 9.3# (0.5–95.4) [µg/g crea]: 5.2# (1.7–30.3); 6.0# (1.6–390); 5.0# (0.2–40.3)	4.4# (1.4–31.6); 2.3# (0.7–5.9) 3.8# (1.6–10.0)			

Table 2 (continued)

Study	Occupation Exposure Age (MV (range)/ MV ± SD)	n	Exposure			Test batteries	Significant changes in neuropsychological performance in terms of a decline in performance
			Al in urine	Al in plasma [µg/L]	Al in air [mg/m³]		
Letzel et al. 2000	aluminium powder production, exposed for 12# (2–37) y, 2nd examination 5 years later after occupational hygiene was improved 41# (26–60) y	exposed group n = 21 control group n = 30	[µg/L]: exposed group 98.8# (5.0–336.6); control group 7.6# (2.6–73.8) [µg/g crea]: exposed group 77.1# (4.6–321.4); control group 9.0# (1.9–51.8)	exposed group 8.5# (5.4–25.0) control group 4.3# (1.6–7.1)		multiple choice vocabulary, digit span, symbol-digit substitution, block design, trail making, syndrome short, sustained attention	exposed group performed poorer in examination 2 than in examination 1 on: • object assembly control group performed poorer in examination 2 than in examination 1 on: • sustained attention
	control group 42.5# (26–60) y	exposed group 5 y later n = 21 control group 5 y later n = 15	[µg/L]: exposed group 24.1# (3.4–218.9); control group 6.5# (2–25.4) [µg/g crea]: exposed group 19.8# (3–202.7); control group 4.5# (2.2–15.9)	exposed group 6.7# (1.6–20.6) control group 4.3# (1.9–12.9)			

Aluminium: 1 µmol/L = 26.98 µg/L
Abbreviations: PRE = pre-shift; POST = post-shift; U = urine; P = plasma; S = serum; y = years; MV = mean value; SD = standard deviation; creatinine = crea
* mean
# median