

INTERNATIONAL UNION OF PURE
AND APPLIED CHEMISTRY

ANALYTICAL CHEMISTRY DIVISION
COMMISSION ON MICROCHEMICAL TECHNIQUES AND
TRACE ANALYSIS*

**DETERMINATION OF ALUMINIUM IN
BIOLOGICAL MATERIALS BY GRAPHITE
FURNACE ATOMIC ABSORPTION
SPECTROMETRY (GFAAS)†**

Prepared for publication by

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†Series title: Critical Evaluation of Analytical Methods for Determination of Trace Elements in Various Matrices

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Determination of aluminium in biological materials by graphite furnace atomic absorption spectrometry (GFAAS)

Abstract. - A survey is given over various methods for the determination of aluminium in biological materials. Graphite furnace atomic absorption spectrometry (GFAAS) is the most widely used technique since it is sufficiently sensitive and simple to operate. The limitations inherent in GFAAS-procedures are critically discussed. Reported results for aluminium in blood, serum and tissues differ largely showing that the determination of this element is subjected to large errors due to contamination during sample handling.

INTRODUCTION

Accurate determination of aluminium in biological materials has become of great importance, since this element is suspected to be implicated in the aetiology of various neurological disorders, such as Alzheimer senile and presenile dementia, amyotrophic lateral sclerosis and Parkinson dementia of Guam, as well as in dialysis encephalopathy. The increased incidence of osteodystrophic lesions observed in dialysis patients has also been associated with aluminium toxicity. A common characteristic of all these pathological conditions is significantly increased concentrations of the element in the target organs, the grey matter of the brain and the bone (ref. 1). Only a few studies have so far been focused on the bioavailability of aluminium in relation to its chemical form. A recent study on rats (ref. 2) showed that when fed with aluminium citrate there was, in contrast to aluminium hydroxide, a significant accumulation of aluminium in brain and bone.

One of the major problems encountered in aluminium assays is the control of contamination including all steps from sample collection and storage to the handling procedures preceding injection of the sample into the measuring device. A major source of aluminium is airborne, which means that a prerequisite for reliable determinations is that dust is effectively excluded (ref. 3). This can be realized by working under an environmental hood with a laminar flow of class 100 air, where reagents and samples are prepared (ref. 4). Ideally, collection of samples should also be performed in a virtually dust-free environment. Ordinary glassware should not be used and any materials involved should be cleaned in acids or by EDTA-extraction (ref. 3). Plastic materials like polycarbonate, polypropylene and Teflon or quartz are recommended, but all materials involved must be frequently screened to highlight possible sources of aluminium contamination (ref. 3). In order to obtain low blanks, the use of purified acids (sub-boiling distillation) is necessary. It should be mentioned that commercially available nitric acid of suprapure quality is sold in glass bottles, which means that the aluminium concentration can be expected to increase with time. Additives such as anticoagulants tend to enhance the blank value, and hence deteriorate detection limits. The risk for contamination is also increased with the number of sample pretreatment steps like centrifugation or homogenization. In a digestion procedure following all precautions with respect to contamination, blanks of the order 0.001 µg/g (brain tissue or blood) were obtained (refs. 2,16).

Approaches to trace aluminium analysis in biological tissues have, for the most part, involved the use of techniques which determine bulk levels. These methods include proton induced X-ray emission (PIXE), neutron activation analysis and atomic emission- and atomic absorption spectrometry. For localization of aluminium in, for example brain tissue, other methods have proved more efficient. A few recent studies have used the scanning electron microscope to detect aluminium deposits by energy dispersive X-ray analysis. In spite of the fact that this technique is not particularly sensitive, Smith et al. (ref. 5) were able to locate aluminium deposits within the glomerular basement membrane of humans. An alternative approach providing better sensitivity is the use of laser microprobe mass spectrometry. In this technique an intense laser beam is directed towards a specific organelle, and species vaporized from that region are then analyzed in a mass spectrometer. This technique has been used to localize aluminium in the lysosomes of Kupffer cells in liver tissue from patients on chronic hemodialysis. For speciation studies, NMR has proven to be a very promising technique (ref. 6).

Among the methods mentioned above for bulk aluminium determinations, X-ray fluorescence does not appear to be sensitive enough in its present state to detect the trace levels in, for example, serum (ref. 7). Neutron activation analysis, on the other hand, has been used by several authors to determine the aluminium content of biological samples (refs. 8-10).

Sodium and chloride ions, however, must be removed before irradiation of the samples otherwise they mask the aluminium peak during the counting procedure (ref. 8). The reagents and resins used to remove interfering ions usually contain significant amounts of aluminium, and thus the level of aluminium in the blank affects the detection limit (refs. 8, 11). Other difficulties include the short half-life of ^{28}Al (2.27 min) which is formed during the irradiation procedure, and the conversion of phosphorus and silicon to ^{28}Al . The necessity of having access to a reactor also makes neutron activation analysis unsuitable for routine determinations.

Atomic emission spectrometry (AES) using inductively coupled plasma (ICP) has been successfully used for aluminium determination in biological materials (refs. 12-13). However, a major problem with using the argon-plasma technique is the intense and broad emission of calcium which increases the background and the detection limit for aluminium. In a recent paper (ref. 13) an improved background correction system made it possible to reach a detection limit of $3 \mu\text{g L}^{-1}$ in serum. One drawback, however, with this technique is the relatively high cost and complexity of the instrumentation which will therefore exclude its use from many routine laboratories. Matusiewicz and Barnes (ref. 14) used an electrothermal vaporizer coupled to an ICP which gave a detection limit of $1.6 \mu\text{g L}^{-1}$ in plasma. Recently, Baxter et al. (ref. 15) used graphite furnace AES with a constant temperature atomizer and reported a detection limit of $0.3 \mu\text{g Al kg}^{-1}$ for samples like whole blood and cortex. Other techniques like flame atomic spectrometry or spectrophotometry are not, in general, sufficiently sensitive or selective for trace determinations in biological materials.

The greatest success achieved by any of the techniques used for the determination of aluminium in biological specimens, has been with graphite furnace atomic absorption spectrometry (GFAAS). The reason why GFAAS has become the method of choice can be explained by the fact that it offers the best combination of sensitivity, simplicity and low cost.

The purpose of this paper is to make a compilation of reported results (normal values), as well as proposed procedures for the determination of aluminium in various types of biological materials using the GFAAS technique. Based on this material, some conclusions will be drawn concerning the direction of future analytical research should take in order to increase the reliability of trace aluminium determination.

DETERMINATION OF ALUMINIUM IN BODY FLUIDS

Tables 1a and b summarize "normal values" reported by different authors for serum, plasma and whole blood (refs. 11, 16, 17-44).

The values given in Table 1a, i.e. values equal to or larger than $10 \mu\text{g L}^{-1}$, are regarded as unreliable in view of the fact that the vast majority of recently obtained values are much lower than $10 \mu\text{g L}^{-1}$. The mean values for each group of subjects published later than 1977 are presented in Fig. 1. As can be seen, there is a trend towards lower levels at least until 1980. As regards the lower reported values, the question arises as to which data represent the true aluminium contents of normal serum and whole blood, and whether the

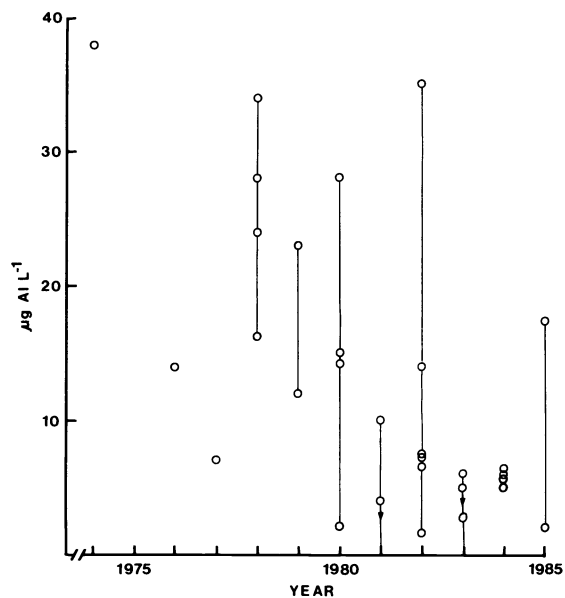


Fig. 1. Mean values ($\mu\text{g L}^{-1}$) reported for serum, plasma and whole blood during the years 1974-1985 using GFAAS

TABLE 1a. Normal concentrations ($\mu\text{g/L}$) in serum, plasma or whole blood obtained with GFAAS

Authors	Year	Ref	Mean	S.D.	Range	Subjects
Fuchs	1974	(11)	38*		10-92	29
Vallentin	1976	(17)	14**	7.1	4.0-34.5	40
Langmyhr	1977	(18)		28***	50-590	48 [†]
Clavel	1978	(20)	24	8	10-45	59
Gorsky	1978	(21)	28	9	12-46	23
Pegor	1978	(22)	34	3.5	28-40	20
Elliott	1978	(23)	16.2	-	-	20
Salvadeo	1979	(24)	12	4.0	-	12
Zumkley	1979	(25)	23	7.3	-	20
Gilli	1980	(27)	14.2	12.2	-	44
Toda	1980	(28)	28	3	-	2
Smeyers-V	1980	(29)	15	-	-	1
Gardiner	1981	(31)	10 [§]	-	3.2-32.4	15
Bertram	1981	(32)	-	-	1-35	-
McKinney	1982	(33)	35	3.7	-	7
Wawshinek	1982	(35)	14	-	3-39	54
Bettinelli	1985	(43)	17.3	6.1	2-36	40

* recalculated values assuming a serum or blood-specific density of 1.026 or 1.055, respectively.

** median

*** at a concentration of 350 $\mu\text{g/L}$

[†] whole blood

[§] referred to the level to which contamination could be reduced

TABLE 1b. Normal concentrations ($\mu\text{g/L}$) in serum, plasma or whole blood obtained with GFAAS

Authors	Year	Ref	Mean	S.D.	Range	Subjects
Kaehny	1977	(19)	7	2		13
Alderman	1980	(26)	2.1	2.2	0-7.6	14
Oster	1982	(30)	<4	-	<2.5-7	37
Frech	1982	(16)	1.6	1.3	-	11 [†]
Frech	1982	(16)	7.5	6.41	-	43 [†]
Parkinson	1982	(34)	7.3	-	2-15	46
Leung	1982	(36)	6.5	4.1	2-14	28
Alfrey	1983	(37)	6	3	-	-
Sjögren	1983	(38)	<5			-
Kostyniak	1983	(39)	2.7	0.6	-	4
Guillard	1984	(40)	5.95	0.53		30
Brown	1984	(41)	5.7	-	2.7-9.6	1
Buratti	1984	(42)	5.0	2.8	0.5-13	- [†]
Buratti	1984	(42)	6.4	2.2	0.8-11	-*
D'Haese	1985	(44)	2.0	0.4	-	10

[†] whole blood

* plasma

differences found should be ascribed to analytical errors rather than to biological variation. Frech et al. (ref. 16) reported a mean value in whole blood of $7.5 \pm 6.11 \mu\text{g Al L}^{-1}$ in 43 normal individuals. These samples were taken and processed in hospital surroundings, taking the usual precautions. Additional experiments using blood samples collected from 11 young, healthy volunteers living in the same area and performed in a controlled class 100 atmosphere, gave a mean aluminium value of $1.6 \pm 1.29 \mu\text{g Al L}^{-1}$ (values not corrected for blank). These results emphasize the importance of a controlled environment for sample collection when normal values are to be established.

The major differences between the methods used by the authors listed in Table 1a and b can be related to sample pretreatment. Direct methods which involve centrifugation of the sample and measurement of the aluminium in the supernatant reportedly give incorrect results, because the precipitate contains appreciable amounts of aluminium (Smeyers-Verbeke). However, such methods can be adequate for routine use in controlling the aluminium concentration in (e.g.) the blood of hemodialysis patients. The direct methods that do not include a separation step are considered troublesome for several reasons: buildup of carbonaceous residues in the atomizer, sample splutter during heating, difficulties in delivering repro-

ducible amounts of sample, and volatile losses of aluminium as its chloride. Some of these difficulties can be overcome by diluting samples with e.g. water (refs. 29, 40-41), Triton X-100 (ref. 34), nitric acid (ref. 32), EDTA/ammonium hydroxide/sulfuric acid (ref. 26) and/or by adding oxygen to the purge gas during ashing (ref. 43). Some authors recommend the addition of magnesium nitrate to serum samples, but according to Gardiner et al. (ref. 63) this modifier does not influence the aluminium signal. However, magnesium nitrate may have a beneficial effect during ashing, since it is known to promote the decomposition of organic materials. Analytical reagent magnesium nitrate is liable to contain aluminium contamination and therefore a suprapure quality should be used. The acids presumably augment the decomposition of organic materials in the sample. Ammonium hydroxide assists in the removal of chlorine by the formation of volatile ammonium chloride. EDTA prevents the precipitation of insoluble phosphates in the alkaline diluent mixture.

A digestion procedure using nitric acid has been described (ref. 16), but due to the increased risk of contamination during sample pretreatment the method is cumbersome when large sample throughput is required. Nevertheless, a wet digestion procedure should be useful for reference purposes since such a method minimizes possible losses of e.g., endogenous aluminium since organic aluminium compounds are likely to be converted into non-volatile inorganic aqua complexes. The large samples employed in this method should also be advantageous in levelling out errors resulting from an uneven distribution of aluminium in frozen blood samples. Such effects can be caused by proteins denaturated during freezing (ref. 45). Besides, a digestion procedure eliminates the need for anticoagulants.

Unfortunately, no certified serum or blood reference materials are available, which means that it is not possible to judge the accuracy of the reported results. Recently a bovine serum reference material with a recommended value of $13 \mu\text{g L}^{-1}$ became available from NBS.

DETERMINATION OF ALUMINIUM IN BIOLOGICAL TISSUES

The determination of trace elements in biological tissues normally includes a mechanical homogenization procedure which reduces the amount of sample necessary to permit a representative analysis. If the homogeneity of the sample with respect to a certain element is sufficient, however, then the homogenization step can be excluded. Little is known about the sample amounts required to obtain representative samples for aluminium determinations, and no procedure for contamination-free homogenization has yet been published. As discussed above, tissue samples should be prepared in a dust-free environment, and uncontaminated tools like acid-washed quartz knives must be used. Although several methods of analysis for aluminium in serum, plasma and blood have been described, there are only a few procedures specifically concerned with its measurement in tissue. Table 2 summarizes the GFAAS-based procedures found in the literature.

Some authors recommend dry ashing at 400°C (refs. 46-47, 51) followed by an EDTA-extraction or dry ashing at 600°C (ref. 48) or 650°C (refs. 49, 53), and subsequent simple dissolution of the ash in nitric acid. However, dry ashing should only be used if dust can be excluded. It should be noted that otherwise a systematic error could arise when correcting for the blank, since the uptake of aluminium from the air (as well as from the vessels) can vary depending on whether or not a sample has been added. The proposed wet digestion methods include the use of mineral acids like nitric acid (refs. 2, 44, 54), a mixture of nitric and perchloric acid (ref. 48) and mixtures of nitric, perchloric acid and sulfuric acid (refs. 52, 54). Recently Stevens (ref. 54) used hot aqueous tetramethylammonium hydroxide for the dissolution of soft tissues, followed by dilution with ethanol. He compared this technique with nitric acid digestion and EDTA-extraction and found close agreement with only the former method. The lower values obtained by EDTA-extraction disagree with the findings of Alfrey (ref. 51), who provided convincing arguments for the completeness of his extraction method. One reason for the discrepancy might originate from the fact that Alfrey (ref. 51) used much higher temperatures in the dry ashing step.

As can be seen in Table 2 the values reported for control subjects are in general high and of the order of one mg Al/kg tissue (dry weight). For such high values contamination should not constitute as severe a problem as for blood and plasma at normal levels, provided that recommended precautions are taken. However, difficulties involved in aluminium determination, even at higher concentrations, are reflected in the large deviation in the results reported for animal muscle by the International Atomic Energy Agency (ref. 55), where aluminium values are included for orientation. The participating laboratories reported values for aluminium in the interval 2 to $30 \mu\text{g/g}$. Consequently, it has not even been possible to check the accuracy of the higher, reported aluminium values by reference to independent standard materials. The results reported by Slanina et al. (ref. 2) (control Sprague-Dawley rat brains $0.01\text{-}0.02 \mu\text{g/g}$) are significantly lower than the other ones, which again raises the question as to whether the higher values reported in the animal studies are subject to contamination errors. It should be mentioned that by following the procedures recommended by D' Haese et al. (ref. 44) and Slanina et al. (ref. 2), it is possible to detect 0.05 and $0.002 \mu\text{g Al per g tissue}$, respectively.

TABLE 2. Procedures suggested for the determination of aluminium in biological tissues using GFAAS. The values within parenthesis represent results in mg/kg dry tissue obtained in control subjects

Authors	Year	Ref	Type of tissue	Procedure
Alfrey et al.	1976	(46)	muscle (1.2) brain (1.3)	human dry ashing (brain 400 °C) plus EDTA-extraction
Le Gendre et al.	1976	(47)	bone (2.4-3.9)	
McDermott et al.	1976	(48)	brain (1.3) brain (1.3) * liver (0.4) * kidney (0.4) * cortex (0.7) * liver (0.3) * kidney (0.3) * cortex (0.4)	human human animal dry ashing 600 °C wet ashing HNO ₃ /HClO ₄ dry ashing 600°C animal wet ashing HNO ₃ /HClO ₄
Ariefff et al.	1979	(49)	brain (grey 0.9, white 0.4) brain (grey 0.7 ± 0.3)	human vacuum dried 45°C plus EDTA-extraction
Crapper McLachlan et al.	1983	(50)	brain (1.9)	human dry ashing 650°C
Alfrey	1983	(51)	brain (grey 2.2 ± 1.3)	human dry ashing (brain 400°C) plus EDTA-extraction
Thornton et al.	1983	(52)	liver (0.7 ± 0.3) cortex (2.3 ± 0.5)	animal wet ashing HNO ₃ /HClO ₄ /HClO ₄ 200°C
Krishnan et al.	1983	(53)	brain	human dry ashing 650°C
Slanina et al.	1984	(2)	* brain (0.01-0.02) * bone (0.4)	animal wet ashing HNO ₃
Stevens	1984	(54)	NBS 1577 Bovine liver (<0.5)	animal 1. wet ashing TMAH** 90°C 2. wet ashing HNO ₃ HClO ₄ /H ₂ SO ₄ 3. dry 120°C, EDTA-extraction
D'Haese	1985	(44)	liver, bone	human 1. wet ashing HNO ₃ 200°C 2. wet ashing, bomb, 90°C 3. wet ashing HClO ₄ /HNO ₃ /H ₂ SO ₄

* wet weight; ** tetramethylammonium hydroxide

GFAAS-PROCEDURES

The purpose of the graphite tube atomizer in atomic absorption spectrometry is to produce an atomic vapour in the light path emanating from a monochromatic source of radiation. If the element of interest can be formed in a monoatomic state, light is absorbed in proportion to the total amount of the element in the light path. The duration of the signal is dependent on the physical dimensions of the atomizer, the heating characteristics and the gas environment. For aluminium, argon instead of nitrogen should be used for obtaining maximum sensitivity. The total length of an absorbance signal is in the order of 1 second. Unlike in flames, a steady state number of free atoms is never reached, therefore the measurement conditions must be rigorously kept constant to achieve reproducible results. Either the peak value or the integrated area of the entire absorption pulse can be used for evaluation of the atomized amount of the element. It should be mentioned that a prerequisite for obtaining a true representation of the absorbing species in the graphite tube as a function of time is that the read-out of the spectrometer is sufficiently fast. Obtaining undistorted signals is essential when reactions in graphite furnaces are investigated and for optimization of the analytical procedure.

In most determinations, a three-step heating of the atomizer is used. When a sample is analyzed as a liquid, the solvent must be driven off smoothly in order to avoid violent boiling, where sample can quite simply sputter out of the tube. This step should not give rise to any problems, however, since the only requirement is to distill off the solvent at a suitable rate. When, on the other hand, organic liquids (serum or whole blood), have to be dried, some difficulties can occur if the surface tension of the liquid is high. The sample

can form a bubble that splits quite firmly. Such problems can, however, be avoided if a 'wetting' agent like Triton X-100 is added to the sample in order to lower the surface tension.

The next step in the determination is to remove the matrix as completely as possible. The matrix can give rise to non-specific absorption and to interference effects in both the condensed (loss of analyte) and gas phases (formation of analyte molecules). Aluminium and aluminium oxides are relatively involatile, and therefore high temperatures can be used during thermal pretreatments in a graphite furnace. As a consequence of this, the major part of the biological matrix can be removed before atomization. Hence, problems caused by non-specific absorption are small. Nevertheless, for measurements close to the detection limit, even a small background may give rise to a large error if it is not correctly compensated.

Non-spectral interference effects in aluminium determinations may occur during both the pretreatment step, through losses of volatile aluminium compounds like trichloride (ref. 56), and during the atomization step, through formation of stable molecules like aluminium monochloride (refs. 57-58), aluminium cyanide and aluminium carbide (ref. 59). The analytical sensitivity and the degree of inter-element effects for this element are also known to be critically dependent on the properties of the graphite surface (refs. 47, 60, 61).

Substantial improvements with respect to the analytical conditions for aluminium determinations on a routine basis have been realized through the introduction of pyrocoated, high density graphite tubes in combination with the L'vov platform technique and stabilizing agents, (ref. 62). Samples are placed on the platform, and since this is heated primarily by radiation from the tube wall, there is a time lag between the heating of the tube and the platform. Samples are therefore vaporized into an atmosphere of relatively high temperature more favourable for the dissociation of molecules. For that reason, gas phase interference effects are, in general, minimized when the platform technique is used. It should be emphasized that optimum platform conditions can normally only be reached by stabilizing the analyte, and by converting potential interfering sample constituents to more volatile compounds, to be removed from the furnace during the thermal pretreatment. Furthermore, it is essential to heat the furnace rapidly to a preselected optimum temperature in order to achieve a sufficiently large temperature difference between tube and platform. This temperature difference can be maximized by allowing the tube and hence platform to cool down before atomization. Magnesium nitrate is recommended for stabilization of aluminium, but for biological materials dissolved in nitric acid, no stabilizer is normally added when using the platform technique, since these types of samples contain stabilizing species (ref. 15). Peak area evaluation is to be recommended, because the integrated signal often varies only slightly with the composition of the matrix, which means that standardization is greatly simplified.

Although calibration is feasible using aqueous solutions (ref. 43) or pooled serum samples (ref. 63) when following recommended procedures, the method of standard additions should still be used for verification, in view of the difficulties involved in controlling all factors which can influence the result, e.g. pretreatment temperature, the graphite surface, impurities in the sheath gas etc.

CONCLUSIONS

Few analytical methods are readily available for the determination of aluminium in biological materials at low levels. Therefore, there is a special need for standard reference materials with certified values. Unfortunately, none have been produced so far, probably because of the difficulties involved in finding suitable independent methods, as well as problems associated with the preparation of homogeneous, non-contaminated materials. For these reasons, the accuracy of control values reported in the literature is unknown. Future analytical research should thus be directed towards the development of alternative methods with sufficiently high sensitivity and selectivity. Furthermore, the conditions for contamination-free sample pretreatment procedures must be established.

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