

# Aluminum in the Environment and Human Health

by John R. J. Sorenson,\* Irene R. Campbell,\* Lloyd B. Tepper,\* and Robert D. Lingg\*

The review of over 800 references on aluminum (Al) published since the mid-fifties covers the occurrence of Al in soil, air, water, plants and food products, as well as air and water pollution problems. In addition, the existing quality criteria, the biology and toxicology of Al, and the therapeutic and medical uses are presented. It is concluded that absorption and retention or accumulation of Al in humans occurs at lower levels of intake than had been assumed formerly. However, levels of 5 to 50 times the normal daily intake do not appear to interfere with other metabolic processes. The adverse effects of Al reported in the more recent years resulted from the inhalation or ingestion of Al in concentrations many times greater than the amounts present under normal circumstances. As in the past, there is still no need for concern by the public or producers of Al or its products concerning hazards to human health derived from well established and extensively used products.

## Introduction

In 1957, several members of the Department of Environmental Health of the University of Cincinnati collaborated in a review of the hygienic status of aluminum in the environment of man (1). The review encompassed the history of the development and use of metallic aluminum and of the principal aluminum salts, the chemistry and analysis of aluminum in various media, its natural occurrence in the human environment, the uses and suitability in the processing and storage of foods and beverages, the concentrations encountered in raw foods and those cooked or stored in aluminum ware, the fate of aluminum entering the body by various routes (including toxicology), and the medical uses. In the concluding and summarizing remarks, R. A. Kehoe presented

the following facts gleaned from the review as to the important practical aspects of human risk.

1. The quantities of aluminum which are required within the animal organism to induce harmful effects are large as compared with those found in the body tissues under the severest conditions of ordinary or occupational exposure to aluminum and its compounds or as compared with the quantities of certain other metals known to be dangerous.

2. Despite the abundance of aluminum compounds in the earth's crust and in the natural environment, and despite the artificial increase in the environment of modern man, the absorption of aluminum into the bodies of animals and man occurs to only a slight extent.

3. The quantities of aluminum and its inorganic compounds which are absorbed into the body are independent, for all practical purposes, of the quantities in the environment—specifically, in the food and in the atmosphere.

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\*Department of Environmental Health, College of Medicine, University of Cincinnati, Cincinnati, Ohio 45219.

Concerning the use of aluminum, he stated: "There is no reason for concern, on the part of the public or of the producer and distributor of aluminum products, about hazards to human health from well established and extensive, current use of such products. Nor need there be concern over the more extended uses which would seem to be in the offing."

In 1972, opportunity presented itself to survey and evaluate the literature published since 1957 within the same scope as before and, in view of the more recent emphasis on environmental pollution, to add the air and water pollution aspects.

In harmony with the form in which aluminum is present in the human environment, only the element, in metallic or ionic form, and its inorganic compounds are here considered, as they had been in the earlier review. This, of course, does not exclude such complexes or compounds as may be formed after aluminum enters the body or plant tissues. The arrangement of the material follows closely that of the first publication, with some modifications or omissions deemed to be appropriate.

## Uses of Aluminum and of the Principal Aluminum Compounds

In 1865, the master of imagination and inventor of science fiction, Jules Verne (2) wove a tale around the intrepid Professor Impey Barbicane, president of the Baltimore Gun Club, who proposed the building and sending of a cylindroconical "projectile" made of aluminum to the moon as a project worthy of the Club's activities. The amazing thing about the story is that he proposed aluminum as the metal on the basis of the success of Henri Saint-Clair-Deville's producing it "in a solid mass" in 1854 (about 40 yr before it became available in commercial quantities through industrial production), describing it as a metal "as white as silver, as unchangeable as gold, as tough as iron, as fusible as copper and as light as glass." To add to the fascinating story, the first manned mission, preceded by an experimental launch with a cat and squirrel in a small prototype projectile, was "blasted off" by a huge cast iron cannon at Stone Hill, Tampa, Florida, with Barbicane and two fellow astronauts inside,

seconds before the latest meteorologically predetermined time, witnessed by 5 million people.

Jules Verne's fantasy has become a reality within the last 16 yr when manned aerospace explorations have taken place, in which aluminum has played a prominent role in its numerous applications (3). The uses of aluminum in all man-bearing craft, whether in various altitudes of the strato- and troposphere, the surfaces of the earth and moon, or to the ocean floor, and in nuclear energy programs (4-7) are many and need not be enumerated here. Suffice it to say that wherever man dwells and works, this metal has been used for construction, electrical equipment, furnishings, various appliances, implements and containers.

The amazing growth of applications of aluminum in the last 15 yr alone is well portrayed in the statistics compiled by the Aluminum Association (8) which show 7850.4 million pounds of domestic primary aluminum production in 1971 compared with 3295.4 in 1957, while preliminary data on world production give 11,349,000 short tons in 1971 against 4,950,000 short tons in 1960. Considering that large scale production of aluminum became feasible only in 1886, and the first production data for 1893 in the U.S. showed only 0.2 million pounds, the growth rate through the years has been truly phenomenal. As stated by Stamper of the Bureau of Mines (9) the growth rate of aluminum in recent years has been three times the combined growth rate of all other metals, and, except for steel, its use exceeds that of any other primary metal. Further, an evaluation of possible technologic changes and social developments led to the prediction that by the year 2000 the total domestic requirements will be between 22.4 and 44.4 million short tons, or an increase of 5 to 10 times the 1968 level. The worldwide increase is expected to be of the same order of magnitude.

Aside from sheet, plate, foil, extruded, and wire forms, aluminum in powder and particulate form are used widely in paints, pigments, coatings, missile fuels, chemical explosives, putties, etc. (4). In addition to its use in the production of metallic aluminum, aluminum oxide ( $Al_2O_3$ ) or alumina in its various forms (activated, hydrated, calcined, and tabular) finds wide applications ranging from high temperature-resistant refractories, ceramics,

whiteware (10) to products reaching the immediate environment of man, such as toothpastes, dental amalgams (11), all sorts of prostheses, cigarette filters (12), food additives, pharmaceuticals, and cosmetics (4). Other compounds will be mentioned in connection with the use of aluminum compounds in food and water, and as therapeutic agents.

## Analytical Methods

An intractable chemical nature coupled with the lack of specific reagents combine to make aluminum (Al) one of the most difficult of the commonly occurring elements to determine chemically. Any sample taken from the environment will contain a wide range of inorganic substances, among which there will be present almost always a metal ion or counterion to cause interference effects. Therefore, separation, masking, critical control of pH, etc., must be performed routinely during chemical analyses for Al. Much effort has gone into making chemical methods more reliable, but the results have not always been completely satisfactory.

Spectroscopic methods, such as emission, nuclear, or atomic absorption, are more specific for Al and overcome to a large extent the problem of interferences from the matrix. Emission spectroscopy has been in use for a long time and its specificity and sensitivity are well documented. Within the past decade, neutron activation and atomic absorption techniques have been developed to a high level of sensitivity and specificity. With both of these methods, a minimum of sample handling and preparation are required. The cost of neutron activation equipment is prohibitive for an average laboratory, but atomic absorption equipment is easily within the means of the average laboratory and can be expected in the future to enjoy a greatly expanded application for determining Al in environmental samples.

## Separation and Preconcentration

Separating Al from interfering substances remains a formidable chemical problem. There are no known reagents specific for Al, so the analyst must choose from a variety of reagents and methods the one which best suits his needs. This choice must be based on knowledge of the

approximate amount of Al one expects to find and the potential interfering substances. One may choose to isolate the Al from the matrix of the sample, or to selectively remove ions which cause interference effects.

A basis for the choice of separation and preconcentration methods begins with a decision on the analytical method to be used. The sensitivity of the technique, methods of sample preparation, and a list of possible interferences are recorded in the literature along with a description of the procedure itself. In some samples, Al can be determined *in situ* by selective complexing of the interfering substances, careful control of pH, or employment of compensating solutions. These are, however, seldom satisfactory, and a separation method involving precipitation, ion exchange, or extraction must be employed prior to analysis.

The amounts of Al encountered in environmental and biological samples range from semimicro to micro quantities. Precipitation can be used to separate and preconcentrate Al: semimicro amounts can be determined gravimetrically after precipitation (13), or for micro amounts, emission spectroscopy of a precipitated mixture is usually preferred (14, 15). Oxine (8-hydroxyquinoline) is the favored reagent for the separation and precipitation of Al. Precipitation can be made over a wide range of pH, but quantitative separation from other elements requires careful control of pH (13). Since 8-hydroxyquinoline reacts with up to 30 elements, this reagent can be used for the preliminary separation of interfering elements. In the presence of Na tartrate and Na hydroxide, Al will not be precipitated by 8-hydroxyquinoline while other metal ions are quantitatively removed (13).

Ion exchange can be used to separate and preconcentrate trace quantities of Al. With anion exchange, advantage is taken of the fact that Al is not absorbed from hydrochloric acid solutions, 9M or stronger, while the chloride complexes of metal ions such as Fe<sup>3+</sup>, Mn<sup>2+</sup>, Co<sup>2+</sup>, Ni<sup>2+</sup>, Cu<sup>2+</sup>, and Zn<sup>2+</sup> are (16). Cation exchange can be used with HCl as the eluting agent for separating Al<sup>3+</sup> from Na<sup>+</sup>, K<sup>+</sup>, Mo<sup>2+</sup>, Ca<sup>2+</sup>, and Fe<sup>3+</sup> (17).

Extraction methods are capable of separating micro amounts of Al. The same reagent favored

for precipitation, 8-hydroxyquinoline, is the reagent of choice for extraction, but because of the broad spectrum of elements with which it complexes, masking agents and pH control must be properly manipulated to achieve separation of the Al from the other ions. A colorimetric determination of Al can be made by complexing it with fluoride ion, removing interfering ions by ion exchange and extraction, then making the Al reactive to 8-hydroxyquinoline in chloroform, and measuring the resulting complex photometrically (18).

In atomic absorption analysis, extraction serves two purposes: it preconcentrates the Al, and the organic solvent increases the sensitivity of the instrument (19).

### Colorimetric and Fluorescence Methods

The colorimetric determination of Al is based on the formation of strongly colored lakes with certain organic reagents (20). Among these, in approximate order of decreasing popularity, are aluminon (21), Eriochrome Cyanine R (22), Alizarin Red S (23) and hematoxylin (24). Comparison studies (21,24) of these reagents favor aluminon, but no single one of these is sufficiently superior to warrant exclusion of the others. In most situations, the choice of reagent is largely determined by the material to be analyzed because of the peculiar properties of each reagent toward potential interfering ions. Most notable among these are  $\text{Fe}^{3+}$ ,  $\text{F}^-$ , and  $\text{PO}_4^{3-}$ , all of which may be encountered at significant concentrations in environmental samples. Some satisfactory schemes employing masking, complexation, reduction, or extraction of the interfering ions have been worked out (21,22). One rather unorthodox approach for the elimination of the  $\text{Fe}^{3+}$  interference involved the use of a new colorimetric reagent, xylenol orange (25).

The nature of the complex between Al and the lake-forming organic reagent is not fully understood. Therefore, when using these reagents, careful control of conditions affecting lake formation, such as temperature and pH, is required to insure reproducibility. With organic solvents, some complexing agents form a true solution chelate with Al: a complex is formed between Al and 8-hydroxyquinoline

in chloroform and the resulting complex is determined spectrophotometrically (18).

The most sensitive chemical methods for determining Al are the fluorescence methods (26). Reagents used for the fluorescent detection of Al are Pontachrome Blue Black R (27), morin (28), 2,4-bis-[*N,N'*-di-(carboxymethyl)aminomethyl] fluorescein (29), and 8-hydroxyquinoline (18). Sensitivities in the nanogram (ng) range can be obtained. A minimum detectable concentration of 2 ng/ml has been reported (27) with the use of the reagent Pontachrome Blue Black R.

Unfortunately, the fluorescence techniques are subject to the same interferences and problems associated with the colorimetric procedures. The high sensitivity coupled with the deleterious effect of minute traces of interfering ions require that a complete analysis for each sample type be worked out. In addition, careful control of factors affecting the development of the fluorescence are necessary in order to obtain reproducible results.

### Titrimetric Procedures

Titrimetric procedures for the determination of Al employ the versatile reagent ethylenediaminetetraacetic acid (EDTA) (13, 30,31) or derivatives (32). These reagents complex a large number of metal ions, so that the formation constants of the complex with each metal ion present will determine the need for a prior separation step. If the formation constants are sufficiently different, a stepwise titration will be observed. The formation constant for the Al complex is moderately high ( $\log K = 16.13$  at  $20^\circ\text{C}$ ), but the rate of formation is slow. Therefore, back titration is usually employed: excess EDTA is added, the solution is boiled to form the EDTA complex, and the noncomplexed EDTA is titrated with another metal ion. The endpoint is determined by using indicators or by potentiometry (33).

### Emission Spectroscopy

Emission spectroscopy is a sensitive and specific method for the determination of Al in almost any type of material (34-37). Preparation and manipulation of the sample are kept

to a minimum to reduce the possibility of contamination that is often encountered in other procedures. Direct reading spectrographs are now used in place of the time-consuming photographic plate method (34,35). Absolute detection limits of  $10^{-6}$  to  $10^{-8}$  g are regularly reported for Al (23,35,37) (absolute detection limits meaning minimum detectable amounts introduced to arc).

Most determinations involve multielement analyses, so that the conditions which optimize Al may not always be realized. With some samples, a chemical separation may be necessary because of matrix effects. A statistical study of multielement analysis by emission spectroscopy showed somewhat less precision for Al than by the chemical methods (38).

### Atomic Absorption

Al can be determined in aqueous solution with a sensitivity of  $1 \mu\text{g/ml}/1\%$  absorption by atomic absorption spectrophotometry by using a nitrous oxide acetylene flame (39). The method is specific, and interferences are few, but the flame conditions and position are critical (40,41). Addition of miscible organic solvents to the aqueous solution or chelation-extraction into immiscible organic solvents results in a significant improvement in sensitivity. Using benzene as the organic phase, a sensitivity of  $0.01 \mu\text{g/ml}/1\%$  absorption has been claimed (42).

When determining Al in biological materials, it is best for the analyst to make a study of interference effects from the common ions encountered in these materials, especially  $\text{Na}^+$  (43). Also, the wide distribution of Al requires that care be exercised in the choice of ashing vessels and control of blanks when preparing samples for analysis by atomic absorption. Because of the relative simplicity of the technique, one can expect analysis of Al by atomic absorption to be more widely used for biological and environmental samples, especially if the extraction procedures receive more development.

### Neutron Activation

Neutron activation analysis (NAA) is the most sensitive analytical technique available

for determining Al. Activation of Al occurs by a  $(n, \gamma)$  reaction which produces the very active  $^{28}\text{Al}$  nuclide with a half life of 2.3 min. Under interference-free conditions, only  $0.004 \mu\text{g}$  of the element is required to be present in the sample in order to be detected.

For some samples, NAA can be used as a direct instrumental technique requiring no sample preparation or destruction. This technique has been particularly well suited for air filter samples, where as little as  $0.04 \mu\text{g}$  of Al has been detected on filters containing up to 33 elements (44-46). Unfortunately, trace Al determination in biological samples having high P levels requires a preirradiation separation step (47,48). The high-energy neutrons required for trace analysis induce nuclear transformations which result in the production of the active nuclide  $^{28}\text{Al}$  from  $^{31}\text{P}$ .

Two important developments in equipment technology have made possible the accurate determination of Al by NAA: (1) rapid sample-handling equipment enables the short-lived nuclide  $^{28}\text{Al}$  to be delivered to the counting device before appreciable loss in activity is observed; (2) the high background or continuum observed when counting  $\gamma$ -rays with scintillation counters, which is particularly bothersome in  $^{28}\text{Al}$  counting, has been nearly eliminated with the introduction of high resolution lithium-drifted germanium [Ge(Li)]  $\gamma$ -ray detectors.

### X-Ray Fluorescence

Little use has been made of x-ray fluorescence for the determination of Al in environmental and biological samples. The outstanding advantages of this technique are simple sample preparation and nondestruction of material. The lighter elements are not the most amenable to x-ray techniques and Al is no exception: a sensitivity of 0.002% w/w can be obtained, a relatively high value when speaking of trace element determinations. Interelement effects cause an interference if mass absorption coefficients vary by more than 5%, but can be compensated by proper calibration.

Plant and fecal materials have been analyzed for 0.01 to 1% Al content using x-ray fluorescence. A comparison with chemical tests for Al showed the results of the latter were inconsistent with the x-ray fluorescence values, while re-

sults between the two methods for most other light elements were consistent. It is believed that this inconstancy reflects the difficulties encountered in the chemical methods rather than the opposite (49).

### Polarographic Methods

The half-wave potential of Al ion is  $-1.75$  V versus the standard calomel electrode (SCE), too close to the discharge potentials of alkali metals and alkaline earths for satisfactory development of the Al wave if these ions are present in appreciable concentrations. The reduction wave of hydrogen ion just precedes that of Al, although satisfactory curves can be obtained if the hydrogen ion concentration does not exceed Al (13).

An approach to the problem of determining Al polarographically is based on a change in the reduction wave of certain organic dyes such as Pontachrome Violet S.W. (50). This reagent in an acetate buffer produces a wave at  $-0.3$  V versus the SCE, but in the presence of Al the step is reduced in height and a second step, proportional in length to the concentration of Al, appears at  $-0.5$  V. This method suffers from interferences by several metal ions (51).

Applications of the polarographic methods for the determination of Al in environmental media are relatively few. A level of  $0.1 \mu\text{g Al/ml}$  was determined in water using cathode ray polarography with the dye Pontachrome Violet S.W. (52).

## Occurrence of Aluminum in the Environment

### Aluminum in Soil and Plants

In view of the abundance of Al in the earth's crust (8.13%) (53), its presence in all soils, though in greatly varying amounts, can be taken for granted. For example, as shown in the earlier review, concentrations as high as  $265,449 \mu\text{g/g}$  were found in Virginia subsoils (54). In a recent geochemical survey of vegetation in Missouri (55), the soils from six vegetation-type areas had alumina contents of 2.8–11% ( $4829$ – $58,201 \mu\text{g Al/g}$ ), and certain soils in Hawaii were found to contain as much as 15–60% alumina ( $79,365$ – $317,460 \text{ g Al/g}$ ) (56). The literature re-

flects a great deal of continuing research on the forms in which Al occurs in soil and on its reactions and interactions with other elements. Since the solubility of Al is in large part determined by the acidity of the soil which, together with high Al content, is detrimental to the growth of many plants, much work has been done to modify such soils by the addition of certain elements or fertilizers. McLean (57) summarized in 1965 the role of Al in soil as a preface to his evaluation of the methods of its analysis by stating that the status of Al in acid soil is significant and that in fact in many if not most soils the entire soil acidity component of importance in liming practices appears to be Al. There is no need to add more to the earlier review, for the presence of Al in soil in excessive quantities and toxicity in plants belong in the field of agronomy.

Consonant with growing interest in the content of trace elements in the environment of man, Al has been included among analyses of plant materials of various types for the uptake of these elements from soil and distribution in the various parts of plants. Examples of such studies are: extractability of elements from soils (58); effect of soil pH (59); seasonal variations (60); effect of physical properties of soil (temperature, compaction, moisture) (61); effect of fertilizers (62). To point out analytical errors attributable to contamination of plant tissues which ordinarily contain Al in the order of a few micrograms per gram in contrast to the generally more than 10% in soil, Webber (63) performed analyses on washed and unwashed oats grown in the field and cereals grown in a growth cabinet, which were contaminated experimentally with montmorillonite clay. Washing (with 0.3% Alconox) reduced the Al concentrations in field-grown oats from 20.5 and  $36.0 \mu\text{g/g}$  found at ignition temperatures of 500 and  $1000^\circ\text{C}$ , respectively, to 5.67 and  $6.61 \mu\text{g/g}$ ; in the contaminated oats, soybeans, and buckwheat grown in the cabinet, the respective concentrations dropped from 194.9, 72.4, and  $3136.7 \mu\text{g/g}$  to 7.8, 11.2 and  $2299.7 \mu\text{g/g}$ .

The occurrence and distribution of Al in food plants is discussed further below.

Along with numerous investigations on the effects of soilborne Al, either alone or with

other elements, on plant growth, there have been additional reports on the role of Al as a "micronutrient" for certain plants: vine grafts (64), corn (65), *Chlorella vulgaris* (66); in reversing lime chlorosis (67), and in increasing resistance of plants to salts (68). The accumulation of Al in certain plants (the so-called "accumulators" containing more than 1000  $\mu\text{g/g}$  of soluble Al) was reviewed by Harris (69) who pointed to the wide range of tolerance to Al of 16 of the main species of climax flora in the British Guiana coastlands. Other reported accumulators are: six species of lycopods in which topochemical detection revealed up to 19.5% Al in ash (70); 13 of 23 species (grasses and orchids) growing in Hawaii on highly leached latosol soil of low pH with high Al content (up to 60%  $\text{Al}_2\text{O}_3$ ) which contained more than 1000 and up to 16,000  $\mu\text{g/g}$  of dry matter (56). Oke (71,72), who had analyzed the Al content of numerous food plants in Nigeria, found 1659 and 765  $\mu\text{g/g}$ , respectively, in the nonedible and partly edible portions of *Corchorus olitorius* and 1300  $\mu\text{g/g}$  in mushrooms. No sign of injury was evident during harvest, leading the author to conclude that the plants had developed a high resistance to Al. In addition, Gorsline et al. (73) observed genetic control of the concentrations of a number of metals, including Al, and B in the ear leaf of corn, with some degree of environmental influence. In the case of Al, a genetic correlation with Fe was found.

### Aluminum in the Atmosphere and Atmospheric Precipitations

In spite of mounting concern over air pollution, particularly since around the mid-sixties, relatively few investigations have included Al in atmospheric surveys. As the foremost example of this in the U.S., the National Air Sampling Network survey reports, begun in 1953, do not mention Al. This may be accountable by what has been said in the 1957 review (1): Al is the most widely distributed metallic element in the earth's crust and its presence in airborne particulate matter may, to a certain extent, be taken for granted as a consequence of its occurrence in soil. The data reported are not representative of

the average concentrations generally inhaled by man, because the amount of dust present in the air may vary greatly depending upon meteorologic conditions, extent and nature of vehicular traffic; location of the sampling site (paved or unpaved roads) as well as on the type of samples, whether they represent settled dust, in which case the large and therefore nonrespirable particles are collected, or whether they represent only that portion of the suspended matter which has physiologic significance.

Nonetheless, more investigations since 1957 have included Al than had been found earlier. This, in turn, may be explained in part by the development of newer analytical methods, particularly neutron activation, capable of determining nanogram quantities of pollutants in air and other media. The determination of pollutants in atmospheric precipitations is of more recent interest. The concentrations of Al in air and in atmospheric precipitations included in such reports as could be seen in the original, and in some published abstracts when the original was not obtainable, are shown in Tables 1 and 2, together with concentrations of Si, next to oxygen the most abundant element in the earth's crust, and Fe, the next most abundant metal.

Two of the reports concern entirely the "natural" concentrations of a number of elements, including Al. Poetzl (74) analyzed aerosol samples collected at a mountain station (1800 m altitude) near Garmisch-Partenkirchen and found Al to range from 0.09 to 0.18  $\mu\text{g/m}^3$ . Hoffman et al. (75) included determination of Al with Na, Cu, and V, in the particulates of the lower atmosphere between California and Hawaii, one station being a 20-m high tower on the windward coast of Hawaii, the other a ship in the Pacific Ocean. The results showed the Na/Cu, Na/V, and Na/Al ratios for seawater to be considerably greater than those for the particulate matter, indicating a nonmarine source for Al, Cu, and V, and the source of Al (0.005–0.032  $\mu\text{g/m}^3$ ) to be dust from the weathering of aluminosilicate crustal material.

The other reports point to differences in concentrations of various elements between relatively nonpolluted areas and those subjected to man-made pollution (see also Air Pollution): Keane et al. (76) compared their results on daily samples from Salford, England, with those of

**Table 1. Concentrations of aluminum, silicon, and iron in the atmosphere.<sup>a</sup>**

	Al, $\mu\text{g}/\text{m}^3$	Si, $\mu\text{g}/\text{m}^3$	Fe, $\mu\text{g}/\text{m}^3$	Reference
<b>Canada</b>				
Alberta, Jasper Natl. Park	0.13–0.23	—	0.13–0.28	(84)
Manitoba, Riding Mt. Natl. Park	0.27–0.39	—	0.22–0.36	(84)
N.W. Twin Gorges Hydroelec. Proj.	0.04–0.10	—	0.05–0.11	(84)
Summer	0.17 <sup>b</sup>	—	0.01 <sup>b</sup>	(84)
Winter	0.04 <sup>b</sup>	—	0.81 <sup>b</sup>	(84)
Ontario, Algonquin Prov. Park	0.19–0.28	—	0.25–0.38	(84)
Summer	0.24 <sup>b</sup>	—	0.23 <sup>b</sup>	(84)
Winter	0.25 <sup>b</sup>	—	0.30 <sup>b</sup>	(84)
Saskatchewan, Prince Albert Natl. Park	0.12–0.23	—	0.09–0.28	(84)
<b>German Federal Republic</b>				
Wank Mt. nr. Garmisch-Partenkirchen	0.09–0.18 <sup>c</sup>	0.11–0.50 <sup>c</sup>	0.04–0.15 <sup>c</sup>	(74)
<b>Industrial areas</b>				
Iron works, at 800 m	6.46 <sup>d</sup>	7.38 <sup>d</sup>	11.19 <sup>d</sup>	(112)
Pumice works, at 800 m	3.76 <sup>d</sup>	7.94 <sup>d</sup>	5.11 <sup>d</sup>	(112)
Cement, kaolin works, at 400 m	5.50 <sup>d</sup>	36.44 <sup>d</sup>	—	(112)
Cement, kaolin works, at 300 m	7.41–14.29 <sup>d</sup>	14.95–73.82 <sup>d</sup>	6.71 <sup>d</sup>	(112)
Cement, kaolin works, at 200 m	67.73 <sup>d</sup>	94.84 <sup>d</sup>	—	(112)
Chalk works, at 30 m	42.86 <sup>d</sup>	64.47 <sup>d</sup>	18.18 <sup>d</sup>	(112)
Munster, residential city	5.29–10.58 <sup>c</sup>	14.02 <sup>c</sup>	2.45–10.49 <sup>c</sup>	(81)
Oberhausen, industrial city, residential area	1.06–12.43 <sup>c</sup>	1.40–35.04 <sup>c</sup>	≤31.47 <sup>c</sup>	(82)
<b>Italy</b>				
Pavia, summer	0.86	—	—	(730)
Pavia, winter	0.07	—	—	(730)
<b>Japan</b>				
Osaka	1.60–6.20	—	3.90–12.90	(731)
Keiyo, industrial area	2.34–12.59	—	0.90–12.50	(732)
<b>Union of Soviet Socialist Republics</b>				
Leningrad	6.33–12.20 <sup>e</sup>	—	3.30–13.08 <sup>e</sup>	(733)
<b>Over oceans</b>				
N. hemisphere	0.12 <sup>e</sup>	—	0.18 <sup>e</sup>	(734)
S. hemisphere	0.01 <sup>e</sup>	—	0.01 <sup>e</sup>	(734)
<b>United Kingdom</b>				
Chilton	0.15–0.25	—	—	(76)
Lerwick	0.06–0.11	—	—	(76)
Milford Haven	0.05	—	—	(76)
Salford, industrial city	0.88	—	—	(76)
<b>United States</b>				
Hawaii, at 20 m altitude	0.005–0.032	—	—	(75)
Illinois, Chicago, metropolitan	0.48–3.20	—	—	(735)
Indiana, E. Chicago	2.18 <sup>b</sup>	—	13.80 <sup>b</sup>	(46)
Central Fire Station	0.96 <sup>b</sup>	—	2.10 <sup>b</sup>	(84)
Markstown Park	1.00 <sup>b</sup>	—	2.25 <sup>b</sup>	(84)
Hammond, Gary Whiting	1.38–3.10	—	1.42–13.00	(736)
Massachusetts, Cambridge	0.15–2.50	—	1.00	(44)
<b>Michigan</b>				
Ann Arbor	0.57–0.70	—	1.20–1.30	(84)
Mackinac Island	0.14–0.22	—	0.39–0.57	(84)
Summer	0.25 <sup>b</sup>	—	0.24 <sup>b</sup>	(84)
Winter	0.18 <sup>b</sup>	—	0.25 <sup>b</sup>	(84)



**Table 1. Concentration of aluminum, silicon, and iron in the atmosphere. (Continued)**

	Al, $\mu\text{g}/\text{m}^3$	Si, $\mu\text{g}/\text{m}^3$	Fe, $\mu\text{g}/\text{m}^3$	Reference
<b>United States (cont.)</b>				
Niles	1.20 <sup>b</sup>	—	1.90 <sup>b</sup>	(46)
rural area, diurnal variations.	0.65–2.90	—	<0.60–3.00	(737)
Missouri, Columbia	1.30–1.58	—	0.70–1.10	(738)
	0.47–1.26	—	—	(739)
<b>New York</b>				
Bayside	0.30–1.20	0.90–3.00	—	(740)
Buffalo	1.00–8.00	—	0.10–12.64	(45)
New York, metropolitan	2.04 <sup>e,b</sup>	4.84 <sup>e,b</sup>	2.98 <sup>e,b</sup>	(83)
Ohio, Cincinnati, industrial area	0.33–3.1	—	—	(739)

<sup>a</sup> Neutron activation analysis unless otherwise indicated.

<sup>b</sup> Means.

<sup>c</sup> Colorimetry.

<sup>d</sup> Method not stated.

<sup>e</sup> Emission spectroscopy.

**Table 2. Concentrations of aluminum, silicon, and iron in atmospheric precipitations.**

	Al, $\mu\text{g}/\text{ml}$	Si, $\mu\text{g}/\text{ml}$	Fe, $\mu\text{g}/\text{ml}$	Reference
<b>Rain</b>				
Canada, S.E. Ontario	0.52–1.12 <sup>a</sup>	0.00–0.26 <sup>a</sup>	0.13–1.80 <sup>a</sup>	(87)
Uganda, Kampala	0.04 <sup>a</sup>	—	0.05 <sup>a</sup>	(88)
<b>Union of Soviet Socialist Republics</b>				
Crimea, soluble	0.013 <sup>b,c</sup>	—	0.009 <sup>b,c</sup>	(86)
Crimea, insoluble	0.27 <sup>b,c</sup>	—	0.64 <sup>b,c</sup>	(86)
Otkaznen reservoir	0.002–0.044 <sup>b</sup>	—	0.001–0.031 <sup>b</sup>	(741)
<b>United States</b>				
Florida, nr. Ona	0.00–0.90 <sup>d</sup>	—	0.00–0.13 <sup>d</sup>	(143)
New Hampshire, Hubbard Brook	$\leq 0.10$ <sup>a</sup>	0.10 <sup>a</sup>	—	(742)
<b>Ice</b>				
Greenland	0.017 <sup>e</sup>	—	—	(91)
<b>Snow</b>				
Canada, S.E. Ontario	0.07–1.30 <sup>a</sup>	0.00 <sup>a</sup>	0.12–2.70 <sup>a</sup>	(87)
<b>United States</b>				
Maine, Beddington	0.03–0.07 <sup>a</sup>	0.14–0.47 <sup>a</sup>	—	(743)
Sierra Nevada, N.	0.00–1.20 <sup>e</sup>	0.00–7.94 <sup>e</sup>	0.00–3.1 <sup>e</sup>	(744)

<sup>a</sup> Colorimetry.

<sup>b</sup> Spectroscopy.

<sup>c</sup> Means.

<sup>d</sup> Atomic absorption spectrophotometry.

<sup>e</sup> Method not stated.

samples collected and analyzed over periods of several months in Chilton, Lerwick, and Milford Haven with relatively little pollution. The Salford concentrations were 2–10 times those from Chilton (local pollution apparently limited to the nearby incinerator at the Atomic Energy Research Establishment at Harwell). Similar differences were also indicated for industrial areas of Pecs, Miskolc, and Győr in Hungary (77, 78) where  $\text{SiO}_2$ , Fe, and Al particles constituted more than 10% of the settled dust, and those of Tokyo–Yokohama and two other cities in Japan, where alumina was among the “medium” components and Al content was 6–8% larger near industrial plants (79, 80). In Germany, Einbrodt et al. (81) found that in an essentially residential city the total dust content seldom exceeded  $150 \mu\text{g}/\text{m}^3$ , 15.3% of which was  $\text{SiO}_2$ , 6–12%  $\text{Al}_2\text{O}_3$ , and 3–10%  $\text{Fe}_2\text{O}_3$ . In the residential section of an industrial city (82), the total dust content ranged from 100 to  $460 \mu\text{g}/\text{m}^3$ . The contribution of  $\text{Al}_2\text{O}_3$  and  $\text{SiO}_2$  did not differ much from the above, being 8.5–24 and 3–12%, respectively, but the  $\text{Fe}_2\text{O}_3$  content was considerably higher, 6–23%. In an analysis of 10 elements in suspended particulate matter in metropolitan New York, Morrow and Brief (83) observed that Al, Ca, Si, and Mg correlated with each other. This led them to conclude that even at relatively urban sampling locations these elements are of mineralogical origin and that their relative proportions agree well with those in the total lithosphere.

In the aim of assessing the impact of distant aerosol sources on the trace element composition of surface air in remote regions of North America, Rahn (84) determined some 30 elements on Mackinac Island and several sites in Canadian parks to represent areas remote from man-made pollution, in Niles and Ann Arbor, Michigan, as semiurban and intermediate sites, and in East Chicago, Indiana, as an industrialized site. Al was one of the elements associated with the larger aerosol particles which appeared to have soil and soil dust as their main source, particularly in the remote locations. The concentrations found are shown in Table 1. It was interesting to note that the geometric mean of Al concentrations for all stations (25) was  $1.95 \mu\text{g}/\text{m}^3$ , for the industrialized sites 1.85, and for the semirural 2.00  $\mu\text{g}/\text{m}^3$ . Only one re-

port was found which showed the Al content (among 13 metals) of plants growing in an urban area. Smith (85) analyzed washed leaves and twigs of the previous year's growth of six tree species in New Haven, Connecticut, to evaluate the potential effect of pollutants on plant health. Al contents were among the “slightly above normal” amounts, the means ranging from 122 to 702  $\mu\text{g}/\text{g}$  dry weight basis. Except for the Norway spruce, where higher concentrations occurred in the twigs (342  $\mu\text{g}/\text{g}$ ), Al was higher in the leaves, and the highest levels were found in the leaves of the pin oak, Norway maple, and eastern hemlock. Analyses performed on sugar maple (leaves and twigs together), growing in remote sections of northern New Hampshire and Vermont gave Al content of 360–702  $\mu\text{g}/\text{g}$  (vs. the urban mean of 179  $\mu\text{g}/\text{g}$  in leaves and 122 in twigs).

As concerns atmospheric precipitations, Belyaev (86) found that concentrations of Ni, Cu, V, Mo, Ti, Al, Fe, and Mn in rain over the southern shore of Crimea were approximately the same as in the surface waters of the Black Sea (mean of soluble Al in rain was 0.013  $\mu\text{g}/\text{ml}$  and in seawater, 0.015  $\mu\text{g}/\text{ml}$ ). However, insoluble suspended particles constituted more than 70% of the metal content in precipitations (Al, 0.267  $\mu\text{g}/\text{ml}$ ). A correlation of  $\text{SiO}_2$  and Al contents in precipitations with those of surface waters was found by Rutherford in southeastern Ontario (87). Comparison of various constituents in rainwater in Kampala, Uganda (Al content of 0.04  $\mu\text{g}/\text{ml}$ ), with water mixed with dust (0.27  $\mu\text{g}/\text{ml}$ ), and Lake Victoria water (<0.001  $\mu\text{g}/\text{ml}$ ) led the author (88) to conclude that Al, N (both  $\text{NH}_3$  and  $\text{NO}_2$ ), and Ca are derived from dust. The influence of urban pollution on the trace element content of dusts and rain is evidenced in Schroll's data (89). In a total of 5.03  $\text{g}/\text{m}^2/\text{mo}$  precipitates over Vienna, he found 6.2%  $\text{Al}_2\text{O}_3$  (311.9  $\text{mg Al}/\text{m}^2$ ) and in a total of 2.86  $\text{g}/\text{m}^2/\text{mo}$  precipitates over noncontaminated Vienna Woods (Wienerwald), 2.28%  $\text{Al}_2\text{O}_3$  (65.2  $\text{mg Al}/\text{m}^2$ ). In an analysis of the chemical composition of precipitations in the Leningrad vicinity, Al, Fe, Mg, P, Na, and K were present to the extent of several per cent, while both Si and Ca exceeded 10% (90). Finally, in a search for  $^{26}\text{Al}$  and  $^{10}\text{Be}$  in Greenland ice, production of which is attributed to cosmic rays in the

atmosphere, 0.017  $\mu\text{g Al/ml}$  was found in the ice water (91).

**Industrial:** In spite of the fact that the accusing finger of environmentalists has been pointed long and, seemingly, more frequently at the aluminum industry than at any other metallurgical industry or other industries using Al-bearing minerals in their processes, the reason for concern has not been the release into the air of Al *per se*, but of other substances such as  $\text{SO}_2$  (92), tars (93) and particularly fluorides. The latter evolve from the use of cryolite ( $\text{Na}_3\text{AlF}_6$ ), natural or synthetic, as a flux in the electrolytic reduction of alumina to aluminum. The fluoride problem has long been recognized and has been met by the aluminum industry with constant research toward improved control of effluents, particularly in the past 25 yr or so. The costs of this are enormous, and had been estimated by Rothman in 1966 (94) to represent 12–15% of the total cost of an aluminum production unit. With the enactment of the latest amendment to the Clean Air Act in 1970 (95), these costs will be higher. This was recently indicated in a report of a systems analysis applied to the entire U.S. aluminum production industry of expected costs for overall upgrading the control efficiency from the present 74% to 92%. By applying the best demonstrated control technology, the invested industry capital would increase from \$51 to \$175 per capacity ton and would raise the industry's operating cost of pollution control from \$13 to \$43 per ton of aluminum produced at capacity (96). That F emissions are still a problem is evidenced by the priority for issuing quality criteria suggested in a report of the Committee on Public Works, U.S. Senate (97), and the fact that the first evaluative report by the National Research Council Committee on Biologic Effects of Atmospheric Pollutants (98) concerned fluorides. The worldwide literature on the biological and related aspects of F has been followed in our Department for many years (99). It has been striking to find but very few publications in which Al compounds not associated with F were reported among the effluents of aluminum industries, and none showed the Al content in the surrounding area (air or vegetation), in spite of the fact that  $\text{Al}_2\text{O}_3$  is used as the chief component of

the aluminum production process. To be sure,  $\text{Al}_2\text{O}_3$  may be considered as one of the components of total particulate effluents which soon settle on the ground. For instance, in a recent report on the size distribution of particulates emitted from aluminum reduction cells for the purpose of F analyses, the mass mean diameter was 5.5  $\mu$  with a standard geometric deviation of 25; about 50% particulate F compounds by weight were more than 13  $\mu$  diameter and less than 10% of the total particulate sample by weight was F (100). One report (101) claims Al to constitute about 13% of the fallout from a primary aluminum plant, principally as  $\text{Al}_2\text{O}_3$ ,  $\text{AlF}_3$ , and  $3\text{NaF}\cdot\text{AlF}_3$ ; another report estimates about 2% from a secondary plant (102). In an investigation of the F problem, aerosol concentrations within a 2-km radius of an aluminum factory averaged 1.23–5.49  $\text{mg/m}^3$ , depending on the distance from the plant (103). However, the percentage contents of only  $\text{SiO}_2$ , organic substances, and F are given.

In the production of primary aluminum, acidic dense white plumes of hydrogen chloride and chlorine,  $\text{AlCl}_3$  and  $\text{Al}_2\text{O}_3$  have posed a corrosion problem. These materials arise during the fluxing of the molten metal periodically with chlorine to separate impurities from the metal. In a report describing a control system for this process (104), the particulates in the plume are stated to be a combination of  $\text{AlCl}_3$  and  $\text{Al}_2\text{O}_3$ , mainly the latter, which may amount to 2.0–20.0 grains/standard  $\text{ft}^3$  during the chlorination period.

In a paper presented at the Second International Clean Air Congress on recent developments in the control of air pollution from aluminum smelters in the U.S., Rossano (105) describes a new system developed by the Aluminum Company of America for treating gaseous and particulate F compounds from reduction cells. The basic method consists of chemisorption of HF on  $\text{Al}_2\text{O}_3$  and subsequent removal of the sorbed F by a fabric collector. Particulate F compounds are removed by simple filtration in the same collection system. In addition to its high pollution control performance, advantages include absence of a contaminated liquid stream or solid waste disposal problem, and reuse of spent  $\text{Al}_2\text{O}_3$  from the collector system as feed material for the pots; the sorbed F helps main-

tain the required F level in the molten bath. The process, Alcoa 398, also described by Cook et al. (106) is reported to recover 99% of the treated gases. A recent compilation by the Environmental Protection Agency of air pollutant emission factors from various industrial and other sources (107) includes primary and secondary aluminum processes which are given a rating of "above average." Aside from particulate and gaseous F compounds,  $\text{Al}_2\text{O}_3$  and carbon particulates are mentioned as emissions from the primary processes. It is stated that extensive controls are applied to collect the vast amounts of dust generated in the calcining of  $\text{Al}(\text{OH})_3$  for the production of  $\text{Al}_2\text{O}_3$  because of the value of these dusts.

Several reports have noted the presence of  $\text{Al}_2\text{O}_3$  in emissions from industries other than aluminum, such as iron foundries ( $\text{Al}_2\text{O}_3$  present to the extent of 0.05–17.50% by weight) (108, 109); cement works [2.49–7.38% (110); 3.97% of total dust content of 300–600  $\mu\text{g}/\text{m}^3$  at a distance of 400 m and 4.20% at 1000 m from plant (111)]. Poetzl and Reiter (112) determined the  $\text{Al}_2\text{O}_3$  content in the atmosphere, along with  $\text{SiO}_2$ ,  $\text{Fe}_2\text{O}_3$ , and  $\text{CaO}$  at various distances from various factories (cement, pumice, kaolin, iron foundry) and in a fluorspar mine, as sources of exposure. The primary purpose of this study was the development of a four-stage cascade impactor as a model of pulmonary retention of particulates. The results are included in Table 1. Determination of Al was included in an investigation in the U.S.S.R. of the content of nine elements in the discharges of metallurgical and coke plants and their contents in the foliage of several tree species at distances up to 7 km from the industrial center (113). The Al content of the dusts collected from the horizontal flue in the open-hearth refining process amounted to 15.27% of ash. The content of Al in leaves of trees at 1 km distance from the center ranged from 0.0164–0.3773% dry weight; at 7 km, 0.0400–0.529%, depending upon the month of sampling and the species; the control trees at 35 km distance contained 0.0291–0.1956% Al. Total ash content was 7.1–16, 5.2–13.10, and 5.4–11.9%, respectively.

Among both industrial and domestic sources of air pollution, the regular presence of  $\text{Al}_2\text{O}_3$

in fly ash must be borne in mind. This was mentioned in a recent publication (114) as an example of "classical pollutants," and pointed out in the earlier review (1) for areas where coal is burned. There, the  $\text{Al}_2\text{O}_3$  content of coal ash was shown to be 5.3–52.3% (Al 28,042–276,719  $\mu\text{g}/\text{g}$ ). The high content of  $\text{Al}_2\text{O}_3$  and, for that matter of  $\text{SiO}_2$  and Fe oxides, was confirmed by Rees and Sidrak (115) who found  $\text{Al}_2\text{O}_3$  to constitute 15.5–29.34% (82,010–155,238  $\mu\text{g}/\text{g}$  Al),  $\text{SiO}_2$  43.40–51.8%, ferric oxide 8.25% and ferrous oxide 5.96% of the ash produced after combustion of pulverized coal. In Germany, fly ash containing Al and Si is recovered from power plants as a valuable material and sold to the U.S. (116). Recent atomic absorption spectrophotometric analyses of the metal content of Pennsylvania and Utah coal gave Al concentrations of 24,500 and 29,900  $\mu\text{g}/\text{g}$ , respectively (117).

**Automotive Exhausts:** In a publication pointing to lead as a noxious pollutant, Oelschlaeger (118) reported the content of 26 trace elements in automobile emissions; the Al content was 35 mg/kg of dust-form exhaust. In grass growing along the Echterdingen airport expressway, the Al content was 0.002  $\mu\text{g}/\text{g}$  higher than the normal mean of 120  $\mu\text{g}/\text{g}$  indicating therefore no change.

**"Self-pollution":** An example of this type of human exposure, the Al content (among 13 metals) in tobacco and smoke became available through Cogbill and Hobbs' publication (119). In tobacco per cigarette, Al ranged from 630 to 930  $\mu\text{g}$ ; in smoke, and average of 0.02  $\mu\text{g}$ , and per puff, 0.002  $\mu\text{g}$  were found.

**Occupational Exposure:** Concentrations of Al in workroom air also seem to be rarely reported, particularly in the aluminum plants where the F compounds constitute the major hazard to workmen, along with tars (120, 121). Publications which included interpretable figures as to the presence in the air of Al and its compounds indicate the following orders of magnitude of exposure: Aluminum alloy casting (122), maximum total dust 27.00  $\text{mg}/\text{m}^3$  (mostly Al); aluminum powder factory (123), total dust (two sites) 0.94 and 1.46  $\text{mg}/\text{m}^3$  (Al

71 and 60%); respirable fraction 0.24 and 0.38 mg/m<sup>3</sup> (Al 48 and 42%); same type of factory (124), total respirable dust, mean of 95.00 mg/m<sup>3</sup> (81.4% Al, 17% Al hydroxide and oxide); alumina manufacture (125), dust, means of 3.6–76.2 mg/m<sup>3</sup>; alumina unloading from ships (126), 139.9–777.1 mg Al<sub>2</sub>O<sub>3</sub>/m<sup>3</sup>; white synthetic corundum manufacture (127), total dust (Al<sub>2</sub>O<sub>3</sub>, SiO<sub>2</sub>, Fe<sub>2</sub>O<sub>3</sub>, Na<sub>2</sub>O) 55.00–75.00 mg/m<sup>3</sup>; synthetic leather manufacture (128), 30.00 mg Al/m<sup>3</sup>, 24.10 mg kaolin/m<sup>3</sup>. The particle size distribution of Al<sub>2</sub>O<sub>3</sub> in aerosols formed during welding of aluminum has also been studied (129).

**Air Quality Criteria (Permissible Concentrations, Threshold Limit Values):** Because of growing concern, particularly since the mid-sixties, with the human environment and effect of pollutants in the atmosphere to which the general and working population is exposed, the Clean Air Act (U.S. Congress, 42nd 1857 et seq.) has been amended several times in the past decade: in 1963, 1965, 1966, 1967 [also cited as the Air Quality Act (Public Law 90-148)] and 1970 (Public Law 91-604) (95). Another important one, the Occupational Safety and Health Act of 1970 (130) has come into effect. In 1970, in anticipation of the latter Act, Hoesy of the Bureau of Occupational Safety and Health (now National Institute for Occupational Safety and Health) published the priorities for developing criteria for "breathing air" standards and described the methods used for establishing these priorities based on ratings by the Bureau solicited from 10 state occupational health programs and 20 hygienists of private industries (131). Aluminum and its compounds, for which criteria have not yet been set, appear in group 11 of a total of 19 priority groups.

The existing threshold limit values (TLV) or maximum permissible concentrations (MPC) are as follows: ambient air, U.S., none established; U.S.S.R., not listed *per se*; if considered as a "nontoxic dust," MPC for onetime exposure in populated areas, 0.5 mg/m<sup>3</sup> and for mean diurnal exposure, 0.15 mg/m<sup>3</sup> (132); workroom air, U.S., alundum or corundum (Al<sub>2</sub>O<sub>3</sub>) and kaolin listed under "nuisance particulates" (when toxic impurities are not

present, e.g., quartz <1%) TLV 10 mg/m<sup>3</sup> (133). In the other countries including Al-containing compounds and alloys in their MPC's (Argentina, Bulgaria, Finland, Japan, Romania, U.S.S.R., Yugoslavia), these range from 2 mg/m<sup>3</sup> (Japan, Romania, U.S.S.R.) to 6 mg/m<sup>3</sup> (U.S.S.R. for Al<sub>2</sub>O<sub>3</sub> in the form of disintegration aerosols), and 1750 particles/cm<sup>3</sup> (Finland, Yugoslavia) (134, 135).

### Aluminum in Waters

In summarizing the sources and chemistry of Al in natural waters, Hem (136) observes that this, the most abundant metallic element, is highly resistant to removal from minerals by solution during weathering and remains behind persistently in the process of rock decomposition to form the clay minerals in soils and the greater part of shales and similar hydrolyzate sediments. As was stated in the earlier review (1), the concentrations of Al in most natural waters are negligible. Only in waters where a pH below 5 is maintained can Al be present in large amounts (>100 µg/ml). This condition may occur from industrial wastes, mine drainage, or natural phenomena such as in acid spring waters, mires, and volcanic regions. A relationship among pH, trace element content, and rate of water movement was also found. Sparling (137) noted that Al ions change appreciably in concentration within the pH range of 4.1–7.0 and are widespread in mires where low pH prevails because of low water movement; with faster rates of movement, the pH is increased. The trivalent Al ions are almost insoluble at pH above 5.5. The theoretical maximum concentration of Al at pH 4.7 is about 1 µg/ml and at pH 4, about 5 µg/ml. Toth (138) also found that in general the reduced water flows in summer had a tendency to increase the content of the minor elements in New Jersey waterways.

The Federal Water Pollution Control Act of 1956 has provided for a comprehensive program to prevent and control water pollution (139). This surveillance of surface waters went into effect on October 1, 1957, and encompassed the spectroscopic determination of 19 trace metals including Al. As shown in the

latest report, covering a 5-yr summary of the analyses of these metals in rivers and lakes of the U.S. from October 1962 through September 1967, Kopp and Kroner (139) performed 1464 analyses for Al in a total of 1577 samples collected at 130 locations with 456 positive occurrences at an overall frequency of detection of 31%. Soluble Al was found in concentrations ranging from 1 to 2:760  $\mu\text{g/ml}$  (mean 0.074). The highest concentration was a single occurrence in the Yellowstone River near Sidney, Montana. In 1967 the same authors (140) reported results of a study that included concentrations of elements suspended in natural waters, thus measuring the total trace element load in addition to concentrations found in solution. The latter are ordinarily reported on the assumption that any suspended material would be removed before the water reached the consumer. In the rivers under study (Monongahela, Delaware, Allegheny, Kanawha, Ohio), except for the Monongahela which contained 0.030–1.875  $\mu\text{g/ml}$  dissolved Al and 0.003–0.442  $\mu\text{g/ml}$  suspended Al, the suspended Al exceeded the dissolved (0.003–1.440 versus 0.001–0.120  $\mu\text{g/ml}$ ).

The U.S. Geological Survey has published annual records of water quality since 1941, which are then published periodically in volumes. The latest, published in 1970, covered collections of surface waters made from October 1, 1964, to September 30, 1965 (141). Al content was not always determined, for the reason that it is generally present only in negligible quantities. Of the reported values in this source, only those of 1  $\mu\text{g/ml}$  and higher are included in Table 3.

In a geographic differentiation of the trace element content of some major streams of the world, Durum and Haffty (142) found concentrations of most elements to range up to 0.100  $\mu\text{g/ml}$  with medians of 0.010  $\mu\text{g/ml}$  or less. Only Al, Fe, Mn, Ba, and Sr exceeded 0.100  $\mu\text{g/ml}$ . Gulf Coast rivers exceeded continental values for Al, Ba, Cu, Fe, Li, Rb and Ti, while Cr, Pb and Sr were lower. Al and other elements in North American runoff were of the same order as the world averages for ocean waters.

The relationship of the content of various elements in surface waters to that of rainwater

was also studied (143, 144). The values obtained in surface waters were much greater than in rainwater, leading to the assumption that Al in stream water, the concentration of which increases with stream discharge, is wholly acquired from the soil (144).

As can be seen in Table 3, little information on Al content in ground waters (including springs or "mineral" waters) could be added to the data tabulated in the earlier review. Unfortunately, a survey of 34 ground waters in the Derbyshire Dome for trace constituents could not be seen in the original (145).

As to the Al content of ocean waters, Armstrong (146) reported the water of the English Channel to contain 0.008–0.107 (mean 0.037)  $\mu\text{g/ml}$  in suspension and that of the Eastern Atlantic, 0.002–0.049 (0.012)  $\mu\text{g/ml}$ .

In seawater along the Indian coast, 0.027–1.200  $\mu\text{g Al/ml}$  was found (147, 148) and in the Black Sea, a mean of 0.015  $\mu\text{g/ml}$  (86), while in the Kuyal'nik estuary, there was 0.780  $\mu\text{g/ml}$  (149). Atkinson (150) states the source to be primarily continental drainage. In the seawater off the Southeast coast of the U.S. (between Chesapeake Bay and Cape Kennedy), he found particulate Al concentrations to average from 0.0004–0.07  $\mu\text{g/ml}$ . These concentrations were generally lower by a factor of at least 10-fold than the averages found in several rivers draining into the shelf seawaters (0.411–0.873  $\mu\text{g/ml}$ ). In the coastal waters of the Pacific Northwest particulate Al contents ranged from 0 to 1.54  $\mu\text{g/ml}$  (151).

**Water Pollution:** Man-caused increases in the Al content, and for that matter of other metals, in waters are attributable principally to mining activities, especially strip mining for coal which causes low pH because of the high sulfate levels (152–159), with resulting toxicity to aquatic life (152). Al and some other metals, however, were reported to have returned to premining levels within certain periods of time (160). Interestingly enough, alumina-silica gels were found to be most effective in sealing coal refuse piles (161). Another source of pollution is the exposure of geologic formations. In New Jersey, Toth (138) found that two tributaries to the impoundment of Matawan Lake contributed

**Table 3. Concentrations of aluminum in waters<sup>a</sup>**

	Al, μg/ml	Reference		Al, μg/ml	Reference
<b>Rivers and Creeks</b>					
Africa, Ivory Coast			United States (cont.)		
Bandama R.	0.03–0.80 <sup>b</sup>	(745)	District of Columbia,		
			Potomac R.	0.79–0.92	(150)
Canada			Florida, Apalachicola R.	0.07–2.55	(746)
British Columbia, Fraser R.	0.05–0.53	(746)	Streams nr. Ona	0.00–1.00 <sup>g</sup>	(143)
Manitoba, Churchill R.	0.10–0.18	(746)	Great Basin (W. desert		
Nelson R.	0.08–0.66	(746)	region, Ore., Nev., Utah,		
N.W. Territory, MacKenzie R.	0.44–1.41	(746)	Calif.)	0.00–0.03	(139)
Quebec, St. Lawrence R.	0.19–1.05	(746)	Great Lakes, W., Basin	0.00–0.07	(139)
France			Kentucky		
Argens R. trib. Caramy,			Beaver Cr. Basin, W. Fork	0.00–0.40 <sup>b</sup>	(153)
Ribeirotte (bauxite region)	0.06–0.07 <sup>b</sup>	(747)	Coal mine drainage	0.00–85.0 <sup>d</sup>	(153)
German Democratic Republic			Big Sandy R. Basin,		
Elbe and Saale R.	0.16–0.90 <sup>c</sup>	(748)	Russel Fork	3.10 <sup>e</sup>	(141)
Indonesia			Breathitt Co. watershed		
Banjipati R., 12 km from			Before coal mining	0.05–0.19	(160)
Kava Ijen Volcano	222.59 <sup>b</sup>	(749)	2–3 mo after mining	0.15–0.44 <sup>b,d</sup>	(160)
			1 yr after mining	~0.02	(160)
South Africa			Cumberland R. Basin,		
Orange R., Cape Province	0.04–3.6	(750)	Cane Br.	5.30–6.50 <sup>e</sup>	(141)
Union of Soviet Socialist			Tradewater R., at Olney	0.10–21.0 <sup>c</sup>	(141)
Republics			Lake Erje Basin	0.02–0.14	(139)
Ayuta R., coal mine drainage	4.00–387.20 <sup>b,d</sup>	(159)	Louisiana, Atchafalaya R.	0.46–1.64	(746)
Kingissepa region	0.006	(751)	Mississippi R. nr. Baton		
Kuma R.	0.01–0.02	(752)	Rouge	0.28–1.05	(746)
Kurile Islands, Yurieva R.			Maryland, Patuxent R. Basin	0.02–0.62	(758)
draining Ebeko Volcano	435.00 <sup>b</sup>	(753)	Potomac R., N. Branch	1.70–6.20 <sup>g</sup>	(141)
Kuyal'nik estuary, saline	0.78	(149)	Susquehanna R.	0.03–0.10	(746)
Pripyat R. trib.	0.01 <sup>b</sup>	(754)	Minnesota, Chippewa R.		
Viliva R., Lithuania	0.00 <sup>b</sup>	(755)	nr. Milan	0.20–2.90 <sup>g</sup>	(141)
Volga R. and trib.	0.00–0.08	(756)	Clearwater R. at Red		
Yura R., Lithuania	0.13 <sup>b</sup>	(755)	Lake Falls	0.20–1.50 <sup>g</sup>	(141)
United States			Minnesota R. Basin		
130 sampling points	0.00–2.76	(139)	at Montevideo	0.10–1.20 <sup>g</sup>	(141)
Alabama, Mobile R.	0.08–0.82	(746)	Mississippi R. nr.		
Alaska Basin	0.00–0.02	(139)	Royalton	0.10–1.90 <sup>g</sup>	(141)
Yukon R.	0.08	(746)	Red Lake R. nr.		
Arizona, Colorado R.	0.01–0.15	(746)	Redlake	0.20–2.50 <sup>g</sup>	(141)
California, 165 samples	<0.05–1.20	(757)	Thief R. nr. Falls	0.40–2.10 <sup>g</sup>	(141)
Agricultural drainage	<0.20–0.80 <sup>g</sup>	(757)	Mississippi R., Upper,		
Domestic wastes	<0.10–0.38 <sup>f</sup>	(757)	Basin	0.00–0.13 <sup>g</sup>	(139)
Food processing plants	0.90–2.20 <sup>d</sup>	(757)	Lower Southwest, Basin	<0.01–0.59	(139)
	14.00–50.00 <sup>d</sup>	(757)	Missouri, Cedar Cr. nr.		
Metal, chemical plants	<0.10–<2.00 <sup>d</sup>	(757)	Columbia	14.00–76.00 <sup>e</sup>	(141)
Sacramento R.	0.06–1.11	(746)	Little Chariton R. Basin	0.10–3.20 <sup>g</sup>	(141)
Suisun Bay, San Joaquin R.	<2.00	(757)	Rocky Branch, claypit		
California R. Basin	0.01–0.23	(139)	area	0.63 <sup>d</sup>	(163)
Colorado, California Gulch	0.00–11.60	(141)	Missouri R. Basin	0.01–2.76	(139)
Colorado R. Basin	<0.01–0.20	(139)	Montana, Yellowstone R.		
			nr. Sidney	2.70	(139)
			New Jersey		
			Big Flat Brook, acidic site	0.10 <sup>g</sup>	(138)
			Big Flat Brook, cal-		
			careous site	0.07 <sup>g</sup>	(138)

**Table 3. Concentrations of aluminum in waters<sup>a</sup> (cont.)**

	Al, μg/ml	Reference		Al, μg/ml	Reference
Rivers and Creeks (cont.)					
United States (cont.)			United States (cont.)		
Passaic R. nr. Chatham	0.02-1.10	(141)	Virginia		
Various streams	0.09-0.33 <sup>g</sup>	(138)	Rappahannock R. at		
New York, Hudson R.	0.23-0.78	(746)	Fredricksburg	0.37-0.50	(150)
North Atlantic Basin	0.00-0.14	(139)	Roanoke R., Roanoke area		
North Carolina			Landfill, upstream	0.17 <sup>d, h</sup>	(162)
Neuse R.	0.66	(150)	Landfill, downstream	0.40 <sup>d, h</sup>	(162)
Roanoke R.	0.40-0.81	(150)	Meat packing plant,		
Northeast Basin	0.00-0.15	(139)	upstream	0.22 <sup>d, h</sup>	(162)
Ohio River Basin	0.01-0.14	(139)	Meat packing plant,		
Oregon, Columbia R.	0.08-0.24	(746)	downstream	0.24 <sup>d, h</sup>	(162)
Pacific Northwest Basin	0.00-0.18	(139)	Oil industry, upstream	1.23 <sup>d, h</sup>	(162)
Pennsylvania			Railroad yards,		
Kiskiminetas R. Basin			upstream	0.79 <sup>d, h</sup>	(162)
coal mine area	0.00-4630.00 <sup>b, d</sup>	(158)	Railroad yards,		
Kiskiminetas R. at			downstream	0.31-2.23 <sup>d, h</sup>	(162)
Leechburg	15.00 <sup>c</sup>	(141)	Sewage plants,		
Monongahela R. at			upstream	0.32-0.83 <sup>d, f, h</sup>	(162)
Pittsburgh	0.01-1.43	(139)	Sewage plants,		
Schuylykyl R. and			downstream	0.35-1.30 <sup>d, h</sup>	(162)
branches	0.20-4.80 <sup>c</sup>	(141)	West Virginia, Abram Cr.	1.00-10.00 <sup>c</sup>	(141)
Susquehanna R., W.			Buckhannon R. at Hall	1.10 <sup>c</sup>	(141)
Branch	3.90-11.00 <sup>c</sup>	(141)	Lynch Run nr. Glenville	16.00-18.00 <sup>c</sup>	(141)
St. Lawrence R. Basin, trib.			Monongahela R. Basin,		
to Lake Superior	0.00-1.3 <sup>c</sup>	(141)	Roaring Cr.	3.30-12.00 <sup>c</sup>	(141)
Southeast Basin	0.00-1.05	(139)	West Fork R. at Enterprise	6.20-6.3 <sup>c</sup>	(141)
Tennessee R. Basin	0.00-0.09	(139)	Western Gulf Basin	<0.01-0.92	(139)
Lakes, Ponds, Reservoirs					
Hungary, Balaton Lake	0.01-0.03 <sup>c</sup>	(759)	United States		
			California, Yosemite Park Miller		
			Lake	0.04	(761)
Uganda, Lake Victoria	<0.001 <sup>c</sup>	(88)	Florida		
			Lakes nr. Ona	0.00-1.0 <sup>g</sup>	(143)
			Polk Co., phosphate		
			pit lake	0.03 <sup>c, d</sup>	(164)
Union of Soviet Socialist			Lake Erie, at Buffalo	<0.01-0.07	(139)
Republics			Lake Michigan, at Gary	0.00-0.06	(139)
Kurile Islands, volcanic			Lake Superior, at Duluth	0.00-0.03	(139)
acid thermal lakes	2000.00-3000.00 <sup>b</sup>	(753)	Maine, Beddington, Chalk		
Otkaznen reservoir,			Pond	0.03-0.49 <sup>c</sup>	(743)
industrial area	0.00-0.07 <sup>d</sup>	(752)	Missouri, Callaway Co.,		
Rybin reservoir	0.10-1.30	(760)	coal mining area, lakes		
Staro-Beshev reservoir,			Acid, top to bottom		
industrial area	0.001 <sup>d</sup>	(166)	means	212.00-426.00 <sup>d, i</sup>	(156)
Tsimlyan reservoir	0.03	(166)	Alkaline	0.02-0.03 <sup>d, i</sup>	(156)
Veselov reservoir	0.01	(166)	Clay pit area, farm pond	0.63-110.00 <sup>d</sup>	(163)
Volgograd reservoir,			New Jersey, Matawan Lake	>25.00-30.00 <sup>d, g</sup>	(138)
industrial area	0.01 <sup>d</sup>	(167)			
Ground Waters, Springs, Wells					
Bulgaria, saline ground wates	0.02-5.50	(762)	New Zealand, Wairakei		
			drill hole		
			Ionic Al	0.01-0.03 <sup>c</sup>	(763)
Japan, Beppu boiling spring	0.01-0.43 <sup>c</sup>	(763)	Total Al	0.02-0.06 <sup>c</sup>	(763)



Table 3. Concentrations of aluminum in waters<sup>a</sup> (cont.)

	Al, μg/ml	Reference		Al, μg/ml	Reference
Ground Waters, Springs, Wells (cont.)					
Union of Soviet Socialist Republics			United States (cont.)		
Azerbaijan, Istis	0.59	(764)	Casa Diablo, hot, cold springs	<0.20	(757)
Azerbaijan, Sharlanski	0.40	(764)	Imperial Valley, thermal brines	<100.00	(757)
Estonia, drill holes, wells	0.46–1.77 <sup>b</sup>	(765)	Oil Well brines	<0.20	(757)
Otkaznen reservoir shores	<0.02–0.02	(752)	Nr. Salton Sea, springs, wells	<0.05–0.80	(757)
			San Joaquin Valley, wells	<0.02–0.2	(757)
United States			Kentucky, Beaver Cr. Basin, coal mining area	0.00–102.00 <sup>b</sup>	(767)
Alabama, Marengo Co., wells	0.6 <sup>b</sup>	(766)	Missouri	0.01–0.02 <sup>b</sup>	(55)
California			Oregon, Santiam R. Basin, wells	0.00–0.02	(760)
Amboy salt well	<0.05	(757)			

- <sup>a</sup>. Spectroscopy, unless otherwise indicated.
- <sup>b</sup>. Method not stated.
- <sup>c</sup>. Colorimetry.
- <sup>d</sup>. Industrial pollution.
- <sup>e</sup>. Agricultural drainage.
- <sup>f</sup>. Domestic wastes or sewage.
- <sup>g</sup>. Atomic absorption spectrophotometry.
- <sup>h</sup>. Neutron activation analysis.
- <sup>i</sup>. Gravimetric method.

enough sulfuric acid, produced by the oxidation of exposed iron sulfide, to result in a pH of 2.8 in the lake with a soluble Al content of more than 25–30 μg/ml and Fe content of 15–25 μg/ml, enough to kill almost all plant and animal life. He cautions that the damming of a stream to form an impoundment without checking the composition of the tributaries may lead to the creation of a sterile impoundment. In a neutron activation analysis by Furr (162) of eight elements in the waters of the Roanoke River system upstream and downstream from sewage treatment plants, railroad yards, landfills, meat packing plants, and an oil industry, the changes occurring above and below the suspected sources did not always show increases. Sewage treatment plants were by far the most significant contributors. Al concentration was up 56.2% for one of them, compared with a 141% increase in K and a 79.6% increase in Mg. A 96% increase in Al was found at a landfill site and a 238% rise at a railroad yard. In a very recent report, anomalously high concentrations of Al, Be, Co, Cu, Mo, and Ni occurred in the soil, plants and waters of an area adjacent to a

claypit in Callaway County, Missouri, causing metabolic imbalance similar to chronic molybdenosis in beef cattle. The principal sources of the increases were believed to be the exposure of clay, shale, limestone, coal, and pyrite, particularly the latter which, by weathering, produced sulfuric acid, thus increasing the solubility of certain compounds (163). On the other hand, Al concentrations in a phosphate pit lake, formed in phosphate strip mining, were quite low (mean 0.03, highest 0.09 μg/ml at bottom 2 m) or not detected (164).

In the Kazakh S.S.R., it was proposed to use the sludge from coal mining and metallurgic wastes, containing numerous metallic elements (Al and Fe contents from 1–3 x 10<sup>4</sup> to 1 x 10<sup>5</sup> μg/g) as fertilizers for soils deficient in minerals (165). Aside from the above, only few data could be found for the Al content of surface water receiving wastes, or of the wastes themselves. Two publications from the U.S.S.R. report “industrial pollution” of reservoirs, but only 0.001 μg Al/ml was found in settled waters (166,167). An alumina content of 2.15–5.58% in wastes (assumed to be liquid) from an alumina pilot

plant in Kirovabad is also reported (168). In the U.S., the effect of dumping solid aluminum process wastes at one of three locations in the Pacific Ocean 40 miles off the mouth of Columbia River is under study (169). Table 3 includes Al concentrations resulting from domestic and industrial pollution.

The Al content in drinking waters (finished) is discussed in a subsequent section.

**Water Quality Criteria (Standards, Permissible Concentrations):** In a report published by the U.S. Federal Water Pollution Control Administration (170a) (now part of Environmental Protection Agency), the Subcommittee on Public Water Supplies provided for permissible criteria toward the production of "a safe, clear, potable, esthetically pleasing and acceptable public water supply which meets the limits of Drinking Water Standards" (171) after treatment, as well as desirable criteria. The latter are defined as "those characteristics and concentrations of substances in the raw surface waters which represent high quality water in all respects for use as public water supplies." Al is not listed among the metals for which criteria or Drinking Water Standards had been set, for it is not a health problem in these waters (139). It may perhaps be considered as a component of the mineral salts, the permissible limit of which is 500  $\mu\text{g}/\text{ml}$  of total dissolved solids (filterable residue), and the desirable, less than 200  $\mu\text{g}/\text{ml}$ , or water hardness and pH.

The Federal Water Pollution Control Act, as amended by the Water Quality Act of 1965, authorized the States and the Federal Government to establish water quality standards for interstate (including coastal) waters by June 30, 1967. On February 27, 1967, the Secretary of the Interior established the first National Technical Advisory Committee on Water Quality Criteria consisting of subcommittees, in addition to the above, to develop criteria for four more general use areas, including recreation and esthetics (170). Al is included among the tentative trace element tolerances for the agricultural and irrigation waters to the extent of 1  $\mu\text{g}/\text{ml}$  for continuous use on all soils and 20  $\mu\text{g}/\text{ml}$  for short-term use on fine-textured soils only. Although toxic effects on plants have been observed at 0.5  $\mu\text{g}/\text{ml}$ , sandy soils could be expected to reduce

the phytotoxicity of Al to some degree and management practices could be used to avoid marginal toxicity (see also below). For industrial waters, tables showing quality of water used for various processes list Al from 0.01 to 5.00  $\mu\text{g}/\text{ml}$  or "accepted as received," as presenting no problems at encountered concentrations. The quality of raw surface waters for use in the food and canning industry should be that of the Criteria for Public Water Supplies. In respect to fish and other aquatic life and wildlife, Al is mentioned in connection with water hardness to which Al and other metals contribute. However, since they are present in relatively small amounts, their role usually can be ignored. The proposed criteria for water quality, reported in October 1973 (170b), set the limit of Al for continuous irrigation at 5.0  $\mu\text{g}/\text{ml}$ , with a maximum acceptable concentration (MAC) of 20  $\mu\text{g}/\text{ml}$  for fine textured neutral to alkaline soils for a period of not more than 20 yr. The MAC in livestock drinking water is 5  $\mu\text{g}/\text{ml}$ . In marine or estuary waters, concentrations above 1.5  $\mu\text{g}/\text{ml}$  are unacceptable on the basis of toxicity to the most important sensitive species of aquatic life.

In an effort to halt water pollution from primarily industrial sources, the Environmental Protection Agency began issuing effluent guidelines, the first group of which was distributed in 1972, including one for the aluminum industry (172).

Neither in the International nor in the European Standards for Drinking Water (173, 174) is Al listed among substances for which limits are specified; it is only mentioned in tables of recommended analytical methods; in this case, colorimetry using aluminon or hematoxylin solution.

In the U.S.S.R., several authors have recommended maximum permissible concentrations (MPC) for some compounds in water on the basis of animal experiments. One concerned  $\text{AlCl}_3$ , the value being set at 4  $\mu\text{g}/\text{ml}$  (or 0.5  $\mu\text{g}$  Al/ml); that for  $\text{AlF}_3$  was set at 2.2 g/ml (or 1.5  $\mu\text{g}$  F/ml (175). Another one was for  $\text{Al}(\text{NO}_3)_3$ , the limit of 0.1  $\mu\text{g}/\text{ml}$  of the compound being set on the basis of its taste threshold concentration, although about 20  $\mu\text{g}/\text{ml}$  was ineffective during prolonged ingestion by animals (176). The International Standards for Drinking Water resulted from deliberations

of an Expert Committee convened by the WHO in 1971 which included the Deputy Minister of Health of the U.S.S.R. Al is not listed among the chemicals for which limits were set in the above Standards nor in the U.S.S.R. Maximum Permissible Concentrations of Toxic Substances in Water for Sanitary-Household Uses, approved in 1970, listing limits for 294 substances (unpublished document). Thus it appears doubtful that the above recommendations for Al levels had been accepted.

### **Aluminum in Contact with Food, Pharmaceuticals, and Cosmetics**

Before reviewing the growth of the applications of aluminum in food processing, it is well to repeat that food in contact with any metal (even stainless steel) (177) or any other surface material will be affected by it to varying degrees and, conversely, the food itself may affect the metal or surface. In this connection, we must bear in mind that food, be it of plant or animal origin, is a composite of many chemical substances from the complex types of high molecular weight, such as proteins, to the ionic forms of major and trace elements.

The withdrawal or leaching of some toxic metals (principally Pb and Cd) from metal and glazed earthenware food and beverage containers has long been recognized and remains a current problem. As concerns aluminum, exhaustive tests conducted since around 1890, when it became available through the Hall-Heroult processes in adequate quantities, have shown that negligible amounts of Al are dissolved by food. Also, its effect on the food is negligible, for most of its salts are colorless and, in the concentrations in which they may occur, tasteless (in contrast to those of Fe and Cu) (178) and have not been demonstrated to affect the nutritive qualities of food. As was learned earlier, the dissolution or "corrosion" of a metal is the chemical or electrochemical reaction in the environment in which it is placed. In the case of aluminum, its resistance to corrosion is due to the formation of a protective film of the oxide or hydroxide which, under certain conditions, may be broken down. In this case also, the products formed in the pH range from 4 to 9 are mainly Al oxides or their hydrates (1). The conditions under which this may occur have

been reviewed in depth by Juniere and Sigwalt (178). To all practical purposes, this is of concern to the chemical and food industries only.

The leachability of Al from ceramics made from clays containing high amounts of  $\text{Al}_2\text{O}_3$  has been apparently of no concern. Such clays have been used before 5000 B.C., and in the more recent years of space exploration. Al oxides have been utilized in the development of break-resistant tableware and cookware that can be transferred straight from the refrigerator to the oven (4). Alumina is also used in the manufacture of glass and porcelain, as well as in glazes for dinnerware. It was interesting to note that higher additions of  $\text{Al}_2\text{O}_3$  to Pb silicate base glazes reduce release of Pb in acids (179). However, while glass had been generally considered to be nonreactive to food and water, two recent reports deal with the leaching of  $\text{Al}_2\text{O}_3$  and  $\text{SiO}_2$  from this material. In the one, undesirable precipitates of mostly  $\text{SiO}_2$  and  $\text{Al}_2\text{O}_3$  were visible in potassium and dextrose mixtures for parenteral therapy, commercially supplied in glass bottles made of soda-lime material (180). In the other, Complexon III (50 ml of 0.001M solution) placed in 11 flasks, reagent bottles and medical glasses, released 7–23  $\mu\text{g}$  Al from all, and Ca and Zn were found also in several containers (181). These findings are, of course, extreme cases and, unless further data become available, not applicable to table or heat-proof glassware.

### **Industrial Uses**

Among the major applications (or markets) of aluminum, that for containers and packaging has shown the greatest growth since 1960. Of the total shipment of 10,406 million pounds in 1971, that for containers and packaging was 1514 million pounds and represented a 15.7% increase from the 321 of a total of 4732 million pounds shipped in 1960. Although, as shown by The Aluminum Association statistics (8) for the years 1967 through 1971, the total market for cooking utensils decreased from the high of 168 million pounds in 1969, it showed a net gain of 24 million pounds since 1967 (121 and 145 million pounds in 1967 and 1971, respectively). Total household and institutional foil shipments rose steadily in the past 5 yr from 141 to 210 million pounds, and those for metal cans, from

410 to 905 million pounds. While the above figures do not represent exclusive use by food, pharmaceutical and cosmetics manufacturers whose products reach the consumer's immediate exposure, they do reflect increasing applications of aluminum by these industries.

The suitability of aluminum in the processing and packaging of foods and pharmaceuticals has been under investigation since around 1890. This has required, and still does, the combined technical knowledge of the processors and of those engaged in the fabrication of the metal and its alloys. As pointed out earlier, the aluminum industry had learned from experience that not all alloys are satisfactory for use in the food and chemical industries and that aluminum is not suitable for all types of equipment or under all conditions of service. This applies, of course, to other metals as well. In the U.S., the limits of contents of Si and metals (Fe, Cu, Mn, Mg, Cr, Ni, Zn, Ti, and others) in the different alloys, depending on their use, are specified in *Aluminum Standards and Data* published by The Aluminum Association (182). This Association has also carefully recorded all experience to the present time in the compatibility of aluminum in contact with chemicals and foods in its publication, *Aluminum with Food and Chemicals* (183), the bulk of which is an alphabetical listing of substances and food products with brief digests of suitability and special treatment of the surface by anodizing or other type, as required.

In the U.S., wrought aluminum and its alloys are designated by four-digit numbers, the first of which indicates the alloy group, the last two the purity, and the second, modifications of the original alloy or impurity limits. Commercially pure aluminum is alloy 1100 with a minimum of 99% Al and may reach a purity of 99.75% and higher. The 1xxx series possesses excellent resistance to corrosion and other properties to make it suitable for numerous applications, including cladding less pure alloys or other metals (tinplate), although they are not used as such where strength is required. The other resistant alloys are the 3xxx, 5xxx, 6xxx, and the Cu-free 7xxx series which have been used successfully in the chemical and food industries. According to Juniere and Sigwalt (178) who evaluated the suitability of aluminum in the same industries,

particularly from the European point of view, aluminum alloys of 99.5% purity are generally used, and alloys of up to 99.99% ("superpurity") are available. However, here also, alloys with lower purity, but with high resistance to corrosion, are recommended for these industries.

It is clear from the many applications of aluminum in the food industries, enumerated and described by these authors, that wider use has been made in Europe than in the U.S. for all processes, from handling the raw product through processing to storage or packaging in cans, collapsible tubes and foils as such or as laminates with other materials. Through experience and knowledge of the physical and chemical properties of the metal, there are means of avoiding contact with metals of different potential causing corrosion (especially copper) as well as remedying the attach of very aggressive products. The many applications in the food and beverage industries and the numerous reports of compatibility and comparative tests which have been published more recently need not be discussed here individually. In most of these, the resistance of aluminum to corrosion has been found to be equal to or better than that of other metals.

It appears that aluminum has been also used more extensively for canning in the European countries (because of postwar restrictions of steel for tinplate, or unavailability) than in the U.S. and Canada as observed by Gotsch et al. in 1958 (184) although interest in the U.S. has been increasing since 1950 because of expansion of aluminum production facilities. Even so, the authors found that the higher costs of aluminum would be justified only when inside sulfide discoloration or rusting during shipment or storage were problems. More recently, as reported by Farin and Reibsam in 1969 (185), aluminum shipments for container and packaging applications have grown at an average rate of 25.7% annually since 1962. Aluminum beverage cans and ends (particularly the easy-open lids) have been the single most important factor of this growth, although flexible packaging, semirigid food containers, consumer foil, and particularly convenience packaging, have contributed considerably. It was then estimated that in 1970 about 90% of all beer cans would have easy-open aluminum ends. As can be readi-

ly seen at present, many other canned products (fruit juices, various drinks, fats, nuts, etc.) have the same type of ends.

In regard to alcoholic beverages, the compatibility of aluminum with beer was recognized early in the history of this metal, and has been used extensively in the brewing processes. It was interesting to note, according to Hall (186), that the use of aluminum ends on tinsplate can bodies reduces the content of Fe and Sn which, if present in beer in quantities of even fractions of 1  $\mu\text{g/ml}$ , can affect adversely the quality, flavor, astringency, foaming, and storage life, while Al has considerably less effect on these qualities. On the other hand, Ullmann (187) found that beer stored in aluminum cans for up to 1 yr at times contained 10–20  $\mu\text{g Al/ml}$ , which did not alter the taste but caused turbidity. He recommends lacquering of the interior. In wineries, aluminum still finds only limited use. If present in wine in concentrations greater than 10  $\mu\text{g/ml}$ , Al causes turbidity (also caused by Fe at 11  $\mu\text{g/ml}$ ), and at high concentrations, flavor and odor are affected (188–190). Eschnauer (191), who studied this subject carefully, found that aluminum is actually the least aggressive of a number of metals and alloys (Al, Zn, Fe, Ni, Sn, Pb, Cu, steel, brass, Monel); even so, it is not suitable for equipment where prolonged contact is required without special treatment of the surface. He considers the use of rolled anodized superpure Al 99.99R (Raffinal) alloy [also recommended by Evenshtein for both beer and wine (192, 193)] ideal for the brief storage and transport of wine, must, and grapes. Koch (189) found that an Al–Mn alloy was more resistant to corrosion than pure aluminum (99.6%). However, he does not advise use of it for storing fruit juices, because of the resulting high Mn content. Although Al content up to 40  $\mu\text{g/ml}$  was not detectable to taste and is not considered harmful, he advises coating all aluminum tanks. However, Shmeleva et al. (194) found that even coatings do not prevent contamination of wines and brandies.

That aluminum is used extensively by the pharmaceutical and cosmetic industries is obvious by the many chemicals listed by The Aluminum Association (183) and Juniere and Sigwalt (178) in respect to their compatibility with aluminum. To mention a few more recent

reports, experience in Switzerland (195) showed that aluminum tubes coated on the inside with a synthetic lacquer used for various hydrophilic ointments remained intact after 1½ yr storage at room temperature, while tin tubes were corroded. Similar results were observed in Poland in respect to anhydrous and hydrated ointment bases containing palm oil (196). In Czechoslovakia, aluminum foil was considered to offer many advantages from the point of view of stability, compared with other materials in the packaging of pharmaceutical preparations (197).

Concerning aluminum aerosol cans for drugs and cosmetics, sherwood (198) evaluated the favorable characteristics and limitations, the former being their good appearance, light weight, and freedom from external rusting, and the latter, strength, corrosion (external and internal), and economics. The relative cost of aluminum versus tinsplate has been the major limitation in the U.S. and Canada, since the other factors can be readily overcome. In Italy, aluminum has been used in 100% of aerosol dispensers since 1957, in 70% in Switzerland, and nearly 30% in Germany. The corrosion of hairspray cans was attributed mainly to the presence of colophony in the mixture (199). Actually, it appears that a large proportion of metal containers, including those for food products, be they tinsplate or aluminum, are treated on the inside in some manner. As discussed by Schniepp, organic chemicals (mainly thermosetting, thermoplastic and elastomeric resins) are used for enamel coatings, adhesives and sealants. All of these materials are subject to compliance with the U.S. FDA Food Additives Amendment of 1958 and subsequent amendments (200).

### Home Food Preparation and Storage

Never before has there been such an array of cookware available to the homemaker as there is today, particularly of that made of metals. These encompass not only top-of-range and ovenware, but also other kitchenware, both electric and nonelectric, as well as specialty wares such as fondue pots. These come now in a variety of exterior finishes in the modern bold colors to harmonize or contrast with the homemaker's color scheme.

In answer to the many questions raised by homemakers as to the qualities, properties, and uses of the various types of cooking utensils, the Metal Cookware Manufacturers Association has recently prepared a booklet (201) to provide the consumer with the most accurate information possible, based on a careful evaluation of all questions. Here it is pointed out that the chief requisite of a cooking utensil is its ability to transfer heat quickly and evenly from the source to the food. This is best met by metals. The evaluations of the properties of the metals, present finishes and recommendations for use and care, begin with aluminum, followed by stainless steel, cast iron, copper, tin, and chromium-plated steel. In regard to aluminum, its excellent conductivity of heat is given as the reason for its popularity. Stamped or drawn aluminum utensils come in different gauges or thicknesses which determine their quality and durability; the thickest utensils (0.125 in.) are cast aluminum. There is a wide variety of finishes: polished natural aluminum, colored porcelain enamel or organic (acrylic, polyimide, etc.) coatings on the exterior and "sunray" and high polish finishes or nonstick coatings on the interior; the newest utensils have a hidden porcelain coat under the nonstick finish. The high heat conductivity of aluminum is utilized also in the manufacture of stainless steel cookware where it is combined to form the two- or three-ply and bottom-clad utensils, with aluminum (or copper and carbon steel, also so used) on the inside or outside, or as the core with stainless steel on both inside and outside.

The classic early investigations which substantiated the suitability and safety of aluminum for the processing and storage of food and water in respect to migration of the metal into the product (202-212) were carried out, so far as could be determined, with plain, uncoated aluminum, the quality of which may be questioned. With all of the above more recent developments, any migration of the base metal to the food should be obviously reduced to a minimum. In order to confirm the clearly apparent popularity of utensils with the nonstick coatings, information was sought from the DuPont Company, manufacturer of the nonstick fluorocarbon under the trade name Teflon, as to the consumer demand for this type of utensil.

The data (for the year ended March 3, 1972) resulting from the complete marketing research program of the company yielded the following: half of the most frequently purchased frypans and skillets were coated with Teflon; 73% of all aluminum frypans and skillets were so coated; of the total frypans and skillets purchased, 61% were aluminum, 16% stainless steel, and the remainder, cast iron, porcelain enamel, tin and glass; aluminum represented 64% of all metal cookware (this would include electrics and types other than frypans and skillets), 49% of which were nonstick-coated (J.D. Lee, personal communication, Aug. 1972).

That ill-founded notions, rumors, and reported statements against aluminum cookware still persist is reflected by the reprinting in the booklet by the Metal Cookware Manufacturers Association of the *FDA Fact Sheet* issued July 1971 (177), the substance of which appeared in the periodical literature in 1972 (213). This *Fact Sheet* was prepared in response to many inquiries sent to the Food and Drug Administration in respect to the merits and safety of different types of cooking utensils. The FDA first states that it "does not favor any particular type of cooking utensil, nor does it know of any commonly used material such as aluminum, copper, glass, steel or tin which is unsuitable for the types of food utensils in which they are generally used." The greater part of the statement is devoted first to assurance of consumers concerning the safety of nonstick coatings. In this case, the release of F from the coating was the concern. Analyses for F content in hamburgers cooked in newly coated and used coated pans, in a heat-aged pan, and in a plain aluminum pan showed substantially the same amount of F in hamburgers cooked in the newly coated and plain aluminum pans, and a slight increase of F (but still well within safe limits) in those cooked in the heat-aged and old pans. Concerning the release of Al into food, the *FDA Fact Sheet* closes with the following statement: "Many scientific studies have determined that the amount of aluminum ingested as a result of preparing foods in aluminum cookware — even when soda is used in the cooking — is so small as to be of no significance in comparison with the amount of aluminum consumed from other sources."

Remarkably, there have been apparently no rumors against the use of aluminum foil for the preparation or storage of food, particularly meats, cheeses, breads, cakes. The unavailability of another economic metallic foil may be the reason. As it is, there is probably no home in which this foil is not so used nor in which it is not found in the freezers holding, in addition to leftovers, purchased convenience meals and other products packaged by food manufacturers in disposable semirigid aluminum containers. It may be well to repeat here that in an appraisal of the safety of food packaging materials in 1955 by the U.S. Food and Drug Administration, aluminum foils, along with other aluminum containers, were said to be ideal (214).

### **Effects of Aluminum on the Nutritional and Other Qualities of Food**

**Nutrient Loss:** Any changes that may occur in the nutrient content of food processed or preserved in aluminum utensils or containers were the subject of thorough investigations subsequent to the unfounded allegations against aluminum cookware arising from the controversy over the use of "alum" containing baking powders — both based on commercial motives. This aspect was reviewed in depth in 1957 (1), with the conclusion that the processing and packaging of foods in aluminum does not contribute to the destruction of nutrients over and above that caused by the handling of the food in the home or in the food industry. Indeed, aluminum has been found suitable for the synthesis and storage of ascorbic acid, the most labile of the vitamins, to which it is very resistant (178, 183). Other vitamins and yeast are also processed and handled in aluminum for the same reason.

Probably the most complete treatise on the subject of nutrient loss in recent years is the book edited by Harris and Von Loesecke, *Nutritional Evaluation of Food Processing*, published in 1960 and reprinted in 1971 (215). It is pointed out that even before processing, nutrient loss occurs by trimming, peeling, chopping, mincing, etc., as well as in storage. The effect on the ascorbic acid content has been studied most frequently because it is the most labile nutrient and is easily measured. Fewer

studies concerned thiamine, riboflavin, niacin and carotene, and very few the other vitamins, amino acids and minerals. In addition to the nutrient losses incurred in commercial food processing, the book contains chapters on large scale preparation (restaurants, cafeterias) and on home cooking (216, 217). The losses may vary from zero to 98%, depending upon the vitamin; for ascorbic acid, the range is 10–80%. The variations in results on the same products, as reported by different authors, are attributed primarily to differences in conditions, such as amounts of water added, duration and temperature of cooking, holding cooked foods before serving, and refrigerator storage. It was also observed that no significant differences were noted when foods were cooked in enamel, aluminum, glass, or stainless steel pans; however, copper, brass, and Monel could be rather destructive. Similar conclusions were reached in respect to home preparation, both as to nutrient loss and conditions of cooking and type of utensils used. Since particularly thiamine and ascorbic acid are sensitive to alkali, addition of sodium bicarbonate and other alkaline salts to preserve the color of green vegetables and speed the cooking rate is not recommended. (In this connection, it may be mentioned that according to earlier experiments, cooking foods to which baking soda had been added in aluminum pans increased the Al content of the food by only small amounts.)

The more recent periodical literature has yielded relatively little on the subject. In large-scale applications, aluminum milk cans (alloy containing 1% Si, 0.7% Mg) have been in use in Switzerland since the early thirties and in England this use (of a corresponding alloy) was begun in the mid-fifties with excellent success. This alloy was found to be unaffected by milk at all temperatures, imparted no off-flavors as was found with traces of Fe, and had little effect on the vitamin content (218, 219). As reviewed by Bailey (218), in a series of tests with foods cooked in glass, aluminum, and enamel, aluminum was found to be superior to the other materials as regards destruction of vitamin C. This was attributed in part to the good thermal conductivity of this metal, which protected the vitamin from further destruction. In some studies, aluminum ranked second to enamel, ironware,

or stainless steel in the preservation of nutrients in vegetables or khoa (a concentrated, unfermented milk used in India) (220-222). Aluminum foil, either alone or with plastic laminates as packaging material, was found to be the most suitable for the preservation of vitamin C and food dyes in powdered fruit juices and other products (223, 224), and vitamin C and anthocyanins in boysenberry puree (225). Loss of riboflavin in partially baked rolls packaged in heat-sealing aluminum foil-wax paper-wax upon storage was 2-3% compared to 60 and 35% in rolls wrapped in unprinted cellophane and partially printed waxed paper, respectively (226). In the Soviet Union, Evenshtein has compared the effects on ascorbic acid of a superpure aluminum alloy (99.99%), of a 99.5% alloy (0.02% Cu, 0.3% Fe, 0.15% Si) and another, "AMg M-5V" (5-6% Mg, 0.65% Mn, 0.25% Fe, 0.3% Si), with those of glass or enameled ironware, both as plates immersed in distilled water solutions of ascorbic acid boiled for various periods and as casseroles of meat-vegetable combinations kept for 2 hr at 60-80°C after cooking. Vitamin C loss was about twice as great from the alloys of lesser purity as from the 99.99% alloy, that from the latter closely approximating the loss from processing in glass or enamelware (227, 228). He also found that vegetable pigments (carotene and anthocyanins) in red beets, carrots and cranberries were destroyed almost completely by boiling for 30 min in 99.5% aluminum pots, while decoloration by 99.99% Al was no greater than by glass (229). For these reasons, he advocates that superpure aluminum cookware be used or that aluminum alloy cookware be coated on the inside with high-purity aluminum, attributing the effects mainly to impurities (Mg, Fe) in the lower grade alloys. In the light of the evaluation by Harris and Von Loesecke and their collaborators (215-217) of studies of nutrient losses performed before the late fifties, with no mention of the grade of aluminum or other utensils, Evenshtein's results and views may be questioned—in any event, they are not convincing. In the U.S., aluminum ware is made of the 1100 or the 3003 alloys, the first of which is the commercially pure (minimum of 99% Al); the Al content of 3003 is not given; only the limits of other chemicals are specified in the Standards of

The Aluminum Association (182). A study worthy of mention in this connection was carried out in Leipzig upon the request of a sports club (230) to look into losses in vitamins A and C and carotene of an oatmeal and oat-flake dish prepared with egg yolk and a dextran preparation, lightly salted, and of a strong tea with lemon and honey, with or without added vitamin C, if kept in aluminum containers for 8 hr or through a day-long bicycle ride. The grade of aluminum is not stated, but a fair proportion of iron can be assumed from the mention that both Fe and Al were qualitatively determined; these were considered to be without significance physiologically and contributed no metallic taste. The tea was kept in both new and used containers without change in flavor or aroma. The vitamin A content, including carotene, of the oatmeal dish did not diminish through the 8 hr in the three tests performed. The vitamin C content of the tea with added vitamin suffered an 11% loss and that of the tea without added vitamin, a 24% loss. The author considers these losses to be within the expected limits upon prolonged storage, and for this reason he advises the addition of 100 mg synthetic vitamin C per 0.7-liter flask in order to compensate for the loss.

There is no need to add to what has been presented earlier and above concerning the use by the food industry of aluminum foil in various gauges of thickness both for sanitary reasons and to protect the food from spoilage, and for preservation of nutrients and flavor. The wide use of it, either alone or as laminates with various plastics and papers, is evident in food markets.

**Sanitary Aspects:** The finding that aluminum is an excellent packaging material for the preservation of food products led Caserio (231) to investigate whether it had a bacteriostatic effect. He chose fresh beef, two lots of which were wrapped in Al foil of 0.01 mm thickness and two in polyethylene sheets 0.025 mm thick after the load of superficial microbes was determined. After 24 and 48 hr storage at 20-22°C, meat wrapped in aluminum had a substantially lower microbial load than the control on the surface and in the layers immediately below it. He believes that this is attributable to contact with aluminum and not to a limitation of oxygen, since the control samples were



enveloped in a plastic of sufficient impermeability. The hypothesis that a portion of the superficial germs might have adhered to aluminum and thus been carried away, was dismissed by counts made for this purpose. The increase in Al contents in the aluminum-protected meat, 6.28 and 5.89  $\mu\text{g/g}$  versus in the control lots, 2.29 and 4.40  $\mu\text{g/g}$ , was considered unimportant. The author suggested that the control of bacterial growth was due to the formation of an Al-protein complex having a bacteriocidal effect so as to preserve for a certain time period the organolytic and bacteriologic quality of the meat. This aspect was also tested by Evenshtein by exposing either pure aluminum or alloy plates, and plates of other metals (copper coins, gold), aluminum (99.5%) and stainless steel spoons, to various bacteria (dysentery, *Escherichia coli*,  $\beta$ -hemolytic streptococci) with the result that aluminum, especially the 99.99% grade, possessed greater bacteriostatic action than the other metals (232-235). From experiments in which exposure was to bacteria in water (233,234) the author concludes that containers of 99.99% Al may be used for the partial disinfection of fresh water and its preservation during transportation. He, with others (236,237) also proposed adding aluminum hydroxylchloride at 6.9  $\mu\text{g}$  Al/ml for the simultaneous clarification and disinfection of naturally infected river and pond waters for use during expeditions. Regular consumption of water containing this concentration was considered to be safe. It was also suggested that the use of Al sulfate as coagulant in water supply treatment acts as a disinfectant as well (238).

As favorable to aluminum as this may appear, further investigation in this area is needed for confirmation. In the preparation of the earlier review, only four references on the sanitary aspects could be located (239-242) one of which was also by Caserio (239), and one was unfavorable to aluminum (241). The recent reports issue from only two laboratories, one in Italy, the other in the Soviet Union.

#### **Use of Aluminum for Water Storage and of Aluminum Compounds in the Treatment of Drinking Water Supplies**

The use of metallic aluminum for the storage

of water was the subject of probably the first inquiry in 1891 into the safety of aluminum in water and food processed or stored in aluminum (210). Not much more can be added to the earlier review except that aluminum has a very good resistance to most waters and even to some considered very aggressive, such as those of high sulfur content (178). Some industries, such as the electric utilities, require a high-purity water (low hardness, silica, dissolved gases). Tests with welded aluminum tanks (3003 alloy), after conditioning with pure water containing 1  $\mu\text{g/ml}$  ammonia, proved to be most satisfactory, while in earlier experience steel tanks had been found unsatisfactory for the storage of high-purity water (243). In a 2200-hr test an all-aluminum (3003 and 6061 Al alloys) light-weight, transportable seawater still required by the military was shown to be satisfactory after eliminating all copper alloys from contact with feed water. The Al content of the seawater was 0.05  $\mu\text{g/ml}$  and of the distilled water, 0.06  $\mu\text{g/ml}$  (244).

Al compounds and certain Al-bearing minerals represent the major coagulants commonly used in the treatment of drinking water supplies. As reviewed by the American Water Works Association (245), the common coagulants are based on aluminum (Al sulfate, ammonia, and potash Al, Na aluminate or bauxite), and on iron (ferric and ferrous sulfates, chlorinated copperas, ferric chloride). Al sulfate is by far the principal coagulant. Bentonite (a clay) is used as a coagulating aid, and Al ammonium sulfate, as dechlorinating agent. Na aluminate is used sometimes for removal of fine turbidity and/or color bodies in soft, low-pH waters. As was earlier reported, in modern purification practice, use of Al compounds as coagulants results generally in the presence of less rather than more Al in the drinking water than in raw water. This is also shown in Barnett's figures (246) listed in Table 4, although in some treatment plants, a higher Al content was found in the finished water than in the raw supply.

In the Soviet Union, the use of a basic Al chloride ( $\text{Al}_2(\text{OH})_5\text{Cl}$ ) coagulant was proposed as being competitive with Al sulfate in respect to quality; the addition of corrosion inhibitor, catanin, at 0.1 g/l, considered to be nontoxic, was suggested (247).

Table 4. Concentrations of aluminum in drinking water supplies.<sup>a</sup>

	Al, μg/ml	Reference		Al, μg/ml	Reference
Bulgaria			United States (cont.)		
Endemic kidney-disorder regions	0.057	(800)	Georgia		
Control regions	0.053	(800)	Americus	0.007	(469)
Italy			Douglas	0.016	(469)
Pesaro-Urbino Province			New Hampshire		
High cancer region	<0.001 <sup>b</sup>	(801)	Franklin	0.013	(469)
Low cancer region	<0.001 <sup>b</sup>	(801)	Littleton	0.032	(469)
Union of Soviet Socialist Republics			Milford	0.004	(469)
Bryansk, endemic urolithiasis region	trace-0.023	(388)	New York		
United States			Avon	0.023	(469)
380 finished waters before and after passage through softener	0.003-1.600	(802)	Caledonia	0.014	(469)
Alabama, Eufaula	<0.03	(802)	Canastota	0.024	(469)
Colorado, Denver area	0.028	(469)	Geneva	0.016	(469)
Domestic taps	0.074-0.340	(246)	Lima	0.004	(469)
At treatment plants, raw	0.010-0.520	(246)	North Carolina		
At treatment plants, finished	0.006-0.260	(246)	Asheboro	0.047	(469)
Florida			South Carolina		
Bradenton	0.760	(469)	Dillon	0.050	(469)
Kissimmee	0.009	(469)	Lake City	0.008	(469)
			Manning	0.011	(469)
			Vermont		
			Montpelier	0.010	(469)
			St. Johnsbury	0.150	(469)
			Wisconsin		
			Madison	0.200	(257)

<sup>a</sup> Emission spectroscopy unless otherwise indicated.

<sup>b</sup> Method not stated.

### Use of Aluminum Compounds in the Manufacture of Foods and Drugs

Compounds of Al and Al-bearing minerals, such as bentonite particularly, are used extensively in the production of pesticides, of wine, cider, and beer as clarifiers, of animal feed, and as desiccants for the preservation of food (248).

Aside from these rather massive uses, numerous compounds are used in the manufacture of foods *per se* as additives or as substrata in foods and drugs or other purpose in food additives. Numerous patents and articles describe such use. There seems to be no need to cite these individually. Aside from the broad uses in products reaching man directly, enumerated in the introduction, the following, listed under the FDA tolerances for compounds in the *Handbook of Food Additives* (249) may be given as examples: alumina, as substratum for manufacture of FD&C color lakes (tolerance, less than

50%); Al ammonium sulfate, Al sulfate, Al Na sulfate, as miscellaneous and/or general purpose food additives; Al Ca silicate, in vanilla powder and in vanilla-vanillin powder, and precipitated hydrated Na silicoaluminate in salt and seasoning up to 2%, in sugar up to 1%, in baking powder up to 5%; Al nicotinate, as source of niacin in foods for special dietary use; Al oxide, as dispersing agent in mixtures for food or drug use containing Ti dioxide (up to 2%); Al stearate, as a component of defoaming agents in processing beet sugar and yeast (amount not to exceed that reasonably required to inhibit foaming); Na Al sulfate and K alum for optional use as a bleaching agent in flour at not more than 6 parts by weight, alone or in combination with K alum, or Na Al sulfate, respectively, Ca sulfate, etc. The *Food Chemicals Codex*, first published in 1966 by the Food Protection Committee of the National Research Council, spells out the specifications and limits of impurities,

and test procedures of food additives, including all of the above Al compounds (250).

The history of the controversy over the Al-containing baking powder was described in the earlier review. This use has long been sanctioned by the Food and Drug Administration, and the present opinion of this agency is expressed in the *Fact Sheet* concerning aluminum cookware (177): "Aluminum compounds have a number of uses as direct food ingredients, as for example in alum baking powders and in the use of alum in pickles to keep them firm. These uses are generally recognized as safe by scientists qualified to evaluate the safety of food additives."

### Aluminum in Human Food

Because of the abundance of Al, its presence in all foods, although in small amounts, may be taken for granted. Until 1971, Al has been listed among the nonessential elements (251), although in 1915 Trillat (252) and in 1928 Smith (253) stated it to be a normal ingredient of food and present in living matter as an essential constituent. Most recently it is being considered seriously for inclusion among the growing number of essential elements (254). This is further discussed in relation to man and animals in the next section. It is no doubt because of the recent growing interest in "micronutrients" that Al has been included in a comparatively larger number of chemical analyses of foods. On the other hand, there are but few reports that contribute to the question of the magnitudes of Al that may be found in foods as a result of processing or storing in aluminum. This can only be explained on the basis that there was no longer need for such information because of the classic investigations conducted principally from around 1890 through the first third of this century, followed by a few additional data reported until the mid-fifties. Summarizing the results of these earlier investigations, it was found that except for a few isolated instances, the concentrations of Al in foods after being cooked in aluminum fall well within the ranges of concentrations found in raw products. Moreover, those that go beyond this range fall short of physiologic significance (1).

The concentrations of Al reported for various

food products in the more recent literature are shown in Table 5. To permit direct comparisons with the earlier tabulations, the reported concentrations have been converted to  $\mu\text{g/g}$  or ml (or ppm). In some cases, it was difficult to calculate results (essentially of the foreign literature) which, more often than not, were given as "percent of ash," and for this reason have been excluded.

Among the reports on the content of trace elements in food products, the "total diet" studies, and two partial diet studies, are of special interest. Two of the former were made on exact duplicates of foods (including beverages and water), as consumed, to determine the daily intake of nutrients and minerals. Tipton (255) analyzed the content of 17 trace elements in the diets of a man and his wife for 30 days. The Al ingested daily by the wife amounted to 18 mg and by the husband, 22 mg. White (256) carried out her studies on duplicate samples collected by 21 college women, seven of whom ate most of their meals at home; the others ate in university dormitories. The author collected three diet composites, and 15 high school girls provided duplicates of their daily meals, most of them at home, except lunches which the majority had at school. Fourteen elements were analyzed simultaneously by using emission spectroscopy. The range of Al intake by the college women was less than 1.56–2.82 mg and that by the high school girls, less than 1.53–33.3 mg. The author noted that for the group of inorganic elements that included Al, the amounts were so small in most instances that absolute values were not obtainable. Two additional studies may be considered as belonging to the "duplicates" category. Gormican (257) analyzed, in addition to 128 food items, 16 representative hospital menus for 14 inorganic elements. The Al values for the individual items are included in Table 5. In the menus, Al content ranged from less than 1.795–9.006 mg/day in all but one, the Giovannetti diet, which contained 634.5 mg Al and a high Fe value (25.9 mg). These highs could not be explained by the author, since individual items included in the menu were not analyzed. Murphy (258) determined, in addition to the nutrients, nine trace elements contained in the type A school lunches served in five geographic regions (N.E., S.E., M.W., S.W., W.) under the

**Table 5. Concentrations of aluminum in foods and beverages.<sup>a,b</sup>**

	Al, μg/g or ml	Reference		Al, μg/g or ml	Reference
Plant Products					
Cereals and cereal products			Vegetables (cont.)		
Barley			Cooked in stainless steel	26.20 <sup>d,e</sup>	(488)
(Eur.)	5.00–6.70 <sup>c</sup>	(769)	Beans, green	8.00 <sup>e</sup>	(266)
(Ger.)	60.00 <sup>d,e</sup>	(769)	(Eur.)	< 0.10	(264)
Bran, flakes, 40% <sup>c</sup>	<2.00	(257)	Frozen	6.60 <sup>c</sup>	(769)
Rye/wheat (Ger.)	156.00 <sup>d,e</sup>	(769)	Beans, lima, baby, frozen	<1.00	(257)
Wheat (Eur.)	10.00–13.00 <sup>c</sup>	(769)	Beans, wax, canned, salt-free, drained	2.80	(257)
Bread, rye	<2.00	(257)	Beets (Eur.)	0.36 <sup>c</sup>	(769)
White, enriched	3.00	(257)	(USSR)	0.13	(772)
Whole wheat	5.40	(257)	Before cooking (USSR)	3.30 <sup>d</sup>	(229)
Cheerios	4.70	(257)	After cooking in 99.5% Al	9.56 <sup>d,f</sup>	(229)
Corn			After cooking in 99.99% Al	3.96 <sup>d,f</sup>	(229)
(Eur.)	0.4–0.5 <sup>c</sup>	(769)	After cooking in glass	2.84 <sup>d</sup>	(229)
(USSR)	16.00 <sup>c</sup>	(770)	Canned, salt-free, drained	<1.00	(257)
Canned, salt-free, drained	<1.00	(257)	Leaves	56.00 <sup>e</sup>	(266)
Flakes	<2.00	(257)	Root	250.00 <sup>e</sup>	(266)
Yellow, sweet	<0.50–3.10	(264)	Broccoli, frozen	<1.00	(257)
Crackers			Brussels sprouts, frozen	<1.00	(257)
Graham	<2.00	(257)	Cabbage	<0.10	(264)
Saltines	<2.00	(257)	(USSR)	<1.00	(257)
Cream of Wheat			Cooked (Czech.) 90 min in Al	30.50 <sup>d,e,f</sup>	(488)
Quick, enriched, uncooked	25.00	(257)	Cooked in stainless steel	1.50 <sup>d,e</sup>	(488)
Regular	8.00	(257)	Inner leaves (Eur.)	5.70 <sup>c</sup>	(769)
Macaroni, uncooked	<2.00	(257)	Outer leaves (Eur.)	20.00 <sup>c</sup>	(769)
Noodles, egg, uncooked	<2.00	(257)	Sauerkraut soup (Czech.) boiled 30 min in Al	7.10 <sup>d,e,f</sup>	(488)
Oatmeal			Sauerkraut soup, boiled in stainless steel	3.20 <sup>d,e</sup>	(488)
Rolled (quick), uncooked	<2.00	(257)	Carrots	0.40–1.50	(264)
(Eur.)	5.00 <sup>c</sup>	(769)	(Eur.)	<1.00	(257)
Oats (Eur.)	5.10 <sup>c</sup>	(769)	(USSR)	3.80 <sup>c</sup>	(769)
Oats (Ger.)	68.00 <sup>d,e</sup>	(769)	Before cooking (USSR)	0.03	(772)
Porridges with milk (USSR)	0.02–0.06	(262)	After cooking (USSR)	2.45 <sup>d</sup>	(229)
Rice, cooked (USSR)	0.03–0.36	(262)	After cooking in 99.5% Al	10.90 <sup>d,f</sup>	(229)
Krispies	<2.00	(257)	After cooking in 99.99% Al	3.07 <sup>d,f</sup>	(229)
Puffed	<2.00	(257)	After cooking in glass	2.18 <sup>d</sup>	(229)
White, uncooked	<2.00	(257)	Cooked (Czech.) 30 min in Al	420.70 <sup>d,e,f</sup>	(488)
Rye (Eur.)	4.80 <sup>c</sup>	(769)	Cooked in stainless steel	273.90 <sup>d,e</sup>	(488)
Spaghetti, uncooked	<2.00	(257)	Cauliflower		
Wheat			Stems	21.00 <sup>e</sup>	(266)
(Eur.)	4.00–16.00 <sup>c</sup>	(769)	Head	4.00 <sup>e</sup>	(266)
(Ger.)	17.00 <sup>d,e</sup>	(769)	Frozen	<1.00	(257)
(USSR)	42.00 <sup>c</sup>	(770)	Celery	<1.00	(257)
(USSR)	9.56–73.60 <sup>e</sup>	(771)	Leaves	70.00 <sup>e</sup>	(266)
Flour (Eur.)	0.90–10.00 <sup>c</sup>	(769)	Stems	31.00	(266)
Flour, bleached, enriched	<2.00	(257)	Celery, Pascal	<0.10	(264)
Germ (Eur.)	15.00 <sup>c</sup>	(769)	Corn, see Cereals		
Shredded	<2.00	(257)			
Wheaties	<2.00	(257)			
Vegetables					
Asparagus	1.70–9.00	(264)			
Frozen	<1.00	(257)			
Beans (Czech.)					
Cooked 155 min in Al	34.70 <sup>d,e,f</sup>	(488)			

**Table 5. Concentrations of aluminum in foods and beverages<sup>a,b</sup> (cont.)**

	Al, μg/g or ml	Reference		Al, μg/g or ml	Reference
Plant Products (cont.)					
<b>Vegetables (cont.)</b>			<b>Vegetables (cont.)</b>		
Corchorus			<i>Solanum nodiflorum</i>		
Edible species (Nigeria)	343.00 <sup>d,e</sup>	(71)	(Nigeria)	854.00 <sup>e</sup>	(269)
Partly edible species			Sorrel (USSR)	5.10–32.00	(774)
(Nigeria)	765.00 <sup>d,e</sup>	(71)	Spinach (Eur.)	6.90 <sup>c</sup>	(769)
Cucumber	<1.00	(257)	Frozen, uncooked	22.00	(257)
(USSR)	4.00 <sup>e</sup>	(266)	Squash, frozen, cooked	3.40	(257)
Eggplant (USSR)	0.02	(772)	Sweet potatoes, canned	<1.00	(257)
Garlic, see Herbs	0.01	(772)	Tomatoes	0.20–1.10	(264)
Kale, Bowen standard	45.00 <sup>e,h</sup>	(47)		<1.00	(257)
Leek (Eur.)	15.00 <sup>c</sup>	(769)		38.00 <sup>e</sup>	(266)
Lentils (Eur.)	1.50 <sup>c</sup>	(769)	(USSR)	5.50	(775)
Lettuce	<1.00	(257)	(USSR)	<0.20	(772)
(Eur.)	5.50 <sup>c</sup>	(769)	Juice, canned (USSR)	3.72–4.98	(776)
(Peru)	0.61 <sup>d</sup>	(773)	Juice, salt-free	<0.40	(257)
Cooked 15 min in Al			Sauce (Czech.) cooked		
(Czech.)	36.60 <sup>d,e,f</sup>	(488)	15 min in Al	38.70 <sup>d,e,f</sup>	(488)
Cooked in stainless steel	24.50 <sup>d,e</sup>	(488)	Sauce, cooked in stain-		
Iceberg	0.10–0.70	(264)	less steel	31.70 <sup>d,e</sup>	(488)
Mushrooms (Nigeria)	1300.00 <sup>d,e</sup>	(72)	Turnips (USSR)	0.02	(772)
Stems and pieces, canned	4.00	(257)	Vegetable mixtures, canned		
Onions	<5.00–10.00	(263)	(USSR)	0.56–5.90	(777)
(Eur.)	43.00 <sup>c</sup>	(769)	Vegetable soup, strained		
(USSR)	0.32–0.76	(774)	(USSR), probable con-		
(USSR)	0.01	(772)	tact with Al	3.17 <sup>f</sup>	(262)
Dry yellow	0.10	(264)	<i>Vernonia amygdalina</i>		
Fresh, mature	<1.00	(257)	(Nigeria)	932.00 <sup>e</sup>	(269)
Green (USSR)	0.03	(772)	<b>Fruits and berries</b>		
Parsley, see Herbs and			Apples	0.20–0.87	(265)
spices				<0.50	(257)
Peas (USSR)	36.00 <sup>c</sup>	(770)	(USSR)	2.22	(775)
Canned, salt-free, drained	<1.00	(257)	Core	1.10 <sup>c</sup>	(778)
Pepper, hot	3.00 <sup>e</sup>	(266)	Dried, cored	<1.20 <sup>e</sup>	(267)
Sweet	4.00 <sup>e</sup>	(266)	Flesh	1.50 <sup>c</sup>	(778)
(USSR)	0.03	(772)	Juice, canned	0.80	(257)
Potatoes (Eur.)	20.00 <sup>c</sup>	(769)	Juice (USSR)	2.22–24.00	(776)
(Ger.)	15.00 <sup>d,e</sup>	(769)	Peel	13.90 <sup>c</sup>	(778)
(Peru)	9.10 <sup>d</sup>	(773)	Peel (Eur.)	5.7 <sup>c</sup>	(769)
(USSR)	0.02	(772)	Peeled	<0.20–0.20	(265)
(USSR)	1.25–2.54	(774)	Peeled (Eur.)	1.10 <sup>c</sup>	(769)
Fresh	<1.00	(257)	Sauce, canned, drained	<0.50	(257)
Cooked, mashed, prob-			Apricots	2.21	(265)
ably in Al (USSR)	6.42 <sup>f</sup>	(262)	(USSR)	8.32	(775)
Instant	<2.00	(257)	Canned, drained	<0.50	(257)
Peel (Eur.)	308.00 <sup>c</sup>	(769)	Dried, halves	12.50 <sup>e</sup>	(267)
Pumpkin, canned	2.60	(257)	Juice, canned (USSR)	6.39	(775)
Radish, root	180.00 <sup>e</sup>	(266)	Avocados	<0.20	(265)
Rhubarb			Bananas	<0.40	(265)
Field-grown	4.82	(265)		<0.50	(257)
Hothouse-grown	0.82	(265)	Blackberries (dewberries)	3.92	(265)
<i>Solanum melongena</i>			"Blackberry" mountain		
(Nigeria)	35.00 <sup>e</sup>	(269)	ash (USSR)	15.50–20.80	(774)

**Table 5. Concentrations of aluminum in foods and beverages<sup>a,b</sup> (cont.)**

	Al, μg/g or ml	Reference		Al, μg/g or ml	Reference
Plant Products (cont.)					
Fruits and Berries (cont.)			Fruits and Berries (cont.)		
Blueberries	2.40–2.68	(265)	Nectarines	0.95–1.36	(265)
Water-pack, drained	2.60	(257)	Oranges		
Cantaloupes	<0.10–0.14	(265)	Sections, with membrane	<0.10	(265)
	<0.50	(257)	Sections, without membrane	<0.40	(257)
Cherries			Juice, frozen, reconstituted	<0.40	(257)
(Eur.)	35.00 <sup>c</sup>	(769)	Papayas	<0.30	(265)
(USSR)	6.37	(775)	Peaches		
Bing, pitted	<0.30	(265)	Cling, canned, drained	<0.50	(257)
Juice, with pulp, canned			Peeled	<0.20	(265)
(USSR)	3.37–10.10	(776)	Pears		
Royal Anne, canned, drained	<0.50	(257)	Canned, drained	<0.50	(257)
Sour, pitted	<0.30	(265)	Peeled	<0.15	(265)
Cranberries	<0.40	(265)	With peel	<0.30	(265)
(USSR)	3.60–18.00	(774)	Persimmons (USSR)	0.72–1.10	(774)
Before cooking (USSR)	2.01 <sup>d</sup>	(229)	Pineapples	<0.30	(265)
After cooking 30 min in 99.50 Al	7.55 <sup>d,f</sup>	(229)	Crushed, canned, drained	<0.50	(257)
After cooking in 99.99% Al	3.00 <sup>d,f</sup>	(229)	Juice, canned	<0.40	(257)
After cooking in glass	1.98 <sup>d</sup>	(229)	Plums		
Currants, black (USSR)	11.00–70.00	(774)	With peel	<0.30–0.49	(265)
Dates, dried, pitted	4.30 <sup>e</sup>	(267)	(USSR)	3.49	(775)
Dried fruit compote (USSR)			Juice with pulp, canned	3.49–14.20	(776)
With sugar, before cooking	3.80	(228)	Prunes		
After cooking 30 min in 99.50% Al	27.90 <sup>f</sup>	(228)	Cooked	6.20 <sup>i</sup>	(257)
After 2 hr on low heat	36.00 <sup>f</sup>	(228)	Dried, pitted	5.10 <sup>e</sup>	(267)
Figs			Juice, canned	<0.40	(257)
Dried	11.20 <sup>e</sup>	(267)	Quince, various varieties		
Kadota	1.52	(265)	(USSR)	0.12–0.70	(268)
Fruit jelly (USSR), probable contact with Al	4.13 <sup>f</sup>	(262)	Raw material before processing	0.21–0.62	(268)
Fruit juices, commercial, in contact with Al (Ger.)	6.00–10.00 <sup>f</sup>	(189)	Juice, processed in glass	0.04–0.24	(268)
Grapefruit			Preserves	trace–0.07	(268)
Sections without membrane	<0.10	(265)	Stewed	trace–0.08	(268)
	<0.50	(257)	Raisins		
Canned, drained	<0.50	(257)	Seeded Muscat	41.30 <sup>e</sup>	(267)
Juice, canned	0.40	(257)	Seedless	17.90 <sup>e</sup>	(267)
Grapes	<0.50	(257)	Raspberries	3.91	(265)
Juice (Ger.)	0.01–0.52	(779)	Rhubarb see Vegetables		
Juice, canned	1.10	(257)	Strawberries	0.56–2.42	(265)
Seeded	<0.30	(265)	Tangelos, sections with membrane	<0.10	(265)
Seedless	0.63	(265)	Tangerines, sections with membrane	0.24	(265)
Honeydews	0.17	(265)	Watermelons	<0.20	(265)
Lemons, juiced	<0.10	(265)		<0.50	(257)
Limes, juiced	<0.10	(265)	Herbs and spices		
Mangoes, Haden	<0.30	(265)	Allspice	51.00–101.00	(263)
			Basil	167.00–450.00	(263)
			Bay	142.00–730.00	(263)

Table 5. Concentrations of aluminum in foods and beverages<sup>a,b</sup> (cont.)

			Plant Products (cont.)		
	Al, μg/g or ml	Reference		Al, μg/g or ml	Reference
<b>Herbs and Spices (cont.)</b>			<b>Herbs and Spices (cont.)</b>		
Cardamom	23.00-200.00	(263)	Tarragon leaves	175.00-412.00	(263)
Celery seed	200.00-730.00	(263)	Thyme	>500.00-<1000.00	(263)
Cinnamon	48.00-115.00	(263)	Turmeric	500.00-640.00	(263)
Clove	81.00-160.00	(263)	<b>Nuts</b>		
Coriander	27.00-36.00	(263)	Cedar, shelled, dry kernel (USSR)	2.99-6.98 <sup>d</sup>	(780)
Cumin	273.00-570.00	(263)	Peanut butter, smooth	<2.00	(257)
Dill, fresh (USSR)	60.00-70.00	(774)	Peanuts, blanched, salted	<2.00	(257)
Dill seed	48.00-142.00	(263)	Pecans, unsalted	<2.00	(257)
Dill weed	88.00-90.00	(263)	Walnuts, unsalted	<2.00	(257)
Dog rose (USSR)	2.46-6.00	(774)	<b>Oils</b>		
Fennel	45.00-81.00	(263)	Olive (Spain)	0.08-0.38	(781)
Garlic (USSR)	0.59-0.93	(774)	<b>Sugars</b>		
	<5.00-<10.00	(263)	<b>Raw</b>		
Ginger	73.00-200.00	(263)	Cuban	5.29 <sup>d</sup>	(782)
Mace	50.00-182.00	(263)	Formosan	1.48 <sup>d</sup>	(782)
Marjoram	>500.00-1000.00	(263)	Washed		
Mustard	<5.00-<10.00	(263)	Cuban	2.27 <sup>d</sup>	(782)
Nutmeg	<5.00-11.00	(263)	Formosan	0.85 <sup>d</sup>	(782)
Onion, see Vegetables			Brown liquor		
Oregano	>500.00-700.00	(263)	Cuban	0.63 <sup>d</sup>	(782)
Paprika	49.00-700.00	(263)	Formosan	0.85 <sup>d</sup>	(782)
Parsley	74.00-120.00	(263)	Fine liquor		
(Eur.)	45.0 <sup>c</sup>	(769)	Cuban	0.22 <sup>d</sup>	(782)
Pepper			Formosan	0.74 <sup>d</sup>	(782)
Black	48.00-237.00	(263)	Brown	<2.00	(257)
Red	44.00-67.00	(263)	Molasses (Ger.)	110.00 <sup>d,e</sup>	(769)
White	25.00-51.00	(263)	Powdered	<2.00	(257)
Poppy seed	22.00-50.00	(263)	White	<2.00	(257)
Rosemary	320.00-500.00	(263)	<b>Animal Products</b>		
Sage	307.00-500.00	(263)	<b>Dairy products</b>		
Savory	400.00-650.00	(263)	<b>Dairy products (cont.)</b>		
Sesame seed	5.00-<10.00	(263)	Dried skim, bulk (Japan)	52.21 <sup>g</sup>	(784)
			Dried whole, market (Japan)	64.38 <sup>g</sup>	(784)
			Market (Japan)	80.14 <sup>g</sup>	(784)
			Nonfat solids	17.00	(257)
			Raw (Japan)	72.82-81.29 <sup>g</sup>	(784)
			Skim, enriched	2.00	(257)
			Whole, enriched	2.00	(257)
			Sherbet, orange	1.40	(257)
			<b>Meats</b>		
			Beef, various cuts	<1.00	(257)
			Wrapped in Al, 24, 48 hr at 20°C (Italy)	6.28; 5.86 <sup>d,f</sup>	(231)
			Wrapped in plastic	2.29; 4.40 <sup>d</sup>	(231)

**Table 5. Concentrations of aluminum in foods and beverages<sup>a,b</sup> (cont.)**

	Al, μg/g or ml	Reference		Al, μg/g or ml	Reference
Animal Products (cont.)					
<b>Meats (cont.)</b>			<b>Meat—vegetable combina-</b>		
Steak (Eur.)	2.30–8.40 <sup>c</sup>	(769)	tions (cont.)		
Tenderloin	0.90–9.00	(785)	Boiled in stainless steel	2.70 <sup>d,e</sup>	(488)
Heart (Eur.)	0.50 <sup>c</sup>	(769)	Pork and beans, baked	<1.00	(257)
Kidney (Eur.)	0.40–1.00 <sup>c</sup>	(769)	Salt cod-potato soup		
Liver	<2.00	(257)	(USSR)		
(Eur.)	1.20 <sup>c</sup>	(769)	Before cooking	9.50 <sup>f</sup>	(228)
Powder (Canada)	0.28–0.43 <sup>h</sup>	(47)	After cooking 30 min in		
Cattle, Fulani (Nigeria)	73.00 <sup>d,e</sup>	(786)	99.50% Al	65.70 <sup>f</sup>	(228)
Heart	36.00 <sup>d,e</sup>	(786)	2 hr warming thereafter	85.40 <sup>f</sup>	(228)
Kidney	32.00 <sup>d,e</sup>	(786)	Sausage-potato stew		
Liver	77.00 <sup>d,e</sup>	(786)	(USSR) <sup>g</sup> , probable con-		
Tongue	87.00 <sup>d,e</sup>	(786)	tact with Al	4.12 <sup>f</sup>	(262)
Goat (Nigeria)	68.00 <sup>d,e</sup>	(787)			
Lamb	<1.00	(257)	<b>Poultry</b>		
Brain (Eur.)	1.00 <sup>c</sup>	(769)	Chicken, roaster	<1.00	(257)
Heart (Eur.)	0.50–1.40 <sup>c</sup>	(769)	Eggs		
Kidney (Eur.)	0.40–1.00 <sup>c</sup>	(769)	Whole	1.40	(257)
Liver (Eur.)	1.20–11.00 <sup>c</sup>	(769)	Whole (Eur.)	0.20 <sup>c</sup>	(769)
Luncheon, bologna	<1.00	(257)	White	<0.5	(257)
Pork	<1.00	(257)	White (Eur.)	1.00 <sup>c</sup>	(769)
(Nigeria)	58.00 <sup>d,e</sup>	(787)	Yolk	<1.00	(257)
Bacon	<2.00	(257)	Yolk (Eur.)	0.50 <sup>c</sup>	(769)
Ham	<1.00	(257)	Turkey, roaster	<1.00	(257)
Liver	<2.00	(257)			
Veal	<1.00	(257)	<b>Fish and shellfish</b>		
			<b>Carp</b>		
<b>Meat—vegetable combina-</b>			Autumn (USSR)	0.70	(788)
<b>tions</b>			Spring (USSR)	1.00	(788)
Beef, sauerkraut, vege-			Crab, canned, salted	<1.00	(257)
table soup (USSR)			Crayfish (Nigeria)	92.00 <sup>d,e</sup>	(787)
Before cooking	4.90	(228)	Fish, canned (Eur.)	3.50 <sup>c</sup>	(769)
After 30 min cooking in			Fishmeal, menhaden	161.00–615.00 <sup>d</sup>	(789)
99.50% Al	70.10	(228)	Menhaden, heat-transfer	272.00–375.00 <sup>d</sup>	(790)
2 hr warming thereafter	88.00	(228)	Peruvian anchovy	48.00–190.00 <sup>d</sup>	(791)
Beef stew with onion			Haddock, frozen	<1.00	(257)
(Czech.)			Ladyfish (Nigeria)	43.00 <sup>d,e</sup>	(787)
Stewed 180 min in Al	6.70 <sup>d,e,f</sup>	(488)	Lobster (Eur.)	1.40 <sup>c</sup>	(769)
Stewed in stainless steel	0.60 <sup>d,e</sup>	(488)	Salmon, sockeye, canned,		
Fish soup (Czech.)			salt-free	8.20	(257)
Stewed 45 min in Al	18.6 <sup>d,e,f</sup>	(488)	Shellfish, general (Eur.)	2.9 <sup>c</sup>	(769)
Stewed in stainless steel	5.50 <sup>d,e</sup>	(488)	Shrimp, canned, salted	<1.00	(257)
Goulash, Segedin (Czech.)			Snail (Nigeria)	430.00 <sup>d,e</sup>	(787)
Stewed 90 min in Al	0.50 <sup>d,e,f</sup>	(488)	Sole, frozen	<1.00	(257)
Stewed in stainless steel	0.30 <sup>d,e</sup>	(488)	Stock fish (Nigeria)	43.00 <sup>d,e</sup>	(787)
Oxtail soup (Czech.)			Tuna, canned, salt-free		
Boiled 125 min in Al	4.90 <sup>d,e,f</sup>	(488)	water pack	<1.00	(257)
Beverages					
<b>Alcoholic</b>			<b>Alcoholic (cont.)</b>		
Beer			In steel cans, Al lids	0.18–0.66 <sup>f,i</sup>	(792)
In bottles, plastic liners	0.06–0.17 <sup>i</sup>	(792)	In Al cans	0.13–0.55 <sup>f,i</sup>	(792)



**Table 5. Concentrations of aluminum in foods and beverages<sup>a,b</sup> (cont.)**

	Al, μg/g or ml	Reference		Al, μg/g or ml	Reference
Beverages (cont.)					
Alcoholic (cont.)			Alcoholic (cont.)		
In all-tinplate cans, stored 6 mo, upright or on side	0.18–0.80	(186)	Red, in contact with Al	1.30–2.80 <sup>d,f</sup>	(793)
In cans with Al ends (1 or 2), stored as above	0.08–0.83; 2.24 <sup>f</sup>	(186)	White, no contact with Al	0.55–0.88 <sup>d</sup>	(793)
In glass bottles (Ger.)	0.15 <sup>i</sup>	(187)	White, in contact with Al (USSR)	1.00–4.30 <sup>d,f</sup>	(793)
In tin plate cans	0.13–0.26 <sup>j</sup>	(187)	Miscellaneous	1.40–7.40 <sup>d</sup>	(190)
In Al cans, 1 mo–1 yr	3.00–29.00 <sup>j</sup>	(187)	Coffee		
Champagne (USSR) stored in 99.5% Al, lacquered	8.10–11.10 <sup>f</sup>	(193)	Brewed	<0.4	(257)
coated with 99.99% Al	0.54–0.60 <sup>l</sup>	(193)	ground	11.00	(257)
Wines (Ger.)			instant, dry	<10.00	(257)
Red, no contact with Al	0.51–0.93 <sup>d</sup>	(793)	Tea		
			orange pekoe, steeped	2.80	(257)
			bag, dry	1280.00	(257)
Miscellaneous					
Baking powders, commercial			Honey		
Na Al sulfate containing cream of tartar	20,000–26,000 <sup>f,i</sup>	(794)	Dark (Australia)	58.73 <sup>g,i</sup>	(796)
	0.00 <sup>i</sup>	(794)	Light (Bulgaria)	4.76 <sup>g,i</sup>	(796)
Candies, commercial, 13 types	<1.00–20.00	(795)		11.60	(797)
Chewing gum, 2 types	29.00–<100.00	(795)	Vitamins, niacin	1.00–9.90 <sup>h</sup>	(798)
Chocolate sirup	<2.00	(257)	Yeast		
Cocoa	45.00	(257)	Agglutinated (Czech.)	~0.30–1.30 <sup>d,e</sup>	(799)
Dietary concentrates			Nonagglutinated	~1.00–1.80 <sup>d,e</sup>	(799)
Meritene, dry, plain flavor	19.00	(257)	Torula (Ger.)	130.00 <sup>d,e</sup>	(769)
Sustagen, dry, imitation flavor	16.00	(257)			
Total Diet Composites					
Washington, DC, average	13.00–51.70 <sup>e</sup>	(259)	San Francisco, average	5.40 <sup>e</sup>	(259)
St. Louis, average	43.60 <sup>e</sup>	(259)			

<sup>a</sup>Spectroscopy, generally emission, unless otherwise indicated.

<sup>b</sup>United States, unless shown in parentheses.

<sup>c</sup>Method not stated.

<sup>d</sup>Colorimetry.

<sup>e</sup>Dry weight basis.

<sup>f</sup>Processed in Al or with Al food additive.

<sup>g</sup>In ash.

<sup>h</sup>Neutron activation.

<sup>i</sup>Atomic absorption spectrophotometry.

<sup>j</sup>Polarography.

National School Program established by Congress to provide nutritious, reasonably priced lunches. The results showed that lunches from S.E. schools were significantly higher in their contents of the 4 B vitamins and the minerals Cr, Mn, Al, Ba, Ca, Mg, P, K, and Na, than lunches from the other regions. The highest Al contents were found in the S.E., 13.75 mg, and S.W., 9.37, compared with U.S. as a whole, 8.26 mg.

The availability of 20 of the FDA's "total diets," used to measure fallout in food supply, gave Zook and colleagues (259) of the U.S. Department of Agriculture Human Nutrition Research Division the opportunity to determine the content of 10 minerals in food eaten. These were composites of water and 82 food items selected to incorporate cost with nutritive value (according to published U.S.D.A. food plans) and designed to supply boys 16–19 yr old with 4200 calories. The meals, in quantities for 14 days, were prepared with products obtained from Washington, St. Louis and San Francisco supermarkets from 1961 through early 1962. The results showed that food from no single supermarket chain was consistently high or low in any element, nor was any element uniformly high or low in one season except Al found in February (average 5.17 mg/100 g dry fat-free solids). Also, only Al, Na, and B were significantly different in different seasons and tended to be lower in May composites than in other periods. Lowest Al and Mn were found in diets purchased and processed in San Francisco (Al, 0.54 mg/100 g) and highest in St. Louis composites (Al, 4.36 mg/100 g). In Russia, Gabovich (260) sought to determine the daily intake of seven trace elements from diets designed to supply the physiological requirements of the population, which were prepared from a variety of locally available food products of 12 cities and towns in the Ukrainian, Belorussian, Moldavian, and Kazakh S.S.R. to provide 3500 calories for adults, 1315–2291 calories for children. The Al contents, determined only in the adult rations, ranged from 18.0 to 85 mg; the highest, 74.0–85, were found in Vinnitsa (Ukraine), Kishinev (Moldavia), and Karaganda (Kazakh).

None of the above investigations took into consideration the amounts of Al that might have been contributed by preparation in aluminum

utensils. This was, however, considered by Vozar (261) in his review of the Al intake by the Czechoslovakian adult population (based on 3000 calories) with direct reference to the effects of Al on the organism (published in 1959–1960). On the basis of analyses of Al in foodstuffs, he estimated a daily intake of 80.5 mg, which could reach 160.1 mg if all food were prepared in aluminum utensils. He considered the latter figure doubtful since about one-third of the daily food is not subjected to preparation in aluminum utensils. The author concluded that the use of aluminum utensils in Czechoslovakia is safe, except for the preparation of highly acid foods requiring long cooking and those containing anthocyanins (e.g., beets, cherries) which may undergo "organoleptic depreciation."

Babenko et al. (262) of the U.S.S.R. analyzed 11 elements in foods fed to infants and very young children in an infant feeding center. Al contents, determined in a total of 173 samples, varied greatly and were quite high in some, probably due to the use of aluminum utensils in the center. Breast feeding supplied a daily Al intake of 2.7–3.5  $\mu\text{g}/\text{kg}$  of the infant's weight; when supplemented with mixed and artificial food, the intake was 17  $\mu\text{g}/\text{kg}$ , and during the weaning period,  $\geq 170 \mu\text{g}/\text{kg}$ . The authors state that the possibility of toxic doses should be considered at the highest levels.

In viewing the concentrations shown in Table 5, it is obvious that there is a wide variation in the Al content, depending upon the product, plant or animal, and also upon the geographic locations of the producing area. The latter was indicated in the above diet studies, in analyses by Christensen of herbs and spices (263), by Hopkins et al. of vegetables (264), by Zook et al. of fruits (265). To be sure, the analytical methods employed and whether reported as the dry or fresh weight make a difference, and for this reason such information is indicated if stated. In the case of plant products, the edible parts of the plants also make a difference (266) as well as whether they are peeled (265), dried (267), or otherwise processed (268). Of interest are the very high concentrations found in some products, particularly those found by Oke for Nigerian food plants (*Corchorus*, *Solanum*, *Vernonia*, mush-

rooms) (71, 72, 269). Concerning the mushrooms, the concentrations of Al were much higher than those of the other trace elements studied (Al 1300, Fe 726, Mn 67, Zn 64; Mo, B, Cu, 1–37  $\mu\text{g/g}$ ). The daily intake of mushrooms was reported as around 50 g of fresh material (5 g dry matter) per meal, often consumed twice a day (72). In the other vegetables, Al ranged from 363 to 932  $\mu\text{g/g}$  in the edible and partially edible species. High Fe and Mn contents were also found. The author considered that the Al contents in the partly edible and nonedible species (1659  $\mu\text{g/g}$  dry weight for the latter) could be toxic under normal conditions. Among the products examined by Gormican (257), tea (bagged) showed a very high Al content, 1280  $\mu\text{g/g}$ ; the beverage, however, contained only 2.8  $\mu\text{g/g}$ . As an example of a greatly increased Al content by a food additive, the same author found 695  $\mu\text{g/g}$  Al in American cheese, which was attributed to the inclusion of a NaAl phosphate, a permissible emulsifier.

Table 5 shows clearly that most of the available new data concern plant products and that but few analytical data could be found on animal-derived food. Aside from the tabulated values of meats, one study on mineral constituents in edible muscles of eight animals indigenous to India gave only qualitative paper chromatographic results indicating "prominent" amounts of Al in samples from 2 of the animals, and "presence" in the other six (270). Among publications that could not be seen in the original, one report concerns changes in major and trace elements, including Al, in fish muscle during refrigeration storage, with the finding that due to loosening of bonds between the muscle proteins and the ions, the concentrations of the ions increased at the termination of refrigeration; partial freezing of fish caused increases in Cu, Zn, and Al (271). In respect to the trace element content in milk, concentrations of eight elements including Al fluctuated depending on lactation and season, i.e., when cows were transferred to green pastures. Highest Al contents were found in April (272).

The few publications reporting Al content in food products or beverages, processed or stored in aluminum, are limited essentially to

Evenshtein's reports in some of which he compared the 99.5% alloy (containing 0.3% Fe and higher, and other metals) with the superpure 99.99% alloy in respect to ascorbic acid and pigment losses. The reported concentrations are included in Table 5. In one study (273), Evenshtein compared the resistance to corrosion of these alloys by immersing plates in fresh cabbage or sauerkraut soups with meat or salt cod and cooking for the required time (40–90 min), then holding at 18–20°C for 4 hr. At pH 6–6.7 of the mixtures, Al 99.50% lost 2–7 mg during cooking; at pH 5, the loss was 9–12 mg; 4 hr thereafter, 2–9 and 12–15 mg, respectively. The 99.99% alloy lost nothing during cooking, and 1 mg during 4 hr storage (the pH of 2 of the dishes was 5). In the other studies with beets, carrots, cranberries, meat or salt cod and vegetable combinations, and dry fruit compote, cooked for the required time, then kept warm for 2 hr, the increases in Al content from the 99.50% alloy were from 5.54 to as high as 83  $\mu\text{g/g}$ , while those from the 99.99% alloy amounted to less than 1  $\mu\text{g/g}$  (228, 229). The 99.50% alloy is reported to contain approximately 0.3% Fe, 0.15% Si, 0.02% Cu (228). The author states that although this alloy is harder, it loses its chemical stability and therefore corrodes considerably more than the superpure alloy. In comparing the values for food products cooked or stored in aluminum, reported in the earlier investigations (1), no increases of such magnitude were found except for some unusual instances as reported by Beal (205). Generally, the addition of Al from cookware amounted up to only a few micrograms per gram or even none, as compared with cooking in glass. Cooking with sugar greatly decreased the leaching of Al into fruit dishes. The alloy or the quality of aluminum was usually not stated in these studies. On the other hand, in experiments on the use of aluminum for the storage of fruit juices and musts, Koch found an Al-Mn alloy to be more resistant to corrosion than pure aluminum (99.6%), but did not recommend it for this use because of resulting high Mn content in the juices (189). It appears obvious that further studies comparing the leaching of Al and other components from different alloys are needed to furnish convincing results.

Some data concerning the Al content of several vegetables and meat and vegetable combinations, cooked in aluminum and in stainless steel utensils, came to attention after completion of this part of the manuscript. Most of the differences were not significant (see Table 5).

In a review of the toxicity of Al in 1967, Evenshtein came to the conclusion that there is no need to limit the household and consumer uses of this metal and its alloys as regards release of Al hydroxide into food; however, "the presence of soluble Al salts in food is undesirable" because of their reported toxicity to warm-blooded animals (274). The identity of the "soluble salts" is not given. Examination of the earlier reports (1), as well as those of the past 16 yr, revealed no mention of the form in which Al is present in processed foods, except for very early investigations where it was expressed as  $\text{Al}_2\text{O}_3$  (209). It has been generally determined and reported as the ion.

In 1972, an exchange of letters in the *British Medical Journal* and *Lancet* as to the hazards of oral and parenteral administration of aluminum to patients with impaired kidney function gave Shaw (275) and Harrison et al. (276) the opportunity to question the safety of using aluminum containers for cooking and canning foods, as well as the use of Al compounds in various drugs. Shaw calls attention to the article by Jenkins and Blagdon (277) who described the use of improved containers for long-term storage of blood, which resulted in less danger of contamination while preserving good recovery figures for processed cells. The Department of Health and Social Security performed chemical tests (emission spectroscopy) on the Al canisters and the contained water after sterilization. Only Al amounting to approximately  $0.5 \mu\text{g}/\text{ml}$  was found, in addition to Fe, Cu, Mn, Si, Ti, Mg, ranging from traces to 0.21%, which were stated to be within accepted levels for transfusion purposes. Jenkins and Blagdon do not mention the Al value further. Shaw, however, points to the Al content found in the water and urges that additional toxicological analyses be carried out, in particular on blood stored at low temperature, to prevent possible harmful intravenous administration of Al compounds. The need for analyses on the

blood makes good common sense, and it would be interesting to know to what extent this highly complex chemical mixture reacts with metallic aluminum, and how much higher the Al content would be than normally present, which is estimated at  $0.16 \mu\text{g}/\text{g}$  wet tissue as shown in the ICRP Committee II Report on Permissible Dose for Internal Radiation (278). Referring to the tests carried out on all-aluminum seawater stills (243), the above content is almost 10 times higher than the  $0.06 \mu\text{g}/\text{ml}$  found in the distilled water, and further verification is indicated with precise knowledge of the quality of the aluminum or its alloys used. It may be also mentioned that  $\text{SiO}_2$  and  $\text{Al}_2\text{O}_3$  were found to leach from glass bottles holding potassium and dextrose mixtures for parenteral therapy (180).

The British Industrial Biological Research Association reviewed the above-mentioned correspondence (279), and after citing Shaw's apprehension, concluded as follows: "It seems unlikely that Al migration of this order would occur under most of the conditions encountered in the cooking and storage of food, but assuming that some Al does find its way into our diet from such sources, there seems little likelihood that the hazard is any greater than has hitherto been assumed. There is still no evidence to contradict the assumption that the greater part of ingested Al is excreted by man in the feces. Given an adequate diet, the small amounts of Al involved would be unlikely to promote any deficiency of absorbed phosphate, and any Al that may escape this eliminating net can be assumed to be rapidly excreted by normally functioning kidneys."

#### **Tolerances (or Maximum Allowable Concentrations) in Foods and Beverages**

In the U.S., the Food and Drug Administration has established no tolerance for the content of Al in finished food and beverage products other than those shown for food additives, all of which are by prior sanction and/or generally regarded as safe (GRAS). Among the tolerances for pesticide residues, the fumigant aluminum phosphide of processed foods is listed. In this case, however, the tolerance applies to phosphine which is not to exceed

0.1 mg/kg in or on processed food (oats, rice, rye, wheat, sorghum, peanuts) (280, 281). In addition, there are certain restrictions as to the use of bentonite as additive in animal feeds (282).

In other countries, according to a review on trace elements in foods by Jaulmes (283), the Society of Expert Chemists of France proposed a MAC of 20 mg/kg of food products as received in markets and up to 100 mg/kg for food products processed or stored in aluminum. In Switzerland, Rentschler (284) recommended MAC's for Al, Sn, and Cd in fruit juices of 2 mg Al/l for those stored in glass containers and 20 mg Al/l for canned juices; for Sn the respective concentrations are 5 and 250 mg/l, and for Cd 0.1 mg/l, regardless of container.

### Daily Intake of Aluminum

Table 6, showing the determined or estimated daily intakes of Al, includes data reported by Kehoe in 1940 (285) and 1943 (unpublished data, 1943) which were based on analytical results obtained on exact duplicates of foods consumed by two subjects living in ordinary modern American households. Among the more recent values, those reported by Tipton (255) and by White (256) were also obtained on duplicates eaten by the subjects, and those found by Gormican (257) and Murphy (258) were based on meals as served. The other values were derived from composites of total diets consisting of products locally available in various cities to provide daily food of various caloric requirements. In contrast to the earlier studies, no separate estimates were available of the contribution of aluminum cooking utensils or of baking powder, except for that by Vozar (261) who admitted that it was excessive. However, it is only reasonable to assume that there has been contact of some of the food with aluminum in the preparation, processing, or packaging, and use of Al-containing baking powder (which appears to be the only type now available in supermarkets). This contact occurs not only in cooking "from scratch," but also in the purchased canned and convenience foods, cake mixes, unbaked and fully baked goods requiring this type of leavening, in addition to the other Al food additives for the various purposes indicated

above, which are permitted to be included in products processed by the food industries. As shown, the new data are in fairly close agreement with the older data, excluding a very high early estimate (472 mg) for intake from natural diet (286) (not shown in Table 6), and an exceedingly low estimate (<1.56–2.82 mg) among the recent analyses (256). If anything, the recent values tend to be lower. This may be attributed to the limitations in respect to Al of the emission spectroscopic method for multielement analyses which was generally used in these studies.

Two unusually high values are not shown in the table. One was among the data reported by Gormican for the Giovannetti hospital diet, used for patients with severe chronic uremia, which amounted to 634.5 mg. Since the author of the diet advocates  $\text{Al}(\text{OH})_3$  in the treatment of such patients (287), the addition of this compound may be assumed. The other one was reported by Evenshtein (288), who followed the health status of 30 male and 20 female brewery workers whose daily Al intake was 200–400 mg in their food, water and beer (the latter high in Al content because of tanks made of Fe-containing aluminum). His conclusion was that the regular consumption of up to 5.5 mg Al/kg of body weight "does not have an adverse effect on the organism as a whole, since the substance is mainly present in colloid form." The author does not mention how much Al was supplied with food and water and how much was contributed by the beer. On the basis of the daily intake of Al reported for the U.S.S.R. by Gabovich, a maximum of 85 mg (260), and the fact that only those women were chosen for the above study who ingested regularly 100–150 mg Al daily at least 5 days weekly from beer, either the Al content of the beer or the quantity of beer consumed must have been very high indeed.

Although the natural Al content of some individual food products as shown in Table 5 may be quite high (some vegetables, berries, herbs, and spices) and far exceed any amount that may be added by processing and storing in aluminum, or by inclusion of Al-containing food additives, the reported daily intake is relatively low. It can only be assumed that the amounts of these products used for consumption are so small or the use of them so occasional, as to be balanced to a relatively low level of actual daily

**Table 6. Daily intake of aluminum by man.<sup>a</sup>**

Date	Author	Diet	Al, mg	Reference
1940	Kehoe et al.	Duplicate samples of daily food and beverages of 1 male adult for 28 days	36.43 ± 61.97	(285)
1943	Kehoe et al.	Duplicate samples of daily food and beverages of 1 male adult (other than above) for 15 wk Means	< 9.9—> 100.0 17.31 ± SD 27.67	Unpublished
1960	Voinar	Daily "requirement," based on literature	35.00–40.0	
1962	Vozar	Own data, based on 3000 cal diet (Czech.); from natural products if all food were cooked in Al	80.50 160.10	(261)
1965	Babenko et al.	Meals served in infant care center (USSR) From breast feeding Plus artificial feeding in weaning period; probably contact with Al	0.003–0.004/kg infant <sup>b</sup> 0.017/kg infant <sup>b</sup> 0.170/kg infant <sup>b</sup>	(262)
1965	Zook et al.	Total diet composites, including water; based on 4200 cal daily intake by 16-19-yr-old boys, over 14 days Washington, DC San Francisco St. Louis Overall average	8.80–51.60 3.80 31.60 24.60	(259)
1966	Gabovich	Total diet composites adults, 3500 cal daily intake, 12 cities, USSR average	18.80–85.00 43.10	(260)
1966	Tipton et al.	Duplicate samples of daily food and beverages of 2 adults over 30 days Female Male	18.00 22.00	(255)
1969	Kolomiitseva	Total daily rations, USSR; average	49.10	(804)
1969	White	Duplicate samples of daily food and beverages 21 college women and author (33 composites) 15 high school girls (15 composites)	<1.56–2.82 <1.53–33.30	(256)
1970	Gormican	Composites of representative hospital menus General diet, summer General diet, winter Mechanical soft, summer Mechanical soft, winter special diets, including liquid diet, summer special diets, winter	6.97 5.32 5.64 9.01 <1.99–4.39 <1.80–4.84	(257)
1970	Murphy	School lunches, 5 geographic regions, US, average	3.98–13.75 <sup>b</sup>	(258)
1971	Jaulmes	Based on literature, for France From natural diet Processed or stored in Al	10.00–12.00 20.00–50.00	(283)

<sup>a</sup>United States, unless otherwise indicated

<sup>b</sup>Partial diets

intake by the foods of low Al content. On the other hand, the geographic variations in intake, especially in the eastern countries, are evident. This may be due in part to differences in dietary habits as well.

## Biology of Aluminum in Man, Animals, and Lower Organisms

### Normal and Disease-Related Metabolism of Aluminum

The literature on the biological aspects of Al, published since the earlier review (1), clearly reflects the growing interest in trace elements or "micronutrients" and their distribution in animal and human tissues under environmental conditions. There have been a large number of studies in which Al has been included among various trace elements whose distribution in numerous tissues has been followed in states of health and disease with no unusual exposure to Al (289-291).

As was mentioned in the previous section, the essentiality of Al for biological function was suggested as early as 1915, but to date its function in tissues remains unknown (251, 292). Al is the third most abundant element in the earth's crust (8.13%), exceeded only by oxygen (46.60%) and silicon (27.72%) (53). It is well understood that oxygen is an essential element for biological function. Recently it has been established that silicon is essential for growth and that it plays a role in mucopolysaccharide metabolism (293, 294). Failure to demonstrate essentiality of Al has been due to the difficulty of obtaining a diet deficient in this metal. Such a diet is required to show biological deficiency which may be reversed by the appropriate addition of Al resulting in a correction of the deficiency. Hove et al. (295) reported in 1938 that they could not demonstrate essentiality for this reason. Later Lauro and Giornelli (296) suggested that Al plays an essential role in female rat fertility. Very recently, because of the abundance of Al in the earth's crust, both Frieden (254) and Schwarz (personal communication, 1973) have also suggested that it is essential for man.

According to the International Commission on Radiological Protection Committee II, approximately 0.10 g of Al is contained in the

average 70 kg man, which is  $1.4 \times 10^{-4}$  % by weight (278). Tipton (255) analyzed Al (together with other elements) in the diet and excreta of two subjects (A and B, wife and husband, respectively) on an *ad libitum* diet for 30 days. The intake of these two subjects was nearly the same, 0.018 g and 0.022 g. The amount excreted in the feces was 0.017 g and 0.045 g, and in the urine, 0.001 g and 0.001 g, respectively. The 30 day mean balances were 0.000 g for A and -0.024 g for B. This suggests homeostatic control of the Al content of the body although subject B was in a negative balance for this 30 day period. Numerous other estimates of the human daily intake of trace elements have been made on the basis of dietary composition. Those for Al are shown in Table 6. Although balance studies were not done in these cases, earlier results (1) tend to support the conclusion that excessive intake and absorption by a normal individual is followed by prolonged excretion of the excess following a reduction in intake, in a homeostatic fashion.

Tipton et al. (297) and Stich (298) have reported concentrations of Al in tissues obtained after sudden accidental death from individuals who had lived in the U.S. and British Isles. These data are presented in Tables 7 and 8. In addition to Tipton and Stich, others have determined the concentration of Al in various human tissues and body fluids, as can be seen in Table 9.

It should be borne in mind that the concentration of Al found in tissues reflects the geochemical environment of the individuals and of locally raised food and meat products. The effect of geochemical environment is also suggested by the wide ranges of values reported for the concentration of Al in various tissues shown in Tables 7, 8, and 9, by investigators in different locations. Table 10 gives the data obtained by Tipton et al. (299) which were specifically intended to show geographic variations in Al concentration in tissues obtained from adult males who had lived in four geographic locations.

Although the biological role of Al has not been clearly established, it now seems likely that it is an essential metal. As will be shown below, many investigators have found it in measurable concentrations, together with other

**Table 7. Ash and aluminum concentration of normal tissues obtained from individuals living in the United States.<sup>a</sup>**

Tissue	Ash, % of wet weight	Ash, % of dry weight	Concentration, $\mu\text{g/g}$ of tissue ash
Adrenal	0.50 $\pm$ 0.07	1.0 $\pm$ 0.25	480 $\pm$ 290
Aorta	1.7 $\pm$ 0.13	5.1 $\pm$ 0.38	57 $\pm$ 6.4
Brain	1.7 $\pm$ 0.04	6.4 $\pm$ 0.25	22 $\pm$ 4.2
Diaphragm	0.98 $\pm$ 0.02	3.4 $\pm$ 0.07	57 $\pm$ 9.8
Esophagus	0.89 $\pm$ 0.03	3.7 $\pm$ 0.15	99 $\pm$ 14
Heart	1.1 $\pm$ 0.01	4.1 $\pm$ 0.08	35 $\pm$ 3.7
Intestine			
Duodenum	0.81 $\pm$ 0.02	3.8 $\pm$ 0.13	120 $\pm$ 28
Jejunum	0.92 $\pm$ 0.03	4.0 $\pm$ 0.12	71 $\pm$ 9.2
Ileum	0.75 $\pm$ 0.03	3.4 $\pm$ 0.19	290 $\pm$ 180
Cecum	0.67 $\pm$ 0.04	2.3 $\pm$ 0.18	280 $\pm$ 76
Sigmoid colon	0.68 $\pm$ 0.03	2.9 $\pm$ 0.14	160 $\pm$ 22
Rectum	0.85 $\pm$ 0.08	3.3 $\pm$ 0.38	110 $\pm$ 28
Kidney	1.1 $\pm$ 0.02	4.7 $\pm$ 0.09	43 $\pm$ 5.7
Larynx	3.3 $\pm$ 0.22	9.3 $\pm$ 0.57	24 $\pm$ 4.2
Liver	1.3 $\pm$ 0.03	3.7 $\pm$ 0.12	65 $\pm$ 7.0
Lung	1.1 $\pm$ 0.02	4.9 $\pm$ 0.23	2500 $\pm$ 180
Muscle	1.2 $\pm$ 0.02	4.3 $\pm$ 0.11	36 $\pm$ 7.1
Ovary	1.0 $\pm$ 0.05	4.6 $\pm$ 0.38	60 $\pm$ 50
Omentum	0.25 $\pm$ 0.02	0.3 $\pm$ 0.04	520 $\pm$ 130
Pancreas	1.1 $\pm$ 0.03	3.3 $\pm$ 0.17	66 $\pm$ 12
Prostate	1.2 $\pm$ 0.05	4.4 $\pm$ 0.28	270 $\pm$ 200
Spleen	1.4 $\pm$ 0.03	5.0 $\pm$ 0.13	74 $\pm$ 15
Skin	0.79 $\pm$ 0.07	2.0 $\pm$ 0.21	400 $\pm$ 90
Stomach	0.82 $\pm$ 0.03	3.3 $\pm$ 0.2	110 $\pm$ 35
Testis	1.1 $\pm$ 0.02	5.8 $\pm$ 0.23	46 $\pm$ 6.7
Thyroid	1.4 $\pm$ 0.30	5.0 $\pm$ 1.1	190 $\pm$ 68
Trachea	1.9 $\pm$ 0.11	5.7 $\pm$ 0.27	220 $\pm$ 53
Urinary bladder	0.78 $\pm$ 0.02	2.4 $\pm$ 0.12	100 $\pm$ 22
Uterus	1.0 $\pm$ 0.02	4.3 $\pm$ 0.18	47 $\pm$ 6.9

<sup>a</sup>Data obtained by Tipton and Cook (297) with emission spectroscopy.



**Table 8. Range and mean concentration of aluminum in ash for tissues obtained from normal adults who lived in the British Isles<sup>a</sup>**

Tissue	Range, $\mu\text{g/g}$	Mean, $\mu\text{g/g}$
Adrenal	100->1000	950
Bladder	<20->1000	>1000
Bone	<20-200	50
Cartilage	<20->1000	650
Gall bladder	150->1000	1000
Heart	<20->1000	300
Kidney	<20-1000	400
Lung	1000->1000	>1000
Liver	<20->1000	500
Pancreas	20->1000	600
Prostate	100->1000	1000
Skeletal muscle	<20->1000	550
Skin	40->1000	>1000
Spleen	<20-1000	300
Subcutaneous fat	40->1000	>1000
Testis	20-1000	400
Thyroid	200->1000	800

<sup>a</sup>Data obtained by Stitch (298) with emission spectroscopy.

trace metals in all tissues, which appear to change with changes in biological activity of the tissues. In this context we have attempted to present the role of Al in biological processes associated with health and disease states according to the existing literature. Since it was desired that this review have a finite length, discussion of the other metals and their effects in or on the reported biological alterations have been omitted.

Because of the clearly demonstrated variation due to geochemical environment the value reported from one geographic area cannot be quantitatively compared with values reported from others. Therefore, changes in the Al content of tissues and fluids observed in various physiologic and pathologic states are reported

in most instances as being either above or below the normal value found in each case.

An attempt has been made by a number of investigators to use changes in the Al content in blood as an aid in the diagnosis of diseases affecting various organs. The material concerning the metabolism of Al in health and disease is presented by tissue and related body fluid which are listed in alphabetical order.

**Adrenal:** Only a limited amount of work has been done concerning changes in adrenal activity and Al concentration. Soroka (300), using dogs, analyzed the content of several metals including Al in the adrenal following excitation of the central nervous system (CNS) with caffeine and depression with ether anesthesia. The results showed that both CNS excitation and depression resulted in a decrease of about 50 to 65% of the normal Al concentration of the adrenal glands within 1 hr after administration of the drugs, with a gradual return to normal during the second hour.

**Blood:** Since 1957, there have been many publications dealing with the changes in the Al content in human blood. In 1958, Silvestri (301) reported that in human serum, Al was a predominant normal metallic constituent. Sabadash (302) demonstrated that the Al concentration in blood of normal individuals changed in a circadian fashion: it was high at 9 a.m. and low at 6 p.m. However, young males in the state of inactivity were observed to have no change in serum Al content (303). Diurnal variation in blood (302, 304-306) has been observed to be the same in dogs as it is in man. The results of these experiments suggested that the Al concentration in blood is regulated by the autonomic nervous system. At rest the parasympathetic nervous system predominates resulting in an increased accumulation of Al in brain and a decrease in blood and cerebrospinal fluid (CSF), while in the awake state or under adrenal stimulation the sympathetic system reverses these changes. In contrast, adrenalin and cortisone were reported to lower the serum Al content in rabbits (307).

Other observations with regard to the metabolism of Al which suggest its essentiality were those of Leonov (308) and Mikosha (309) that Al could be found in the human fetus.

Blood Al and other trace metals increased between 4.5 and 6 mo of age. At 8 mo of intra-uterine life the elements showed a second period of maximum concentration and dropped sharply following delivery. However blood of premature infants contained more Al than

those delivered at term (290). At delivery it was shown that newborn blood contained a higher level of Al than did the mothers' (310). The content in the blood of female newborns was somewhat higher than that of males.

**Table 9. Aluminum concentrations in normal human tissues and body fluids reported from various geographic locations. <sup>a</sup>**

Tissue and fluids	Al, $\mu\text{g/g}$ or ml	Reference	Tissue and fluids	Al, $\mu\text{g/g}$ or ml	Reference
Adrenals (US) <sup>b</sup>	46.00 <sup>c</sup>	(405)	Brain		
			Adult (US) <sup>b</sup>	244.90 <sup>f</sup>	(405)
Blood			Embryo (USSR)		
Whole			3 mo. <sup>b</sup>	100 <sup>f</sup>	(308)
(US) <sup>d</sup>	0.14	(285)	5 mo. <sup>b</sup>	100 <sup>f</sup>	(308)
(USSR) <sup>d</sup>	0.50 - 1.30	(805, 806)	6 mo. <sup>b</sup>	500 <sup>f</sup>	(308)
(USSR) <sup>d</sup>	6.02	(807)	7 mo. <sup>b</sup>	500 <sup>f</sup>	(308)
(Bulg.) <sup>d</sup>	0.50 - 1.50	(808)	8 mo. <sup>b</sup>	10 <sup>f</sup>	(308)
(USSR) <sup>e</sup>	5.99	(809)	Newborn <sup>b</sup>	1,000 <sup>f</sup>	(308)
(USSR) <sup>e</sup>	112.00 <sup>f</sup>	(312)	Cerebrospinal fluid		
(USSR) <sup>g</sup>	6.24	(809)	(USSR) <sup>d</sup>	0.09	(807)
(USSR) <sup>b</sup>	280.00 <sup>f</sup>	(348)	(USSR) <sup>d</sup>	75.00 <sup>f</sup>	(326)
(USSR) <sup>h</sup>	220.00 <sup>f</sup>	(340)	Feces (US) <sup>b</sup>	170-450 $\mu\text{g/day}$	(255)
Serum			Hair		
(USSR) <sup>d</sup>	75.00 <sup>f</sup>	(325)	(New Zealand) <sup>h</sup>	3.80 and 5.00	(383)
(Ger.) <sup>d</sup>	0.17 <sup>i</sup>	(810)	(New Zealand) <sup>b</sup>	1.20-9.20	(815)
(US) <sup>d</sup>	0.45 - 0.78	(369, 370)	(Hung.) <sup>b</sup>	6.00-50.00	(816)
(USSR) <sup>d</sup>	0.17 - 0.36	(290, 811)	(USSR) <sup>b</sup>	30.00-60.00	(817)
Blood plasma			Heart		
(US) <sup>d</sup>	0.24	(285)	(Japan) <sup>g</sup>	2.70	(818)
(USSR) <sup>e</sup>	0.13	(812)	(US) <sup>b</sup>	33.00 <sup>c,i</sup>	(405)
(Bulg.) <sup>d</sup>	0.10-0.45	(808)	Jejunum (US) <sup>b</sup>	64.00 <sup>c</sup>	(405)
(USSR) <sup>g</sup>	0.36	(812)	Kidney		
(USSR) <sup>d</sup>	2.09-4.47 <sup>j</sup>	(809)	(Japan) <sup>g</sup>	4.10	(818)
Albumin (USSR) <sup>d</sup>	0.64 <sup>j</sup>	(807)	(US) <sup>b</sup>	53.40 <sup>c</sup>	(405)
Fibrin (USSR) <sup>d</sup>	0.21 <sup>j</sup>	(807)	Liver		
Globulins (USSR) <sup>d</sup>	0.56 <sup>j</sup>	(807)	(Japan) <sup>g</sup>	11.10	(818)
Supernatant (USSR) <sup>d</sup>	2.55 <sup>j</sup>	(807)	(US) <sup>b</sup>	168.00 <sup>c</sup>	(405)
Red blood cells			(US) <sup>b</sup>	43.00 <sup>c</sup>	(406)
(USSR) <sup>g</sup>	1.71 <sup>j</sup>	(807)	Lung		
(USSR) <sup>e</sup>	0.82 <sup>j</sup>	(807)	(Japan) <sup>g</sup>	8.5	(818)
(USSR) <sup>d</sup>	7.72(RBC)	(809)	(US) <sup>b</sup>	339.00 <sup>c</sup>	(405)
(USSR) <sup>d</sup>	3.66 <sup>j</sup>	(809)	Milk		
Stroma (USSR) <sup>d</sup>	0.22 <sup>j</sup>	(807)	(USSR)	157.00 <sup>f</sup>	(425)
Nonhemoglobin protein			(USSR)	270.00 <sup>f</sup>	(424)
(USSR) <sup>d</sup>	0.53 <sup>j</sup>	(807)	(USSR)	0.02	(262)
Supernatant (USSR) <sup>d</sup>	1.22 <sup>j</sup>	(807)	Optic nerve (USSR) <sup>b</sup>	179.00 <sup>f</sup>	(380)
White blood cells			Pancreas		
(USSR) <sup>d</sup>	0.02 <sup>j</sup>	(807)	(Japan) <sup>g</sup>	4.1	(818)
(USSR) <sup>d</sup>	11.26(WBC)	(809)			
Bone					
Calvaria (US) <sup>b</sup>	37.00 <sup>f</sup>	(813)			
Rib (US) <sup>b</sup>	27.00 <sup>f</sup>	(813)			
Midshaft tibial and femoral (US) <sup>b</sup>	3.00 <sup>c</sup>	(814)			

**Table 9. Aluminum concentrations in normal human tissues and body fluids reported from various geographic locations. <sup>a</sup> (cont.)**

Tissue and fluids	Al, $\mu\text{g/g}$ or ml	Reference	Tissue and fluids	Al, $\mu\text{g/g}$ or ml	Reference
Pancreas (cont.)			Spleen (cont.)		
(US)	115.00 <sup>c</sup>	(405)	(US) <sup>b</sup>	101.00 <sup>c</sup>	(405)
Prostate (Japan)	3.6	(818)	Synovial fluid (US) <sup>d</sup>	0.30	(369,370)
Seminal fluid (Japan)	3.3	(818)	Testicle (Japan)	4.2	(818)
Seminal vesicle (Japan)	2.5	(818)	Tendon (US) <sup>b</sup>	0.30 <sup>c</sup>	(814)
Spleen			Thyroid (US) <sup>b</sup>	52.00 <sup>c</sup>	(405)
(Japan) <sup>e</sup>	4.1	(818)			

<sup>a</sup>Emission spectroscopy unless otherwise indicated; wet tissue.

<sup>b</sup>Sex not specified.

<sup>d</sup>Men and women.

<sup>e</sup>Women.

<sup>f</sup>Men.

<sup>h</sup>Female and/or male children.

<sup>c</sup>Dry tissue.

<sup>f</sup>Ash.

<sup>i</sup>Colorimetry.

<sup>j</sup>Whole blood.

Blood Al has also been observed to increase in pregnant women throughout normal pregnancy (311-313). These changes have also been demonstrated in gravid dogs (314) and cows (315). However, in early toxicosis blood Al was markedly increased while late toxicosis was associated with a severe decrease (316, 317) in mothers and infants. Similar changes were observed in placental blood in toxicosis and other disease states associated with pregnancy (318).

Lifshits (319) was able to distinguish leukemia from leukemoid reactions on the basis of change in whole blood Al concentration. In the period of exacerbation of chronic leukemia and in the developed phase of acute leukemia, the concentration of Al was elevated. The most marked changes in concentration were related to the increases associated with the formed elements of the blood which did not occur in leukemoid reactions. In Hodgkins disease (290), serum Al was elevated. The concentration of Al in blood and tissue of patients with a variety of neoplasms (320, 321) has been demonstrated to be different from control subjects. Some neoplastic tissues had elevated Al levels while others had depressed levels. This suggested that Al did not cause neoplastic growth. The effect of therapy on blood Al

levels in these diseases is unknown. Studies of the effects of alkylating drugs on the Al concentration in blood of rabbits demonstrated that its content in the plasma and erythrocytes was markedly elevated with both mannomustine, a cytotoxic cyclic nitrogen mustard, and triethylenethiophosphoramidate, another cyclic alkylating agent (322).

Blood disorders in animals have been studied with regard to altered trace element metabolism. Cattle with leukosis were observed (323) to have gradually decreasing serum Al levels as the disease progressed. Cows with lymphoreticulosis had blood Al levels twice as high as healthy cows (324). The serum of sick cows contained three times as much Al as did that of normal cows. This suggested that in this disease state, the freer serum form of Al increased more than the form associated with the cellular elements of blood.

Various brain and nerve related disorders have been studied with regard to changes in trace metal content of the blood. Organic nerve damage (325) viral neuroinfections, pain syndromes of different origin (326) and syringomyelia (327) have all been demonstrated to be associated with a fall in blood Al while blood Al values increase in encephalitis (328). With the first three of these, there

**Table 10. Geographic variation of the median aluminum concentrations found in tissues obtained from adult males (ages 20–59)<sup>a</sup>**

Tissue	Al, $\mu\text{g/g}$ ash			
	United States	Africa	Near East	Far East
Aorta	28	840	1000	450
Brain	16	110	190	63
Heart	20	250	190	180
Kidney	25	250	340	140
Liver	37	170	140	130
Lung	1800	3100	3100	2500
Pancreas	24	150	290	140
Spleen	24	250	220	110
Testis	30	140	460	250

<sup>a</sup>Data obtained by Tipton et al. (299) with emission spectroscopy.

was a concomitant increase of Al in the cerebrospinal fluid (CSF). Brain tissues from abscesses and following cerebral vascular accidents were also observed to contain less Al than normal (329). However, brain and spinal cord trauma resulted in an increase of Al in both blood and CSF. An elevation in blood Al level has also been reported for senility (330).

Some aspects of cardiovascular diseases have also been studied with regard to changes in blood Al levels. With myocardial infarction (331) and coronary atherosclerosis (332) Al levels were markedly elevated, but decreased in angina pectoris (333). Blood Al levels in rabbits with experimental atherosclerosis could not be correlated with the disease state (334).

Blood Al levels have also been studied in gastrointestinal disorders. Over half of the patients with colonic stases (335) had elevated blood Al levels. However, 23% of the more severe cases had decreased Al levels as did patients with adenocarcinoma of the colon (320). The work of Soroka and Sabadash (336) with dogs suggested that the reflex nature of the intestinal tract may depend in part upon trace element metabolism. They demonstrated that an increase in Al concentration in the blood occurred following stimulation of the large colon and the magnitude of the change depended upon the duration of the stimulus. Gastric ulcers (337), gastrogenic iron deficiency

and pernicious anemias were also associated with a general lowering of blood Al. However, in cases of stomach carcinoma the blood Al contents were elevated (338).

Adults with acute kidney disease (339) and children with acute and chronic nephritis (340) all had markedly increased blood Al levels. With acute disease, the male children had higher levels than the females, but this was reversed in the chronic disease state. Interestingly, in chronic renal failure,  $\text{Al}(\text{OH})_3$  is the agent of choice for the prophylaxis of hyperphosphatemia (341, 346).

Patients with infectious hepatitis (347), cirrhosis of the liver, malignant liver neoplasia and chronic hepatocholangitis (290) also had elevated blood Al levels. However, in cholelithic disease and in cancer of the biliary tract a decrease in blood Al concentration has been reported (385).

Pulmonary diseases as studied by several authors have also been distinguished on the basis of blood Al level changes. The Al level in blood or serum of individuals with berylliosis (291), massive pulmonary infarction (331), pneumonia and diffuse fibrosis (349) was elevated. However patients with bronchogenic carcinoma had depressed levels.

Studies regarding diseases associated with pancreatic disorders (350, 351) have demonstrated that in patients with diabetes mellitus the whole blood content of Al was less than in

normal individuals. The reduction was dependent in all cases on the severity and duration of the disease. Patients with chronic liver and bile duct involvement showed increased plasma bilirubin and Al concentrations in whole blood and plasma (352). However, the concentration of Al in the formed elements was below normal. These data suggested that the elevated plasma Al concentration in cases of diabetes with liver involvement was due to the lack of excretory activity of the liver and bile ducts. Change in the concentration of Al in the blood of diabetics was to a certain degree influenced by its migration from cellular content into plasma (351). The observed decrease in blood Al without liver involvement was attributed to a loss of cellular Al in the urine and bile. Improvement in the condition of the patients with treatment was accompanied by a normalization of the Al content in the blood.

In patients with cystic fibrosis, the sweat, urine, duodenal fluid, teeth, finger and toe nails as well as hair, in addition to plasma and serum, contained higher concentrations of Al than normal (353).

Changes in Al content of the blood were studied in numerous skin diseases: lichen planus, lupus erythematosus, cutaneous tuberculosis, eczema (354, 355), infectious eczema (356), bullous pemphigoid, subcorneum pustulosis, benign familial pemphigus (357), psoriasis (358), lepromatous leprosy (359). Generally, Al was below normal, except in the case of psoriasis, where it was higher than normal. In most cases there was either partial or complete restoration to normal levels after therapy. In the case of lepromatous leprosy patients, a direct correlation was found between the decrease in blood, and increase in urine Al concentrations with increasing severity of disease, (360). This led the authors to suggest that these decreases were associated with the migration of Al and other metals from the blood into the infection foci for participation in proliferative processes.

**Bone:** A relatively small number of studies have been undertaken concerning the Al content in bone and the role it plays with regard to bone metabolism. Bone regeneration in fractured frog and pigeon femurs as well as rabbit autografts have been studied with regard to changes in bone Al concentration (361–364).

Al accumulated during early regeneration in the cortical callus of the fracture zones and autografts and in some instances increased up to seven times the control concentration, before returning to normal levels at the end of the repair period. It was also reported that the Al concentration decreased in the opposite uninjured bone depending upon the degree of damage to the fracture zone. The extremities beyond the fracture and the uninjured portions of the bone participated actively in these metabolic processes of bone repair.

Subsequently it was demonstrated that the content of Al in an immobilized rabbit femur increased considerably during the first days of immobilization and fluctuated in the remaining time up to the 360th day (365). During this period, the contents of Al in the humerus and femur of nonimmobilized limbs fluctuated in the same manner but the fluctuation was less pronounced in the humerus. The fact that these changes occurred in bones of limbs that had not been immobilized suggested that immobilization of one limb resulted in mobilization of Al in bone tissue of the entire skeleton.

The increase in bone Al level associated with vitamin deficiency-induced rickets in the rat has been reversed by supplementation with vitamin D (366, 367).

Synovial fluid from rheumatoid arthritis patients has been observed to contain more Al than normal while the serum content decreased (368–371). However, in infectious nonspecific polyarthritis the serum level increased 2-fold.

**Cardiovascular Tissue:** Very little work has been done concerning Al and its role in the metabolism of cardiac tissue. Sauer et al. (372) reported a negative correlation between the Al content in drinking water and the number of deaths due to human myocardial and coronary heart disease. Biochemical studies have demonstrated that Al has a specific activating effect on the myocardial succinate oxidase system (373). Activation was only observed in nicotinamide adenine dinucleotide (NAD) requiring succinate systems containing cytochrome c (374).

In an analysis of the ash from the aorta, calcified plaques, and sclerotic aorta without calcification, obtained from elderly individuals, Berki (375) found the concentration of

Al to be much greater than in the aortic tissue from younger individuals. Popov (376) observed that the ignition residue and Al concentration increased in the aorta with age, but that after age 60, the Al content in this tissue declined abruptly. The hearts of guinea pigs with pericarditis were also shown to have elevated Al levels (377).

**Eye:** The concentration of Al in the eye has been found to decrease according to phylogenetic order, the lowest being obtained for humans and the highest for fish (378). Al in the optic nerve of men and women, obtained following accidental death, was less than in blood and decreased with age (379, 380). However, Al in the lens tissue from rats has been observed to increase with age (381).

**Hair:** The concentration of Al in hair has been used to evaluate the effect of geochemical environment on human and animal metabolism (382). Variation due to geochemical environment may be responsible for the different concentrations of Al in hair reported in Table 9. However, hair Al levels found (383) in two groups of boys from different geographic locations were thought not to differ significantly in spite of a difference in concentration of this element in the soils and in wool from twin wethers pastured in the two locations (384).

Hair and feathers of several domestic animals have been studied with regard to their Al contents (385). Horses reared on a mineral-poor pasture had slightly lower levels of hoof Al than were found in the hoofs of horses reared on pastures with adequate mineral content (386). However, analysis of the hair from both groups demonstrated that the Al concentration was lower for horses on a nutritionally adequate pasture with a similar content of Al. It was pointed out that there was a seasonal variation in hair mineral content, and the highest level of Al was observed in the winter.

**Kidney:** The metabolism of Al in the kidney in health and in disease states has been studied in detail. The most recent data on normal kidney Al content from individuals living in different geographic areas are presented in Tables 7-10. A direct correlation has been found for Al in the geochemical environ-

ment and in urinary calculi obtained from humans (387, 388) but no correlation was found for x-ray transparency of the stones (389).

Significant increases in kidney Al concentrations in two types of human kidney diseases, lipid nephrosis and tuberculoma, have been reported (390). An increase in kidney Al may also be a reflection of an increase of Al in the blood and urine of patients with kidney diseases. Patients with bladder tumors have been shown to have elevated urine Al levels (391).

A study of rabbits and humans from the same environment suggested that the normal kidney contents of Al were comparable (392). Al in kidney tissue of normal dogs has been demonstrated to be distributed between filterable and nonfilterable forms which were regulated autonomically (393, 394). A depletion of kidney Al has been observed in rats following exposure to high levels of dietary F (395).

An increase of urinary excretion of Al has been effected with kidney denervation (396), drugs which increase the cardiac output (397), diuretics (398-400), as well as ligation of the biliary duct, the usual predominant excretory route (401). Changes in urinary excretion of Al following administration of various chelates has also been studied in the normal animal (402).

**Larynx:** In male and female larynges, the highest content of Al was observed at birth, or between birth and the age of 4 mo (403). In adolescence, Al accumulation in the larynx manifested a periodicity which coincided with stages of rapid growth of laryngeal cartilage. In general the Al content remained essentially the same throughout adult life; however a pronounced rise was observed at age 65. In cases of laryngeal cartilage resorption, the content of Al decreased.

**Liver:** The livers from patients with iron storage associated with Bantu siderosis, hemochromatosis, and sickle cell anemia as well as in alcoholics with cirrhosis and early hemochromatosis have been shown to contain less Al than normal (404-406). This observation could be reproduced in rabbits and rats with the administration of iron.

Studies in young and adult cattle have demonstrated that liver Al content was related to the geographic location of their pastures

(407). Diurnal variation in liver content has been observed in rats, which appeared to be regulated autonomically (408). Similar studies in dogs have also suggested autonomic control of storage of Al in the liver and release into the blood as well as its excretion *via* the bile duct (409-413). Biochemical studies have failed to show an effect of Al on rat liver mitochondria and microsomes (414) as well as guinea pig liver mitochondria (415). However, excess dietary F has also been shown to depress the liver Al content (416).

**Lung:** The concentrations of Al normally found in lung tissue are the highest found in all adult tissues studied (Tables 7-10) and are, in part, the result of inhalation of Al-containing dusts which may accumulate with age (417, 418). In addition to this variation, sex and geochemical environment are important modifiers of normal lung Al content.

It has long been recognized that the risk of silicosis in miners is related to the silica content of the ore. The silica content of the lungs and more recently the lymph nodes (419) has been shown to be greater in silicotics than in unexposed individuals. A great deal of work has been done concerning the use of Al to prevent the toxic reactions in the lung associated with the inhalation of silicon dioxide-containing substances. Data concerning the use of Al compounds in the prophylaxis of silicosis are presented in the pharmacological section of this review. Since many toxicity studies have been done in this regard, a portion of the toxicology section has been devoted to this topic.

**Male Genital Tissue:** Al has been found in the prostate, seminal fluid, testicle and seminal vesicle of normal males as shown in Tables 7-10. Marked elevations of Al have been observed in hypertrophied and neoplastic prostate glands (330, 420).

**Milk:** The normal Al content of human milk has been compared to the content found in various metabolic and disease states. Al increases during gestation and in the lactation period. Individuals with hypogalactosia initially had high levels which fell to levels observed in nonpregnant women (421, 422) or lower (290). Milk from mothers with premature

deliveries also contained more Al than the milk from mothers who delivered at term (290, 423, 424).

In addition to human milk, Al has also been measured in the milk of animals. The ash contents of Al in the milk from humans and animals living in the same geographic area were as follows: human, 0.0157%; mare, 0.0209%; cow, 0.0276%; goat, 0.0320%; sheep, 0.0479% (425). The total ash and content of Al increased in the order in which the time required for doubling of birth weight of the species decreased. The Al levels were also observed to increase in cows with mastitis (426). Al in milk obtained from pregnant cows (315) ewes (427), and buffalo (428) was observed to change as reported above for humans and deviated from normal during gestation and lactation in various diseases.

**Muscles and Tendons:** A small amount of work has been done concerning Al metabolism in these two tissues. Rabbit leg immobilization which caused pronounced muscle and tendon atrophy was also associated with a decrease of Al in both tissues (429). Studies of the filterable and nonfilterable forms of Al in skeletal muscles of dogs anesthetized with ether and stimulated with caffeine demonstrated an increase in the filterable bound form in the excited state and an increase in the nonfilterable form in the depressed state (430). An unknown soluble phosphate containing Al, isolated from muscle, has been suggested to be an Al chelate of adenosine diphosphate (ADP) (431).

**Nerve Tissue:** In addition to adult brain data provided by Tipton (297, 299) (Tables 7, 9, and 10) and others (432-438), measurable concentrations of Al in brain tissue of the human embryo have been reported, which gradually increased during gestation and reached the highest level in the newborn (308). These data offer evidence that Al may be essential with regard to brain tissue development and activity. This conclusion was supported by the observations in dogs (304, 439-442) that the diurnal variations in brain and CSF concentrations of Al were regulated by the autonomic nervous system. Al was released from the brain in excitation and accumulated with depression of central nervous system (CNS) activity. Studies have been done which demonstrated

that the decrease in free and bound forms of brain Al in excitation was associated with a marked depression of the free form (443). Conversely, in narcosis, both free and bound forms increased in brain tissue but the increase in the free form was greater. Other physiological studies suggest that Al may be associated with nerve conduction (444) and transmission (445). Studies of both acetylcholinesterase and cholinesterase have demonstrated an activation effect of Al (446).

Studies of brain neoplastic tissue have demonstrated an increase in Al content (329). Extraction of malignant brain and neural tissue as well as benign neural neoplasms removed an Al metalloprotein complex which was different from complexes obtained from normal tissue, although the cholinergic and adrenergic nerve tumor tissue contained less Al (447).

In dogs with experimental allergic encephalomyelitis (448) the concentration of Al in the grey matter and white matter of the brain as well as the spinal cord increased above controls. With the disappearance of the clinical symptoms, the concentration of Al decreased in these areas.

Very recently Crapper, Krishnan, and Dalton (449) reported that very high levels of Al, 9–11  $\mu\text{g/g}$  (dry weight), were found in brain tissue from patients who had Alzheimer's disease. Their age-matched controls had levels of 0.23–0.40  $\mu\text{g/g}$  (dry weight). This observation along with an earlier observation (330) that senility was associated with high blood ash Al levels, 5450  $\mu\text{g/g}$ , may be of etiological significance.

**Pancreas:** In addition to the normal human pancreas content of Al reported in Tables 7–10 which shows a geographic variation, marked differences in Al content of the pancreas of young and adult cattle have been related to the same variation (407). The Al content of pancreatic juice collected from healthy individuals has been studied with regard to amylase, trypsin, and lipase activities (450). Patients with increased pancreatic activity associated with chronic pancreatitis and cholangiohepatitis had higher levels of Al.

*In vitro* studies of dialysis-inactivated crystal-

line trypsin demonstrated a 70% activation with the addition of Al (451). However, addition of  $\text{Al}_2(\text{SO}_4)_3$  to human, pig, rat, and dog amylases was inhibitory. This excess Al-induced inhibition could be prevented by the addition of albumin (452).

**Skin:** High Al concentrations have been found in the skin of the human embryo. This interesting finding may be additional evidence which supports the view that Al is an essential metal. Its concentration although somewhat less was relatively constant during maturity and old age (453). Caution must be observed in interpreting the results of post mortem skin Al determinations, since it has been reported that the Al content of the skin increases up to 18–24 hr after death (454).

Fingernail clippings from 17 normal male and female donors, with ages ranging from 1 mo to 55 yr, have been analyzed for Al with spark source mass spectrometry (455). In this survey of trace elements, the Al values found in fingernails were very high compared to the values found in hair.

**Spleen:** The concentration of Al in the blood flowing from the spleen has also been demonstrated to be regulated by the autonomic nervous system (456). Stimulation of the CNS in dogs caused a decrease in spleen Al with an increase of this metal in venous blood, while narcosis brought about a decrease in blood with an increase in the spleen.

**Tooth:** Al metabolism associated with the development, growth and prevention of dental cavities has received considerable attention. It is generally accepted that Al is a normal constituent of first and adult teeth (457, 458) which fluctuates in the various anatomical portions of the tooth with age (459, 460). Discolored areas of sound teeth have been observed to contain markedly elevated concentrations of both Al and F. Human dental calculus has also been shown to contain high concentrations of Al (461) which have been shown to inhibit alkaline phosphatase (462) and alkaline phosphomonoesterase (463) from human dental plaque. Studies of caries-free, carious, and impacted human teeth have demonstrated that the caries-free teeth



contain more or less Al than diseased teeth, depending upon the anatomical part studied and the stage of the disease (464–466).

There is a basic recognition of geographic variation and caries incidence (467). Studies of geochemical differences and caries incidence have suggested that elevated Al contents of the soil, drinking water, and vegetables were associated with low caries incidence (468, 469). Food or water supplemented with Al and F were cariostatic when given to rats during the period of enamel mineralization (470, 471). Rats on a cariogenic diet had teeth with decreased dissolution rates following topical application of Al and F in combination (472). However, Al alone produced no difference in caries scores between supplemented and unsupplemented animals (472–474).

**Uterus:** Uterine washings from rats, rabbits, and sheep obtained at estrus and in the midluteal phase contained significantly different concentrations of Al (475). In rats and rabbits, estrus phase washings contained a higher concentration of Al; however sheep had much higher concentrations of Al in the uterine washings obtained during the luteal phase.

## Toxicology of Aluminum and Its Compounds

**Acute Toxicity Studies:** Mortality studies with aqueous solutions of  $\text{Al}_2(\text{SO}_4)_3$  given intraperitoneally (IP) (476) and orally (IG) (477, 478) to mice have generated  $\text{LD}_{50}$  values of 0.14 g/kg IP and 6.2 g/kg IG. An  $\text{LD}_{50}$  for  $\text{AlCl}_3$  following oral administration was 3.85 g/kg in mice (478). Acute poisoning with  $\text{AlCl}_3$  caused an increase in the rate of  $^{32}\text{P}$  incorporation in the liver (479), decreased liver glycogen, and increased blood glucose in rats (480).

The intraperitoneal  $\text{LD}_{50}$  for  $\text{Al}(\text{NO}_3)_3 \cdot 9\text{H}_2\text{O}$  was reported to be 0.32 g/kg in male  $\text{PBF}_1$  mice and 0.33 g/kg in female Sprague-Dawley rats (481, 482). The oral  $\text{LD}_{50}$  in rats has been reported to be 0.26 g/kg (176). However, an earlier cited unpublished observation indicated that the acute toxicity was much less, 4.28 g/kg, by the oral route (483). The spread in the oral  $\text{LD}_{50}$  values may be due to the unwillingness of the mice to drink the water containing  $\text{Al}_2(\text{SO}_4)_3$ , and  $\text{Al}(\text{NO}_3)_3$  as has been observed

with  $\text{AlCl}_3$  in rats (342). An important contribution has been the report of the Al content of various tissues obtained from guinea pigs following  $\text{LD}_{50}$  determinations (484).

The most acutely toxic Al-containing compound was Al phosphide, which has an inhalation  $\text{LD}_{50}$  of 1 mg/l in the rat (477). Death associated with use of this grain weevil fumigant has been attributed to the release of phosphine (485, 486). Animal feeding studies with grain fumigated with this material demonstrated no residual toxicity once the phosphine had been lost (487).

**Chronic Toxicity Studies:** Mice fed a daily dose of 100 mg  $\text{AlCl}_3/\text{kg}$  for 6–12 mo showed no changes in growth or reproduction in the first generation (478). However, growth retardation occurred in four subsequent generations. A daily 200 mg/kg dose of  $\text{AlCl}_3$  brought about an increased fecal excretion but did not cause an accumulation of Al in various tissues. This increased fecal elimination accommodated a slight increase in Al intake but larger Al intakes resulted in increased absorption and retention (488). The most pronounced accumulations of Al were observed in the liver, testes, and bone.

Rats fed a diet with a low P/Al ratio brought about by the addition of  $\text{AlCl}_3$  had a positive Al balance with accumulation in the liver, brain, and bones but this did not affect the Ca and P levels in bone (489, 490). Studies of EDTA-chelated Al suggested that the reason for skeletal deposition of Al may lie in its stability as phosphate complexes (402, 491).

Doses greater than 150 mg of  $\text{AlCl}_3/\text{kg}/\text{day}$  given IG brought about a negative P balance, decreased incorporation of  $^{32}\text{P}$  into phospholipids and nucleic acids of liver, kidney, and spleen, as well as a drop of the adenosine triphosphate (ATP) level with a rise of the ADP level in blood. The above disorders of P metabolism were less marked in rats receiving a high Ca diet (492).

Rats fed 1 g of  $\text{AlCl}_3/\text{kg}/\text{day}$  for 18 days had decreased liver glycogen and coenzyme A levels but increased muscle and liver pyruvate levels (493). Chronic intoxication with  $\text{AlCl}_3$  has also been shown to decrease serum glucose, muscle glycogen, and ATP with an increase

in adenosine monophosphate (AMP) and ADP levels (480). The significance of reports that large oral doses of up to 150 g of  $\text{AlCl}_3/\text{kg}$  failed to produce signs of toxicity (494) are doubtful, since it has recently been suggested that rats given water containing 10 g  $\text{AlCl}_3/\text{l}$  failed to drink the water and died of dehydration (342).

Inhibitions of glycolysis and phosphorylation have been suggested as the most significant toxic reactions to Al-containing compounds (495). Enzymatic conversion of isocitric acid to  $\alpha$ -ketoglutarate in the presence of nicotinamide adenine dinucleotide phosphate (NADP) was inhibited in a dose response manner by Al (496). On the other hand, the rate of enzymatic decarboxylation of pyruvic acid could be increased with Al (497). A study of the Al inhibition of yeast and guinea pig hexokinase has pointed out that this Mg-dependent phosphorylating enzyme was most easily inhibited when Mg was present in suboptimal levels (276). A competing complexation reaction between ATP and Al was suggested as the mechanism, which was observable with rate-limiting concentrations of Mg. Possibly all phosphate-transferring systems involving ATP and Mg may be biological targets for excess Al.

In other *in vitro* studies, the aluminosilicate clay, bentonite, has been demonstrated to complex with the free purines and pyrimidines obtained as breakdown products of ribonucleic acid (RNA), deoxyribonucleic acid (DNA), ATP, ADP, and AMP (498, 499). This clay has also been shown to complex with and inhibit nucleoside phosphotransferases (499) and RNAase (500).

The toxicities of bentonite, kaolin,  $\text{Al}_2(\text{SO}_4)_3$ ,  $\text{Al}_2\text{O}_3$ , and  $\text{Al}(\text{OH})_3$  have been studied with rabbits (501), chickens (502), sheep (503,504), cows (505), and hogs (506) with regard to their use as feed additives. In general, beneficial effects such as growth stimulation without adverse effects on Ca and P metabolism were observed with low levels, 1–2% of the diet, of these Al compounds. Higher levels in the feed decreased growth, caused muscle weakness and death with marked disturbances of Ca and P metabolism. Similar studies with large amounts of  $\text{Al}(\text{OH})_3$  and  $\text{Al}_2\text{O}_3$  in chickens (507,508) and rats (342) demonstrated that these compounds were able to affect adversely Ca and P

metabolism and to cause impaired growth with the production of rachitic bone changes (344, 345). Associated with these changes was an increase in bone Al levels.

Recently, the use of  $\text{Al}(\text{OH})_3$  in the prophylaxis of hyperphosphatemia has been questioned because of toxicity reported by Berlyne et al. (509,510). The toxicity seen in uremic rats (5/6 nephrectomy) given subcutaneous (SC) injections or drinking water containing 10 g  $\text{AlCl}_3/\text{l}$ , drinking water containing 10 or 20 g  $\text{Al}_2(\text{SO}_4)_3/\text{l}$ , or 1.98 g of  $\text{Al}_2(\text{SO}_4)_3/\text{kg}/\text{day}$  given IP were periorbital bleeding, lethargy, anorexia, and death. An attempt to reproduce these or toxic manifestations in rats with chronic renal failure (7/8 nephrectomy) demonstrated that  $\text{Al}(\text{OH})_3$  administration leads to increased deposition of Al in bone, impaired growth, and rachitic bone changes in normal rats according to Thurston et al. (344). This effect could be corrected by phosphate supplements. In contrast, no impairment of growth was produced by  $\text{Al}(\text{OH})_3$  in hyperphosphatemic uremic rats, and no other previously reported pathological abnormalities (509,510) could be demonstrated. It was pointed out that patients with chronic renal failure treated with  $\text{Al}(\text{OH})_3$  for prolonged periods had bone Al levels similar to those in uremic rats. The conclusion was that, although Al was deposited in the bone in chronic renal failure,  $\text{Al}(\text{OH})_3$  was nontoxic if hypophosphatemia was avoided.

Death in rats which had been reported following IP injection of  $\text{Al}(\text{OH})_3$  was suggested to have been the result of peritonitis by both Bailey (342) and Verberckmoes (346). This was consistent with the earlier findings of Kay and Thornton (511) following the injection of  $\text{Al}(\text{OH})_3$  in mice. The anorexia reported earlier was consistent with the recent observation that uremic rats given  $\text{AlCl}_3$  in their drinking water did not drink the water and died of severe dehydration (342). Lethargy would be expected with peritonitis or dehydration. The periorbital bleeding could not be independently reproduced by Thurston et al. (344,345), and they suggested it was the result of a possible local infection. Failure to confirm the originally reported toxicity (509,510) suggested that elimination of  $\text{Al}(\text{OH})_3$  from therapeutic use in the treatment of renal

disease was unwarranted, according to Bailey et al. (341), Sherrard (343), and Thurston et al. (344,345).

Regular ingestion of 5.5 mg of Al/kg of body weight in food and drink by humans has been suggested to cause no adverse effects because the Al was present in the less toxic colloidal form (288). This is inconsistent with the observation that the daily intake of more than 3 mg of Al/kg of body weight has been found to increase fecal elimination of phosphate with a concomitant decrease in urinary excretion (1). Maximum drinking water levels of the soluble  $\text{AlCl}_3$ ,  $\text{AlF}_3$  (175), and  $\text{Al}(\text{NO}_3)_3$  (176) were recommended on the basis of animal experiments to be 4 mg, 2.2 mg, and 0.1 mg/l., respectively, in the latter case to avoid an effect on the palatability of water. In studies of  $\text{Al}(\text{NO}_3)_3$ , the effect of this form of nitrate was determined by measuring reduced working capacity and duration of narcotic reflex inhibition in rabbits, with daily oral doses of 0.1, 1, and 10 mg/kg for 6 mo. The working capacity of the rabbits and their oxygen uptake was significantly affected only by the 10 mg/kg dose. Rabbits treated with  $\text{Al}(\text{NO}_3)_3$  at 0.1 and 1 and 10 mg/kg did not exhibit any narcotic effect.

The adjuvant activities of alum (potassium aluminum sulfate) and  $\text{Al}(\text{OH})_3$  have been investigated in guinea pigs and rabbits (512, 513). Following SC injection of antigenic proteins mixed with the Al compounds, there was an increase in antibody production. Separate SC injections of antigen and Al compounds at separate injection sites or  $\text{Al}(\text{OH})_3$  alone failed to produce the same increase in antibody synthesis. Subcutaneous injections of an Al anode material, used for biogalvanic elements as pacemaker energy sources, and  $\text{Al}_2\text{O}_3$  also failed to cause an immune response (514).

It has been noted that the Al contents of the spleen and bone marrow increase during immunization without the metal adjuvants suggesting a possible role for Al in the immune response (512). This observation was consistent with the gradual increase of Al in blood plasma of rats following SC injection of various tissue homogenates. These homoantigens caused a gradual increase in Al which reached its high-

est level 3–6 days after transplantation (515).

It has been shown that the blood Al levels in 30 of 36 workers in a factory exposed to  $\text{Al}_2\text{O}_3$  dust were two to three times the level of the controls (516). Serum intestinal alkaline phosphatase, acid phosphatase, as well as ATP levels were significantly reduced. A number of consistent observations have been made with regard to the *in vitro* effects of Al-containing compounds in blood or serum. An antithrombotic effect has been observed with alum (517) and kaolin. In addition, other aluminosilicates have been shown to be either fibrinolytic (518, 519) or hemolytic (520–523).

Aluminum-induced changes in the physical properties of components or chemicals similar to those found in blood have also been studied. The viscosity of transfusion gelatin has been shown to increase with the addition of large amounts of  $\text{Al}_2\text{O}_3$  and  $\text{AlCl}_3$  (524). Similarly, a pectinic mucopolysaccharide was studied with regard to coagulation following the addition of ionic Al (525). Recently, an unexpected Al contaminant-induced agglutination of RBCs was described, in attempts to label them with technetium generator eluates (526–528). Finally, ferrioxidase (ceruloplasmin), a serum enzyme required for hematopoiesis, has been suggested to undergo a conformational change with the addition of solutions of  $\text{Al}_2\text{SO}_4$  (529). These *in vitro* results are not intended to imply imminent danger associated with the exposure of blood to Al but rather some type-reactions of Al and blood components.

**Carcinogenicity Studies:** Animal studies have failed to demonstrate carcinogenicity attributable to Al metal powder,  $\text{Al}(\text{OH})_3$ ,  $\text{Al}_2\text{O}_3$  or  $\text{AlPO}_4$  administered by various routes to rats, rabbits, mice and guinea pigs (530–532). Sarcomas have been reported in a single rat study following subcutaneous implantation of Al foil (533). Although it is known that Fe-dextran has been used to facilitate carcinogenesis, attempts to establish that Al-dextran was carcinogenic have also been unsuccessful (530) and results even suggested an anti-tumor effect (534). The induction of a complex nutritional deficiency in mice with the addition of bentonite clay to semi-purified rations has been demonstrated to result in the development

of hepatomas in a manner similar to that reported for rats maintained on low protein, low choline rations (535).

**Tissue-Specific Toxicity Studies:** Tissue-specific toxicity studies are presented according to tissue type.

**EYE:** The effects of Al particles implanted in the vitreous of the rabbit eye were studied by using graphic and ophthalmological methods (536). Implantation resulted in the slow reduction of the electric potential in the retina following stimulation by light. Ophthalmologically, only slight toxicological changes were noted. A thin coating on some of the particles was observed following completion of the experiment.

**LUNG:** Industrial exposure to high concentrations of Al-containing airborne dusts have resulted in the production of a number of pneumoconioses. Acute exposures to insoluble Al compounds are relatively harmless compared to soluble compounds (274,537). Chronic exposures to Al-containing compounds associated with the production of  $Al_2O_3$ , as well as stearin and mineral oil-coated Al metal, have resulted in pulmonary disease (274,537-543). An asthma-like disease has also been reported in workers engaged in the production of Al from its oxide (544). Probably, this asthma-like condition was caused by HF evolved from the use of F-bearing materials in the production of metallic Al.

Silicosis, aluminosis (538), aluminum lung (537), bauxite pneumoconiosis (540) are the results of pulmonary fibrotic reactions to silica and Al-containing compounds observed in lung tissue of humans. The effects of Al and silica on animal lungs have been the topic of a great deal of experimental research. Mice, rats, hamsters, guinea pigs, and dogs have been used to study the pulmonary effects of Al-containing compounds, following administration by IP, intratracheal (IT), and inhalation (IH) routes. This section has been divided into three parts depending on the route of administration. The IP route has generally been used to study fibrosis associated with these substances. Intratracheal studies are discussed separately because the significance of the results has recently been questioned (545). On the other hand, adminis-

tration by the IH route appears to be the most acceptable because of its similarity to normal exposure.

**Intraperitoneal Studies:** The rat peritoneal test has been used to study fibrosis induced by various forms of  $SiO_2$ , including kaoline (aluminosilicates) (546-548) and mica (546), quartz ( $SiO_2$ ) (546, 547, 549), cristobalite ( $SiO_2$ ), and beryl ( $3 BeO \cdot Al_2O_3 \cdot 6SiO_2$ ) (547). The most effective inducers of fibrosis were those materials that contained the most  $SiO_2$ . Various Al compounds such as  $Al_2O_3$  (550), Al metal (547,551) and McIntyre powder, 15% metallic Al and 85%  $Al_2O_3$  (552), which do not contain any  $SiO_2$  have also been studied with this test. It was found that these compounds failed to induce fibrosis when amounts equivalent to the fibrogenic  $SiO_2$ -containing materials were injected. When much larger amounts of  $Al_2O_3$  were injected, massive accumulation of collagen resulted in only 5 of 30 mice but not in rats (558). This indicates that  $Al_2O_3$  is far less fibrogenic than the various forms of  $SiO_2$  and silicates.

An immunological mechanism for the quartz-induced fibrotic response has been proposed (553). Protein bound to the quartz particles may become antigenic with the concomitant change in configuration of the bound protein. Subsequently, it was demonstrated that there was a differential connective tissue cellular reaction to uncoated and protein-coated quartz particles (554).

**Inhalation Studies:** In 1952, Serafimov (555) induced experimental silicosis in mice and rabbits placed in IH chambers with atmospheres containing mixtures of  $SiO_2$  and  $Al_2O_3$ . He reported objective symptoms after 3-4 wk, when animals became less mobile, lost weight, and developed alopecia. Gross anatomical and histological changes were also described. In the CNS of the experimental animals varying degrees of change were observed. Gliosis and changes in the vascular network were described. With inhalation of  $SiO_2-Al_2O_3$  mixtures, pseudo-granulomas were observed in the lung, liver, brain, and spinal cord. These granulomas were attributed to the  $SiO_2$ . In light of the recent evidence concerning the effects of Al in the brain

and spinal cord of animals, some of these effects could have been due to the  $\text{Al}_2\text{O}_3$  in the mixture.

Studies of pneumoconioses associated with the inhalation of  $\text{Al}_2\text{O}_3$ ,  $\text{AlPO}_4$ , and condensed corundum furnace fume (1:1  $\text{Al}_2\text{O}_3$  and  $\text{SiO}_2$ ) by rats suggested that  $\text{Al}_2\text{O}_3$  was the most fibrogenic (556). An emphysematous change has been observed in rabbits and rats, similar to that seen in humans following prolonged IH exposure to an industrial dust containing  $\text{Al}_2\text{O}_3$  and  $\text{SiO}_2$  (557). Inhalation studies (558, 559) with mice and rats suggested that  $\gamma\text{-Al}_2\text{O}_3$  may be the causative agent in Corundum Smelters' lung or Shaver's disease but greater significance was attached to the concentration of amorphous  $\text{SiO}_2$  with regard to the etiology of these diseases.

The results of IH studies of Al metal fume and large amounts of powder (20% Al metal and 80%  $\text{Al}_2\text{O}_3$ ) by rats and hamsters (560) demonstrated that pulmonary pathology could be observed in rats but not in hamsters. However, in an intratracheal study of Al metal (545), it was demonstrated that pulmonary fibrosis and other pathologic changes were produced in rats that were not seen in hamsters or guinea pigs.

The physiological responses of the lung exposed to Al metal and  $\text{Al}_2\text{O}_3$  have also been studied in some detail (561-565). It was initially demonstrated that pleural fluid transfer to the lymphatic system increased following Al dust exposure in dogs. This effect could be increased with a bronchoconstrictor or eliminated with a bronchodilator. Pressure-volume measurements with the aid of various autonomic mediators and inhibitors suggested that the guinea pig lung responses were more like that of the human than the responses observed in rats.

Biochemical studies of the effects of  $\text{Al}_2\text{O}_3$  on degranulation of rat mesenteric mast cells demonstrated an increase with decreasing pH and particle size. Glucose utilization, required for degranulation, was unaffected by  $\text{Al}_2\text{O}_3$  (566).

Inhalation studies with  $\text{Al}_2\text{O}_3$ , bauxite and Al silicates such as kaolin (125, 548, 559, 567) and bentonite (548, 568) in rats demonstrated decreased fibrogenicity and increased rate of elimination of these compounds compared to the other Al-containing compounds. Calcined kaolin was somewhat more fibrogenic than kaolin while there was no fibrogenic response to the concentration of bentonite used. Studies of the elimi-

nation of adsorbed metals and retention of these aluminosilicates have been done in mice, rats, and dogs following inhalation (569, 570).

**Intratracheal Studies:** In addition to the IP and IH studies, there have been many papers concerned with studies of various  $\text{SiO}_2$ -containing ores and Al-containing substances using IT instillation. Intratracheal administration of dusts is a useful technique for the study of pulmonary effects of small amounts of material. However, injections into the trachea have been criticized as being non-physiological exposure and reported to cause artifactual pathological tissue changes (545). Since it is a distinctly different technique and useful when only small quantities are available to study pulmonary effects, the information obtained with it has been included in this section of the Al studies concerning the lung.

With this technique a number of natural aluminosilicates, kaolin, feldspar, mica, and loess (548, 567, 571, 572) were shown to produce little fibrotic or macrophage proliferative change in rats. However, combination with  $\text{SiO}_2$  did bring about experimental silicosis. It was unclear as to how much of the fibrotic change was due to silicosis following treatment with the silicates. Intratracheal administration of very large amounts of powdered metallic Al (573) and a mixture of 15% metallic Al and 85%  $\text{Al}_2\text{O}_3$  (552) produced a fibrotic change somewhat similar to that seen with smaller amounts of quartz. However, smaller amounts of Al did inhibit the quartz-induced fibrotic response. Intratracheal injection of hydrated  $\text{Al}_2\text{O}_3$  alone into rats, mice, guinea pigs, and rabbits demonstrated that the amount of fibrosis was species dependent (638). Rats, as was pointed out earlier, uniquely developed numerous dense nodules of advanced pulmonary fibrosis. Mice and guinea pigs developed a reticular network with occasional collagen fibers while rabbits showed a slight reticular response.

Alveolar macrophages have been considered as cells of central significance in the development of silicotic granulomas. Phagocytosis of  $\text{SiO}_2$  particles has been demonstrated in cell culture (574, 575). The damaging effect of  $\text{SiO}_2$  on macrophages has been compared favorably with the degree of fibrogenesis seen in animals

(575, 576). Interestingly, it was suggested that the toxicity was not related to the surface area of the particles, but to the number of particles per cell. Al-containing dusts and compounds were only slightly toxic or inert as compared to  $\text{SiO}_2$ . The general concordance of whole animal and macrophage toxicity supported the hypothesis that the primary dust lesion in animals stems from macrophage injury.

*In vitro* studies of metallic Al coated with  $\text{Al}_2\text{O}_3$ , stearin, or mineral oil demonstrated that mineral oil-coated particles, in the presence of water, were the most reactive in the production of hydrogen;  $2\text{Al} + 6\text{H}_2\text{O} \rightarrow 3\text{H}_2 + 2\text{Al}(\text{OH})_3$  (577). However, IT injection of acetone-washed (uncoated), stearin-, and mineral oil-coated Al powders were equally fibrogenic in rats.  $\text{Al}_2\text{O}_3$  was not fibrogenic (578). The lack of pathogenic difference between washed stearin- and mineral oil-coated stamped powders suggested that the action of pulmonary fluids or cells may be able to remove either coating on contact. It has also been suggested that pathological artifacts are associated with IT injections in rats but not hamsters (545). Pulmonary lesions observed in rats but not hamsters after IT injection of Al metal powders were not only dependent on the artifact of IT injection, but also upon the attainment of critically high doses.

The effect of metallic Al and  $\text{Al}(\text{OH})_3$  on pulmonary clearance has also been studied following IT injection (579). A uranium dose was cleared from treated lungs more rapidly than from controls following treatment with  $\text{Al}(\text{OH})_3$  and metallic Al. The  $\text{Al}(\text{OH})_3$  stimulated clearance to a greater degree than metallic Al.

The fibrogenic actions of several hydroxides, oxides, and phosphates of Al following IT administration (580) to rats were similar to those observed following IH administration as cited earlier. There was a positive correlation for  $\text{Al}_2\text{O}_3$  and  $\text{Al}(\text{OH})_3$  with solubility and fibrogenic activity. However, the Al phosphates were more fibrogenic than their solubility suggested. Pulmonary effects in rats of mixtures of  $\text{Al}_2\text{O}_3$  and bauxite with lime, boron carbide (581) or alloy welding dust (582) as well as various alloys of Al: Fe-Al-Be (583), Be-Al (584, 585) and Si-Al (586) have also been studied following IT instillation. All of the mixtures were more toxic than  $\text{Al}_2\text{O}_3$  (550) or bauxite, and the

alloys were generally less toxic than the pure component metals with the exception of Si-Al. Pulmonary lesions in rats following IT injection of coal particles containing Al were more severe than expected based upon the Al content (587).

**SKIN:** The penetration Al salts into the dermal area of excised human skin (588) and depilated flanks of guinea pigs (589, 590) has been shown to be inhibited by the stratum corneum. Pathological changes associated with the administration of Al chlorohydroxide,  $\text{Al}_2(\text{SO}_4)_3$ , and Na Al lactate by the subcutaneous, intracutaneous, and percutaneous routes in rabbits were observed with the injections only (591). Single or multiple injections of Al-dextran into the subcutaneous tissues of rats or mice were found to lead to the formation of a local depot of Al-dextran, which was poorly absorbed and produced a small amount of fibrosis (592). A model of inflammation has been developed and studied involving SC injections of kaolin into the rat paw (593).

**TESTES:** Morphological changes in rat testes have been reported following endotracheal treatment with  $\text{Al}_2\text{O}_3$  (594) and intratesticular injection of 10.7 mg  $\text{AlCl}_3/\text{kg}$  of body weight (595). The lack of animal data relevant to the observations in humans suggest the need for additional studies.

***Metabolic and Toxicologic Effects of Aluminum in Lower Organisms:*** Lower forms of animal life, as well as insects and microorganisms, have also been studied with regard to Al contents, metabolism, and/or effects of Al.

**FISH:** A number of plankton-eating fish from the Black Sea were demonstrated to contain Al (596). Concentrations of Al were measured in tissues of calico bass reared on normal seawater and seawater obtained from the effluent pipe of a steam generator (597). Ventral and dorsal muscle, gonads, liver, integument, and heart all contained less Al when obtained from fish reared on normal seawater. Eyes of both groups contained the same amount of Al. The toxicity of fine Al precipitates were studied in Japanese killfish, goby and daphnia (598). It was established that Al in the pH range of 6.3–7.8 was not toxic to these aquatic animals. Toxicities of aqueous

Al complexes in rainbow trout fingerlings were also found to be highly pH-dependent (599). Concentrations exceeding 1.5  $\mu\text{g/ml}$  of Al caused anorexia, decreased activity, gill hyperplasia, and mortality. Suspended Al was not as toxic as soluble Al. A red sludge containing Al, discharged into the North Sea by a manufacturer of  $\text{Al}(\text{OH})_3$ , was tolerated to a lesser extent by fish than algae. A threshold value of 1 g sludge/l was proposed which was well tolerated by both organisms (600).

**MOLLUSKS:** Among the shellfish studied, mollusks were found to contain Al (601). Separate analysis of the calcitic and aragonitic parts of single shells failed to show any enrichment of Al. Characteristic differences were found in Al contents of different species, but regional variations were also noted. However, mollusks of the oyster variety were shown to undergo a seasonal variation of the Al content in the meat (602). A characteristic seasonal variation in Al content was observed which was related to physiological phenomena in oysters. It was suggested that Al was absorbed, accumulated, and utilized actively and selectively by oysters within a limited range of concentration in the environment.

**INSECTS:** Total content of Al in the adult and larvae of the insects *Drosophila melanogaster*, *Xylocopa violacea*, *Dociostaurus maroccanus*, and *Thaumatopoea pityocampa* has been measured (603). Al in the spittle of the plant-sucking insect *Philaenus spumarius* has been suggested to be a normal component (604). Fat body and hemolymph Al contents of *Blaberus craniifer* were measured by using paper chromatography and the Al reagent, aluminon (605). Hemolymph of the adult insect contained approximately four times as much Al as larvae. Fat bodies of larvae contained as much Al as the fat bodies of adult insects. Measurement of Al in *Ascidella aspersa* and *Ciona intestinalis* demonstrated that both ascidians had similar Al contents in tissue and blood (606). The Al content of the blood cells of *Ascidella aspersa* was found to be the highest of all metals determined (607). Studies of the toxicity of Al, when added to artificial medium on which *Plodia interpunctella* larvae were reared, suggested that Al was relatively nontoxic with

regard to prevention of development and  $\text{LD}_{50}$  (608).

**MOLDS:** The effect of Al on mold metabolism has also received some attention. A strain of *Penicillium notatum*, which had a much greater tolerance to boron (B) than various wild types, was shown to accumulate large amounts of B in the mycelia. Experiments with Al instead of B demonstrated that Al uptake by the mycelia was far greater in the tolerant strain than in the wild type (609).

**BACTERIA:** Trace quantities of Al have been found in bacteria and spores of *Bacillus cereus* and others (610,611). Culturing *Bacillus megaterium* and *Bacillus subtilis* in the presence of Al and metal-binding agents decreased flagella synthesis at sub-bacteriostatic concentrations (612). A sucrase obtained from *Bacillus subtilis* was demonstrated to be quickly inactivated at elevated temperatures. Stabilization against thermal inactivation was accomplished with the addition of  $\text{AlPO}_4$  (613). Partial protection was afforded by  $\text{Al}_2(\text{SO}_4)_3$ . Dialysis with metal chelating agents diminished this thermal stability. The *Paramecium caudatum* has also been shown to be more heat resistant with the presence of Al, especially in Mg-free medium (614).

Studies of the protective effect of Al against osmotic lysis of *Mycoplasmas* also demonstrated a dependence upon the temperature of incubation (615). The organisms were more resistant to lysis at 0°C than at 37°C. All parasitic strains of *Mycoplasmas* were more resistant to lysis than a saprophytic strain. Al binding by cell wall material obtained from *Staphylococcus aureus* 893, a wound isolate, demonstrated that complex formation was potentially more lethal to these microorganisms than phagocytic white blood cells (616). *Azotobacter* has also been shown to be inhibited by high soil Al concentrations (617).

**FUNGI:** The relative toxicities of Al to a number of fungi have been determined following exposure to aqueous solutions of  $\text{AlCl}_3$  (617). Soil fungi were the least sensitive of the soil microorganisms. It was suggested that Al-rich podzol soils inhibited the development of other soil microorganisms. Interestingly, it has been observed that the yeast *Saccharomyces cerevisiae* BCL 557 prevented

the growth of colonies of *Oospora lactis* (618). Addition of Al to the medium prevented the yeast-induced inhibition of *Oospora lactis*. Very low levels of Al in the growth medium of *Aspergillus niger* were demonstrated to decrease the growth rate which was reversed by the addition of Al to the medium (619). However, studies of the effect of Al on the growth of *Coniophora cerebella* and *Merulius lacrymans* suggested that Al was not essential for either of these fungi (620).

**VIRUSES:** Viral inactivation with Al was observed when dilute suspensions of MS2 and f2 RNA bacteriophages, as well as the S13 DNA phage, came into contact with an Al alloy surface or when diluted with fluids which had been in contact with Al (621). The Al-containing Duralumin center pieces used in ultracentrifugation have been shown to release  $Al_2O_3$  into alkaline solutions above pH 8.6 (622). It has also been demonstrated that the addition of  $AlCl_3$  doubled the survival period of green monkey kidney cells in culture and inhibited plaque formation following artificial or natural infection (623). Measle virus titers in Al-treated experimentally infected cultures were lower than in untreated controls at different incubation times. An antiviral effect was suggested, since  $AlCl_3$  did not change the cells' susceptibility toward the virus.

### **Therapeutic Uses and Pharmacology of Aluminum-Containing Compounds**

**Classical Therapeutic Uses:** The classical therapeutic uses of Al and Al-containing compounds can be found in the U.S. Dispensatory (624), pharmacology texts (625,626) as well as in the list of current Al-containing drugs presented in the *American Drug Index* (627). A discussion of the accepted uses of Al-containing compounds in medicine and their clinical aspects is presented in a subsequent section of this review.

A recent discussion in the literature (509, 510,341-346) concerning the use of  $Al(OH)_3$  in renal disease and its reported toxicity (see Toxicology of Aluminum) made it desirable to present data relevant to its mechanism of action. Patients with chronic renal failure have been treated with 5-10 g of  $Al(OH)_3$ /day to

prevent hyperphosphatemia and calcification of soft tissues. A study of the effects of  $Al(OH)_3$  on Ca, P, and Al balances, as well as the plasma parathyroid hormone levels in patients with chronic renal failure, has been reported (341). In the past, it was generally believed that Al was not absorbed to any considerable degree from the gastrointestinal (GI) tract and acted by binding phosphate in the gut. This inhibition of phosphate absorption was believed to prevent development of hyperphosphatemia and subsequent metastatic calcification. In this study, all patients were found to absorb and retain Al. Although the change in serum Al was small, large quantities were retained in tissues. As expected, plasma P fell in all patients and plasma Ca either did not change or increased only slightly. Similarly, the effect on circulating immunoassayable parathyroid hormone was variable. Where a rise occurred in plasma Ca, there was a proportionate fall in parathyroid hormone. This suggested that the parathyroid gland was responding to changes in plasma Ca rather than plasma P. To explain the fall in plasma P, following the administration of  $Al(OH)_3$ , it was proposed that the absorbed Al combined with phosphate and was deposited in bone.

**Prophylaxis of Silicosis:** The effectiveness of McIntyre Al powder, containing 15% metallic Al and 85%  $Al_2O_3$ , in the prophylaxis of silicosis is believed to result from the coating of silica particles with a layer of crystalline  $\alpha$ -monohydrate of Al (537). It was suggested that this absorbed coating reduced the ability of  $SiO_2$  to induce fibrotic lesions. In the three decades that have followed the initiation of prophylactic treatment of silicosis with Al, it has been repeatedly demonstrated experimentally *in vitro* and *in vivo* that colloidal  $Al(OH)_3$  or powdered Al hydrate act to prevent development of the fibrogenic action of quartz, as well as causing the resolution and healing of immature silicotic tissue reactions. This prophylactic effect has been demonstrated in the IP model of silica-induced fibrosis.

Intraperitoneal injection of  $SiO_2$  into rats has been used as a model of silica-induced connective tissue lesions. Compounds such as  $Al(OH)_3$  (628-630),  $Al_2O_3$  (628,629), McIntyre



powder (552), china clay and diatomite (630), as well as a number of Al chelates: Al chlorhydroxyallantoinate, Al dihydroxyallantoinate, Al salicylate (631,632), Al-dextran, Al-EDTA and Al citrate (633) have been shown to inhibit the silica-induced fibrotic reactions. Prolonged inhibition of the characteristic silicotic reaction and inhibition of immature silicotic lesions were observed. The objective of the Al chelate studies was the search for alternatives to McIntyre Al prophylaxis of silicosis.

The prophylactic effect of Al-containing compounds has also been studied in the lung of rats following inhalation. Inhalation of powdered  $\text{Al}(\text{OH})_3$  was shown to limit  $\text{SiO}_2$ -induced fibrosis to an innocuous proliferation of macrophages (628). Promotion of phagocytosis has also been suggested as the mechanism of elimination of  $\text{SiO}_2$ -containing substances from the blood and restoration of normal prothrombin times following treatment with Al (634). Alunite, a mixture of Na and K alums with  $\text{Al}(\text{OH})_3$ , also decreased the pulmonary fibrotic response to  $\text{SiO}_2$  (635). However, McIntyre powder (15% Al and 85%  $\text{Al}_2\text{O}_3$ ) failed to prevent the fibrosis induced with coal dust containing 25%  $\text{SiO}_2$  (636), although the Al contained in another coal ash was suggested as responsible for the prevention of quartz toxicity (637). Very high concentrations of Al have been reported in two coals which are associated with a low incidence of silicosis (117).

Biochemical studies of rat lungs exposed *in vivo* to 15% Al and 85%  $\text{Al}_2\text{O}_3$  powder, in addition to quartz, also demonstrated that low levels of the Al powder retarded the quartz-induced fibrosis, increase in wet lung weight, and decrease in cytochrome c oxidase activity (638-640).

Other studies have been done in search of alternate prophylactic measures, as well as therapeutic agents. Compounds such as  $\text{Al}(\text{OH})_3 \cdot x\text{H}_2\text{O}$  (629,632), Al-chlorhydroxyallantoate (630,631), and  $\text{AlCl}_3$  (641-644) were tested in rat, guinea pig or macrophage systems and have been suggested as potentially therapeutic in the treatment of silicosis and alternatives to the inhalation of McIntyre Al- $\text{Al}_2\text{O}_3$  powder now used in the prophylaxis of silicosis. Prevention of  $\text{SiO}_2$  and  $\text{Al}_2\text{O}_3$  pneumoconioses in rats has been successfully demon-

strated using a different approach, inhalation of the surface active agent polyoxy-ethyl-tertiaryoctyl-phenol-formaldehyde (645). Other studies have suggested that the inhalation of  $\text{Al}(\text{OH})_3$  (628) or Al-dextran complex in combination with isoniazide (646) may be useful in silico-tuberculosis. In addition to these, two patents have been awarded for new methods of generating respirable particles of Al- $\text{Al}_2\text{O}_3$  for use in the prophylactic treatment of silicosis (647, 648). Although all of these approaches have been demonstrated to be successful initial efforts in the search for alternatives to the use of McIntyre powder by inhibiting  $\text{SiO}_2$ -induced pathologic changes, the use of  $\text{AlCl}_3$  may have undesirable side effects due to the acidity of its solutions.

**Newer Pharmacologic Uses:** A number of new therapeutic uses of Al-containing compounds and mixtures of pharmacologic agents with Al compounds have been reported. Al flufenamate, the Al chelate of flufenamic acid, has recently been reported to have better or equivalent anti-inflammatory properties compared to the free acid. It was also claimed to lack the harmful side effects of the acid on the alimentary canal (649). In the light of these observations it is appropriate to wonder whether commonly used Al and salicylate compounded mixtures may be more advantageous than previously expected.

Successful treatment of arthritic and prearthritic symptoms in the knee joint has been claimed with a paste containing Al silicates, glycerin, boric acid, salicylic acid, Zn oxide, and volatile oils. This mixture was reported to have anti-inflammatory, analgesic and antibacterial effects (650).

Sutures provided with wound healing coatings containing Al have recently been patented (651). Such sutures were useful in promoting wound healing, consistent with the discovery that pure Al accelerated wound healing. It had been reported earlier that treatment with Al accelerated the regeneration of damaged tissues, stopped inflammatory processes, and prevented healing complications (652).

Intraperitoneal injections of kaolin were demonstrated to elevate significantly the pain threshold in rats, in the rat-pressure-pain test

(653). In the mouse phenylquinone-writhing test, kaolin was inactive both orally and subcutaneously at concentrations of up to 16%. In the mouse-hot-plate test, kaolin again produced a significant analgesic effect by the IP route. When administered to parabolic rats, it produced a significant analgesic effect in the rats receiving the injection, but had no effect on their attached partners.

Metal chelates of tris(hydroxymethyl)-aminomethane have been examined for antacid activity (654). The Al chelate was effective in maintaining a pH range between 3 and 5 and possessed a high neutralizing capacity. The Chugai Pharmaceutical Company was awarded a patent (655) for the use of Al chelates of polysaccharide-sulfuric acid esters for the treatment of peptic ulcers. These compounds were reported to have improved antiulcer activity and reduced side effects.

A preparation containing Al nicotinate has been reported to be effective adjunctive therapy in addition to diet and other measures in the treatment of hypercholesterolemia and hyper- $\beta$ -lipoproteinemia. It was also suggested to be possibly effective in reducing xanthomatous tissue cholesterol and useful under conditions which tend to associate a reduction in cholesterol and useful under conditions which tend to associate a reduction in cholesterol levels with a consequent lessening of arteriosclerotic complications (656).

Studies of  $\text{Al}(\text{NO}_3)_3$  (481,482) and  $\text{AlCl}_3$  (657) have failed to show any therapeutic usefulness for the treatment of various neoplasms in animals.

Various Al-containing materials, potentially useful as amalgams or prosthetic implants, have been studied as aids in dentistry. Fibrous crystals of  $\text{Al}_2\text{O}_3$  (11, 658) and Ca aluminate (658, 659) have been suggested, because of their effectiveness and biocompatibility, to be suitable tooth amalgam or root prosthetic substances.

Porous ceramic implants have been studied with regard to future clinical orthopedic applications. Hentrich et al. studied new bone formation in association with ceramic implants composed of  $\text{Al}_2\text{O}_3$  and a  $\text{CaO}-\text{Al}_2\text{O}_3$  complex in Rhesus monkeys (660). Bone was histologically observed to penetrate up to  $100\mu$  into

the  $\text{CaO}-\text{Al}_2\text{O}_3$  complex within 50–100 days. The authors suggested that the Ca phase dissolved in preference to the Al phase in which bone mineralization occurred without adverse reactions.

**Antidotes:** The antidotal activity of montmorillonite derived from bentonite (661) in reducing the gastrointestinal absorption of kerosene, aspirin, and strychnine has been demonstrated to be superior to activated charcoal.

An apparent Al-deficiency bone disorder associated with the excessive intake of F has been the topic of some concern. In 1955, Hirata et al. (662) demonstrated the protective effect of Al with regard to the prevention of bone deformations and general disturbance of growth in chickens due to excess F absorption (bone fluorosis). In a series of experiments, Kortus (663-665) confirmed the protective effect of Al against F intoxication in rats and studied its mode of action. Rats receiving diets with large quantities of F retained less Al, Ca, and P in their bones. The effect of F was correlated with the amount given and the duration for which it was given. Al in bone was reduced by giving small amounts of F over a long period or large amounts of F for a very short period. His results and others demonstrated that there is an antagonistic interaction between F and Al.

This interaction has since been studied by Peters (666), who wished to determine whether the addition of Al would lower the GI absorption of F contained in fish protein concentrate (FPC,  $150\mu\text{g F/g}$ ). He fed  $\text{AlPO}_4$ , as the Al supplement that would not interfere with phosphate metabolism, in doses up to  $400\mu\text{g/g}$  for 27 days in the diet of rats containing FPC in amounts providing up to  $35\mu\text{g F/g}$  of diet. This highest dose of  $\text{AlPO}_4$  produced no deleterious effects with regard to weight gain and bone Al or ash content. The absorption of F from the diet was reduced as evidenced by the increased concentration in feces. Plasma and urinary concentration of F were unchanged.

### **Drug Interactions with Aluminum-Containing Compounds**

Al-containing preparations, such as antacids

containing  $\text{Al}(\text{OH})_3$ , have been shown to decrease the GI absorption of sodium sulfadiazine and quinidine (667), but to increase the absorption of pseudiephedrine (668). Kaolin decreased the absorption of pseudoephedrine, probably by adsorption. A decreased absorption of Na sulfadiazine was also observed following addition of  $\text{AlCl}_3$  (667). Oral administration of Al silicate has been shown to decrease the absorption rate of chloramphenicol (669). Al gluconate and Al orthophosphate complexes of the tetracyclines have also been shown to decrease the absorption rate of these compounds following oral administration (670). However, intramuscular (IM) or intravenous (IV) administration resulted in a prolonged elevation of blood levels. Al pyrophosphate and metaphosphate complexes of the tetracyclines markedly enhanced absorption following oral administration. Al complexation with ascorbic acid has been suggested to lower levels of this acid by an alternative mechanism, anaerobic chemical degradation (671).

### **Use of Alumina in the Production of Models of Various Neurogenic Diseases**

There have been many studies concerning the effect of Al-containing compounds on the CNS, especially the brain, in relation to the production of epilepsy and other neurogenic diseases. Recent data (449) concerning the possible association between high brain Al levels and the human disease, Alzheimer's disease, and high blood levels in senility (330) has prompted the presentation of the reported effects of Al in the CNS in somewhat greater detail. It must be stressed at this point that the intracranial or intraspinal routes of entry used in these studies have no known basis for comparison with regard to environmental or occupational exposures.

In dogs (672), injection of alumina cream, aluminum hydroxide suspension containing about 14%  $\text{Al}(\text{OH})_3$  and 86%  $\text{H}_2\text{O}$ , into the amygdaloid nuclei produced electroencephalographic and clinical signs of epilepsy similar to those induced by SC injection of metrazol. Similarly, following multiple injections of alumina-cream suspension, cerebral cortical lesions associated with focal and generalized

convulsions were observed in another breed of dog following abrupt withdrawal of Na barbital given in gradually increasing doses (673).

In monkeys, altered brain activity was also noted after injection of alumina cream into the cerebral hemisphere (674, 675). Development of epilepsy was also studied following intracortical (676) and intracisternal (677) injections. Of 23 metals tested, Al, cobalt, beryllium, and lead were the most effective in producing chronic experimental epilepsy. Al was the most epileptogenic of the four, especially as the powder, compared to the pellet form (678).

Intracerebral injection of alum phosphate into rabbits produced a severe convulsive state accompanied by neurofibrillary degeneration (NFD) throughout the CNS (679). The experimental production of neurofibrillary (NF) changes was recognized as important for the elucidation of the nature of a similar alteration in human brain cells known as Alzheimer's NFD or Alzheimer's disease. Electron microscopy of the alum phosphate lesion revealed remarkable NF aggregates (680). The filaments involved in these Alzheimer-like tangles were similar to those previously described in other animals and in man. Traces of Al were found in the affected rabbit neurons with the use of an electron-probe analyzer. These alum-induced tangles were also contrasted with the lesions observed as distended axons in rats treated with imidodipropionitrile. In addition to Holt's adjuvant, Al lactate, Al acetate, and  $\text{Al}(\text{OH})_3$  were observed, with light and electron microscopy, to cause NF damage following intracerebral injection (681-683). However, no NFD was observed after intracranial or continuous IV administration.

Cells of rabbits with NFD were noted to lack lysosomal and Golgi enzyme activities (680), and have impaired capability of protein synthesis (684). In addition to the nuclear and subcellular disorders, supernatant bound Al suggested cellular impairment due to the inhibition of cytoplasmic components (683).

Induction of NFD changes in rabbits has also been caused by compounds which have in common the ability to inhibit mitosis, namely vincristine (685), colchicine, vinblastine, and podophyllotoxin (686, 687). Subsequent production of vincristine-induced NF tangles in

cultures of fetal rabbit dorsal root ganglia were contrasted with  $\text{AlPO}_4$ -induced spheroids (688). Vincristine-induced tangles were compared to NF changes typical of Alzheimer's disease, while  $\text{AlPO}_4$ -induced spheroids were likened to the NF inflammatory changes characteristic of post-encephalitic Parkinsonism.

Changes in blood lipids, lipoproteins, proteins, and globulins have also been observed following the injection of kaolin into the cisterna magna of rabbits (689). Albumin and  $\alpha$ -lipoproteins decreased;  $\alpha$ -globulins,  $\beta$ -lipoproteins and cholesterol increased; while  $\beta$ -globulins and  $\gamma$ -globulins remained unchanged. Single injections of this aluminosilicate clay interoccipital-vertebrally caused the development of hydrocephalus in 15%, 70%, and 90%, respectively, of the treated rabbits, rats, and cats (690).

In the cat, subdural spinal injections of  $\text{Al}(\text{OH})_3$  produced massive NFD of the neuronal perikarya and cell processes, in addition to marked gliosis with conspicuous intranuclear fibrillar aggregation along with hyperirritability (691, 692). Comparison of reactions of young and adult cats to chronic irritation with intracerebral injections of alumina cream revealed gross differences in the reaction depending on whether the intracerebral injection was made before or after myelination (693). Particularly striking was the finding that in nonmyelinated white matter of young animals, there was no edema and no subsequent gliosis. Although alumina was observed to spread into the tissue surrounding the focus, subsequent myelination appeared to be normal, even in the regions close to the site of injection. In contrast, injection into the brains of adult animals was followed by edema, widespread demyelination, and gliosis of the white matter near the site of injection.

Studies of the electroencephalographic effects of alumina cream injected into the region of the substantia nigra and caudate nucleus also demonstrated epileptic activity in cats (694). The number of epileptic seizures could be increased by perfusing the dorsal hippocampus with CSF containing potassium (695). Injection of alumina cream into the caudate nucleus produced, besides a picture of catalepsy, a characteristic vertical nystagmus

(696). There were no seizures in cats in which the injection was onto the cortex. The stereotactics of alumina cream induction of cat epileptic attacks (697) and its use in young and adult cats have been studied in the development of a model of convulsions similar to those seen in human grand mal epileptic seizures (698, 699). This mode was successfully used in the search for antiepileptic drugs (700).

In 1973, Crapper, Krishnan, and Dalton (449) reported that concentrations of Al approaching those used in the production of experimental epilepsy had been found in regions of the brains of patients whose diagnosis was compatible with Alzheimer's disease. Pathological examination of a portion of the brain revealed brain atrophy, extensive NFD, senile plaques, and hippocampal pyramidal cell granulo-vascular degeneration. In studies with cats,  $\text{AlCl}_3$ -induced encephalopathy was correlated with elevated brain Al levels and poor acquisition of an avoidance task.

Although Al may be a neurotoxic factor in Alzheimer's disease, it was suggested that the identification of tissue binding sites in both experimental NFD and Alzheimer's disease was needed to further establish the role of Al in the pathogenesis of the disease (449). Finally, not all of the pathological changes in Alzheimer's disease were readily explained by this most recent study which did not exclude the possibility of other environmentally related etiological factors.

## Clinical Aspects of Aluminum and Human Health

### Occupational Disease Due to Aluminum

A careful examination of the recent scientific literature does not reveal examples of distinctive pulmonary fibrosis and emphysema in  $\text{Al}_2\text{O}_3$  abrasive (corundum) workers, as described by Shaver and Riddell (701). On the other hand, a lung disease in workers exposed to finely powdered Al has been clearly documented (124, 702, 703). The material associated with these cases is primarily a very finely flaked particulate produced by stamping and used in paints, explosives, and pyrotechnical

devices, from which the special Al flake gets the name "pyro." Various grades of pyro may be treated with mineral oil or stearin to prevent agglomeration; however, the epidemiological pattern does not suggest that these additives materially affect the incidence or character of disease. A coarser variety of Al dust produced from molten metal or by means other than stamping appears to be much less dangerous, although radiological changes of the lungs may be associated with exposure (702, 703).

The clinical picture consists of dyspnea, cough, pneumothorax, and variable sputum production, and fatal outcome has been observed. The chest film and histopathology are typical of a nonnodular interstitial fibrosis. Airway obstruction, emphysema, and impaired alveolar-capillary gas diffusion are not prominent. The absence of severe emphysema distinguishes to some degree the pulmonary fibrosis caused by Al dust (pyro) from that considered typical of Shaver's disease. Silica content of the fume responsible for the latter disease may be relevant to the dissimilarity. Prominent encephalopathic events accompanied a case of pulmonary fibrosis described by McLaughlin (123). The association between Al dust exposure and neurological phenomena could not, however, be proved as causal.

Animal studies (577, 578) support the view that Al rather than an additive is the fibrogenic agent. Other studies also confirm the active fibrogenic potency of stamped powders, as compared with granular dusts.

There is evidence that intensive occupational exposure to  $\text{Al}_2\text{O}_3$  dust in the production of Bayer-process alumina is associated with increased serum Al levels (516). In those exposed, as compared with controls, the mean observed levels were 1.03 and 0.34  $\mu\text{g}/\text{ml}$ , respectively. Serum intestinal alkaline phosphatase, acid phosphatase, and ATP levels were significantly reduced in the group with high serum Al levels; however there was no evidence of phosphate depletion or osteomalacia. The reduction in ATP levels is consistent with observations with Al hydroxide; however in the latter situation serum Al levels were higher and hypophosphatemia existed (704). The relevant mech-

anisms, therefore, remain undefined.

Al and  $\text{Al}_2\text{O}_3$  can hardly be considered as highly or even moderately toxic industrial materials, and the substitution of alumina for siliceous bedding material in the firing of chinaware has contributed to the control of silicosis in the industry (705). Nevertheless, the accumulating evidence does not justify designating Al and  $\text{Al}_2\text{O}_3$  as "inert." It was so designated in the latest edition (1971) of the American Conference of Governmental Industrial Hygienists' Documentation of the Threshold Limit Values for Substances in Workroom Air (706). However, since 1971,  $\text{Al}_2\text{O}_3$  and other Al-containing compounds have been listed among the "nuisance particulates" in the annual TLV's on the basis that there is no dust which does not evoke some cellular response in the lung when inhaled in sufficient amount. The limit for these particulates is 10  $\text{mg}/\text{m}^3$  (133).

### Medicinal Uses of Aluminum

**Antacids:** A number of Al compounds are used in clinical medicine, the predominant application being in the control of gastric hyperacidity.  $\text{Al}(\text{OH})_3$ , either alone or in combination with Mg compounds, is probably the most widely used antacid. It has been postulated that its function in the treatment of peptic ulcers lies in the ability to both neutralize acid and adsorb pepsin (707); however, evidence is strong only for the neutralization. All antacids are anti-peptic in the sense that peptic activity decreases as pH increases and that pepsin is irreversibly inactivated at above pH 7. Al antacids tend to be constipating and consequently are often mixed with Mg compounds, which counteract this undesired effect.

At the present time the sole approved legal standard of effectiveness for antacid compounds is based upon an *in vitro* determination of the compound's capacity to neutralize hydrochloric acid (708). There is currently no standard *in vivo* test of efficacy; however efforts are being made toward this objective. Based upon the existing criterion of effectiveness, the following Al-containing compounds have been judged effective: Al carbonate;  $\text{Al}(\text{OH})_3$

[Al(OH)<sub>3</sub> hexitol-stabilized polymer, Al(OH)<sub>3</sub>-Mg carbonate co-dried gel, Al(OH)<sub>3</sub>-Mg trisilicate co-dried gel, Al(OH)<sub>3</sub>-sucrose powder hydrated]; dihydroxyaluminum aminoacetic acid and dihydroxyaluminum aminoacetate (DHAA); dihydroxyaluminum sodium carbonate; hydrated Mg aluminate; and AlPO<sub>4</sub>.

Various specific antacid properties have been attributed to certain Al compounds used for the control of gastric hyperacidity or upper GI symptoms which are not known to be related to acidity of gastric contents. Such symptoms include "indigestion," "gas," "upset stomach," "belching," and the like. Evidence to support such claims is not conclusive. While it is claimed that the polymeric Al(OH)<sub>3</sub>-hexitol complex produces a more acceptable pH-time profile in the intragastric contents, studies are not yet available which would clearly document the clinical superiority of this compound. Other relatively new compounds include DHAA (709), hydrated Mg aluminate (monalium hydrate), and dihydroxyaluminum sodium carbonate. Proponents of these agents point to fast and prolonged action and an improved pH-time curve.

While it is not unlikely that one of these compounds will show advantages in comparison with Al(OH)<sub>3</sub>, such advantages remain to be clearly documented in controlled studies.

In man the only reported adverse effects arising from the use of Al-containing antacids are intestinal obstruction by masses of Al(OH)<sub>3</sub>, and consequences of intractable and blood phosphate sequestration. Both phenomena are infrequent, and the latter occurs only if the patient is on a very restricted phosphate intake, has chronic diarrhea, or has an intrinsic disorder affecting Ca and/or P metabolism.

Al compounds have been shown experimentally in man to interfere with the absorption of tetracycline. Similar studies in animals suggest that Al compounds used in man as antacids may impair the absorption of many important drugs including barbiturates, warfarin, quinine, quinidine, and certain anticholinergics.

**Antiperspirants:** Al compounds are widely used in antiperspirants. While the mechanism

of action is not well understood, it is probable that Al compounds act as protein precipitants with a low cell-penetration capability. Consequently, their action is limited to the cell surface and the superficial interstitial spaces. This astringent action is accompanied by a swelling of the opening of the sweat gland, which becomes blocked, reducing the flow of sweat. Of the Al applied in this manner very little reaches the dermal area, and the Al salts apparently remain bound to proteins in the stratum corneum. The percutaneous application of these compounds in suitable preparations does not produce significant pathological changes (591). Al chloride has been one of the most popular antiperspirants; however, this compound is damaging to certain textiles which come in contact with the treated skin. Al chlorhydroxide retains the antiperspirant qualities of the chloride but releases less acid, which is destructive to textiles. Al phenolsulfonate is a useful astringent of moderate acidity and has the additional valuable property of being soluble in alcohol, an advantage in liquid aerosol formulations which utilize nonpolar propellants. Al chlorhydroxylactate (chloracel) is formed by complexing Al chlorhydrate and Na lactate. This agent is compatible with Na stearate soaps used in antiperspirant sticks.

**Aluminum Adjuvants for Vaccines and Toxoids:** Al adjuvants are widely used in the preparation of vaccines and toxoids for human use (710), although the practice is not unanimously endorsed (711). There are two principal methods of preparation: the addition of antigen solution to preformed Al(OH)<sub>3</sub> or AlPO<sub>4</sub> suspensions or the addition of a solution of alum, usually potassium alum, to the antigen to form a precipitate *in situ*. The World Health Organization Technical Report No. 61 (712) indicates that "the expression 'alum-precipitated toxoid' describes a laboratory procedure and in no way defines the nature of the material obtained either quantitatively or qualitatively."

While various mechanisms have been suggested as responsible for the adjuvant properties of Al compounds, there is as yet no single well-supposed hypothesis. Edsall (713) has sug-

gested that the adjuvant properties of Al compounds are related to their ability to convert soluble antigens into particulates, which are readily subject to phagocytosis by immunologically competent cells. Diphtheria and tetanus toxoids and poliomyelitis vaccine gain enhanced antigenic potency when an aluminum adjuvant is used. Such adjuvant does not appear to improve the protective capacity of pertussis vaccine or, probably, that of typhoid vaccine.

**Aluminum-Penicillin Preparation:** Al monostearate (2% w/v) is used as a dispersing agent in long-acting repository parenteral penicillin G. The preparation, Sterile Procaine Penicillin G with Aluminum Stearate Suspension, U.S.P., provides clinically significant circulating penicillin levels for periods as long as several days. The Al compound keeps the active principle in a homogeneous suspension in oil, slows absorption by its water repellency, and imports thixotropic properties to the preparation, i.e., permits the gel to assume an easily injectible form when shaken.

**Aluminum Hydroxide in Renal Failure:** Al(OH)<sub>3</sub> is administered orally in renal failure to limit the accumulation of phosphate, hyperphosphatemia, and the consequent development of metastatic calcifications (714). The treatment induces phosphate loss by rendering phosphate non-absorbable in the gut. While it has been assumed that Al administered in this manner does not cross the intestinal wall, there is accumulating evidence that Al is absorbed and retained, especially in uremia (509, 715), when Al dosing and decreased excretory capacity co-exist. In patients with renal failure, Al-cycle resins used for the control of hyperkalemia may also represent an additional Al load.

The use of Al(OH)<sub>3</sub> in the treatment of phosphate retention has been questioned, principally by Berlyne and his colleagues (510, 715, 716), and has been defended by others actively engaged in the management of advanced renal failure (287, 343, 346, 717). Evidence that Al therapy may be injurious is based upon both clinical and animal studies, the former to some degree reflecting inappro-

priate utilization of the agent. Bloom (718) described a patient with spastic colitis and without renal disease who, unbeknownst to her physician, ingested 30–60 1-g Al(OH)<sub>3</sub> tablets/day for 6 yr. Obvious osteomalacia and pseudofractures were attributed to profound phosphate loss. Lotz (719) presented evidence for a phosphate depletion syndrome in man marked clinically by debility, muscular weakness, anorexia, and malaise and biochemically by a decreased urinary excretion of phosphate, hypercalciuria, hypophosphatemia, resorption of skeletal Ca and P and increased absorption of Ca from the GI tract. An explanation of the clinical picture was offered by Lichtman (704), who observed that erythrocytic ATP is markedly reduced in the presence of hypophosphatemia induced by the administration of Al(OH)<sub>3</sub> gel in uremia. The discontinuation of this treatment resulted in a prompt and complete reversal of clinical and biochemical abnormalities. That dietary Al(OH)<sub>3</sub> can cause marked hypophosphatemia and diminished ATP levels had been shown in the chick (720) and in the rat (478). Whether the reduction in ATP levels is due to disturbances of phosphorylation mechanisms by Al or to impaired availability of phosphate has not been established.

Berlyne (715) pointed out that serum Al levels were distinctly elevated in perhaps one-third of patients with concurrent renal failure and Al(OH)<sub>3</sub> treatment. In control subjects, the serum Al levels were found to be less than 2 mg/l by neutron activation analysis or less than 0.3 mg/l by atomic absorption spectrophotometry. Treated patients showed levels as high as 110 mg/l. Evidence that renal failure itself promotes the retention of Al was seen in one patient with a serum Al level of 14 mg/l who had received neither dialysis nor Al-containing drugs. Other studies (721) showed bone concentrations of Al some 10 times normal in renal failure. There was no good correlation between Al levels and the amount of Al taken, but there seemed to be correlation between such levels and duration of uremia.

Experimental animal work (478, 509) shows that high doses of dietary Al impair growth, apparently through interference with phosphate metabolism. No impairment of growth

occurs in experimental situations when hypophosphatemia is avoided (344). Berlyne's (509) study with 5/6 nephrectomized rats was designed to demonstrate toxicity when test animals received Al sulfate or chloride in the drinking water or when these compounds and the hydroxide were given by gavage, IP, or SC. Almost all animals receiving one of the acid salts by mouth showed anorexia, lethargy, and periorbital bleeding and died. A similar outcome followed IP dosing with  $\text{Al(OH)}_3$ , while gavage or SC administration of the hydroxide appeared less injurious. Although the serum concentrations of Al in some of these animals may approximate those observed in Al-treated patients with uremia, the relationship of these experiments to the situation in man is unclear. The oral administration of Al sulfate or chloride, irritating astringent acid salts, or the IP injection of  $\text{Al(OH)}_3$ , an insoluble mechanical irritant, do not lead to clear inferences. An extensive editorial exchange has been published on this subject (48, 342, 345, 346, 510, 717).

While the biological implications of Al absorption continue to invite comment (275, 276), there is no sound clinical evidence that the use of  $\text{Al(OH)}_3$  in renal failure is hazardous as long as hypophosphatemia is avoided. Patients with uremia have been treated with 5–10 g  $\text{Al(OH)}_3$ /day for at least 6 yr without evidence of clinical bone disease or significant histological signs of metabolic bone disturbances (343).

That some patients with renal failure may be protected from high circulating Al levels by periodic dialyses is a possibility to be considered, however.

**Aluminum in the Prevention and Treatment of Silicosis:** Although Al powder has been used for over 25 yr in the prevention and therapy of silicosis, there is still no unequivocal evidence that the procedure is of clinical utility. The approach is based on the observation that small quantities of metallic Al inhibit the solubility of siliceous materials in the lungs of experimental animals or combine with such materials so as to diminish their fibrogenic properties (722). These observations were substantiated by Gardner (723) and his

associates at the Saranac Laboratory. Subsequently, American and Canadian workers using Al dust prepared according to the McIntyre Foundation technique claimed positive results in prophylaxis and therapy.

The powder is prepared by grinding Al pellets so as to produce particles 96% of which are  $1.2\mu$  or less in diameter. The powder is readily dispersed in the atmosphere of change-rooms in which the treatment is administered. Upon generation, the particles become oxidized to  $\text{Al}_2\text{O}_3$ , which is considered to be the active  $\text{SiO}_2$ -inhibiting agent. It is estimated that over 40 million preventive treatments have been given in the gold mining industry.

More recently the efficacy of Al inhalations in reducing the incidence of silicosis has been claimed by Perry (724) and Hannon (725) in ceramics workers, and by Campbell (726), Dix (727), and Godin (728) in Canadian gold miners. Advocates of Al treatment point out that industrial hygiene measures are of paramount importance but describe the several beneficial ways in which Al favorably influences health in  $\text{SiO}_2$ -exposed workers. The late Thomas Shipman asked the critical question, however, when he drew attention to the lack of controlled clinical studies, which are essential to removing bias on the part of workers, management, and physicians in establishing the utility of the procedure. It may be true that there is less silicosis or silicosis with a more benign course at those installations in which Al inhalation has been used. In the absence of controls, however, one cannot be sure that the improved health experience is not due to improved mine hygiene and air cleaning rather than to Al inhalations.

An earlier study by Kennedy (729) demonstrated no usefulness with regard to Al inhalation therapy in the treatment of established silicosis. It has subsequently been shown that Al inhalation therapy is effective in preventing the continued development of immature and initial lesions but ineffective against mature lesions (537).

The problem of silicosis has engaged the attention of many researchers. Much has been learned concerning the pathogenesis of this industrial disease, as well as the basic principles underlying the handling of inhaled parti-



cles by the lung. However, a clear concept of therapy is still lacking. It is true today, as it was a century ago, that silicosis once fully established remains an incurable disease. This observation has led some to the search for more therapeutically effective Al-containing compounds (629-631, 641-644) (See also Therapeutic Uses and Pharmacology).

## Summary and Concluding Comments

The increased interest in trace elements in the human environment has stimulated extensive research on the presence of these elements in the principal sources of exposure and intake by humans and animals, and on their fate and effects in the body. Many of the studies have included Al as one of the minor elements. Aside from this, the growing concern over the quality of the environment has contributed to the wider inclusion of Al environmental as well as biological investigations.

Despite the abundance of Al in the earth's crust and hence in the soil, where its content varies from relatively low to extremely high levels, the concentrations in the air are generally low, except in the vicinity of industries processing alumina, bauxite, or other Al-containing compounds and in areas where coal is burned. The finding of higher concentrations of Al in certain rural and remote areas, as compared with urban and industrial areas, points to the terrestrial origin of Al in the atmosphere.

Concentrations of Al in rivers, lakes, oceans, and ground waters are generally low. For this reason, Al is frequently not included in analyses, for it presents no human health problem. High concentrations occur in areas of volcanic activity and in waters that carry acid drainage from mines and exposed rock formations, causing hazard to aquatic life.

The Al content of food and beverage products varies widely, depending upon the product, the parts used for consumption, the processing, as well as upon the geographic areas in which they are raised.

The growth of the uses of aluminum by the food and beverages industries for the processing, handling, and packaging or preservation of their products, and by manufacturers of kitchen utensils has resulted in a more extensive contact of

the public with this metal. In addition, numerous Al compounds are used as food additives for various purposes, as clarifiers of beverages, and in the treatment of public water supplies. In the last instance, the Al content of the drinking water is generally lower than in the raw water. The wide use of Al compounds in drugs constitutes another source of intake.

In contrast to the earlier review (1), which included many investigations of the quantities of Al contributed to the content of food cooked or processed in aluminum, only few additional such data could be added from the more recent literature. This can be only interpreted to mean that the questions that had been raised earlier had been answered to the satisfaction of reliable investigators. The fact remains that the available new data on the daily human intake from foods and beverages, including water, are similar to those reported earlier, despite the obviously increased contact of foods and beverages with the metal and Al-containing food additives, whether purchased in food markets or prepared at home, and the extremely high Al content of some of the natural products. The latter far exceed any amount of Al that may be added by processing and storing in aluminum or by use of food additives. Obviously, the quantities of these products used for consumption are so small or the use of them so occasional as to be balanced to a relatively low level of actual daily intake by the foods of low Al content. The contribution of airborne Al to the daily intake has apparently not yet been determined.

The U.S. Food and Drug Administration has recently repeated its assurance of the safety of the use of aluminum cookware as well as of the use of Al-containing food additives as leavening agents, for the firming of pickles and certain fruits, as well as other purposes in the processing of food products. These additives or ingredients are included in the list of compounds generally recognized as safe.

Biologically, it now seems highly probable that Al should be viewed as an essential metal. Man and animals have a definite need for this abundant element in normal metabolism. Within the range of usual intake, there is an apparent homeostatic regulation of tissue levels, a balanced absorption and excretion. Aluminum is present in all tissues, and its concentration

changes with biological activity. Other points of evidence suggesting essentiality are: circadian rhythmic changes under apparent autonomic control; maintenance of fertility; fetal accumulation in concentrations greater than those found in mothers; increases in fetal tissues associated with periods of increased development as well as postnatal tissue growth and maturation; regular storage and release; a well defined excretory pathway, and apparent requirement for some enzyme activities. Exposure to Al, in quantities usually found in the environment, most likely provides the amounts required for normal metabolism and prevents the occurrence of deficiency.

It is recognized that in normal metabolism, the quantities of Al from the environment enter the body in quantities directly related to exposure. Absorption must be considered as more than slight based upon metal levels reported for various tissues. Residence of this metal is viewed to be regulated by the normal homeostatic mechanisms which control absorption and excretion of all essential metals. The route of absorption, dermal, pulmonary, gastrointestinal, etc., does cause a variation in the amount absorbed. However, aside from this consideration, the chemical form of this metal greatly affects the absolute amount absorbed and distribution to tissues. The form *in vivo* is no doubt a chelate with the ligands being derived from the milieu in which Al is contained. Absorption, distribution to various tissues, their cells and extracellular spaces is then affected by the physical-chemical stability and solubility properties of these chelates. These chemical parameters are of primary importance with regard to exchange with other chelating agents *in vivo* resulting in distribution and ultimately, biological activity. That dissimilar Al compounds, especially the inorganic compounds, cause similar effects *in vivo* is most likely related to the conversion of the Al into chelates of similar nature. This then is meant to imply a need for an awareness of the anionic or ligand portion of the Al-containing substances in all aspects of the biology of Al.

The change in Al content of tissues in numerous disease states has been suggested to be of diagnostic value. Well defined and consistent variations of Al levels in blood and/or other tissues have been reported in association with

many disorders or disease states. Unfortunately not enough work has been done to fully explain the physiological and biochemical roles of Al in disease related or normal metabolism of the various tissues. Although in the normal response increases in tissue Al levels are seen in some disease states, they are also seen following exposure to large concentrations of this metal.

The requirement of Al in normal metabolism does not imply that its accumulation from excessive exposure does not lead to toxicity. As predicted, soluble Al salts are much more toxic than insoluble compounds. Exposure to very high levels of Al, in occupational environments, has been reported to result in at least one fairly well documented Al related disease. Pulmonary fibrosis due to exposure to finely divided coated-Al metal has been clearly established. However, this disease can be prevented by reducing the dust level in the worker's environment. Similarly the incidence of other pulmonary diseases has decreased following the installation of good industrial hygiene procedures. There is still a need to study, in all such workers, the subacute toxicity associated with exposure to high levels of Al or its compounds. In the past, the seemingly innocuous nature of Al and its compounds encountered in occupational exposures and their lack of recognized acute or chronic toxicity has relegated them to less interesting categories requiring less intense study. However, biological studies should continue to be done to provide better indices for the establishment of occupational TLVs.

As an aside, Al has been suggested to be carcinogenic. However, there are no relevant human or animal data to support this suggestion. Many attempts to evaluate this possibility lead to the conclusion that administration of Al and its compounds by various routes, with the exception of Al foil implantation in rats, do not cause neoplastic growth.

Consistent with the human experience, many pulmonary studies in animals have shown that dusts of Al and some of its compounds can be fibrogenic when the animals are exposed to very high levels. Animal studies also suggest that, as with the human experience, the most susceptible metabolic process with regard to Al toxicity may be phosphate metabolism. Under conditions of usual exposure, the amounts taken in

daily do not adversely affect phosphate metabolism. However, gross toxicity seen with high concentrations of Al, such as inhibition of growth, tissue development, and maintenance may be the result of adverse effects on phosphate metabolism, especially with a concomitant magnesium deficiency. Biochemical reactions associated with phosphate utilization appear to be easily affected by excess Al. There is little doubt that such inhibitions have to do with the interaction between Al and other metal requiring metalloenzyme systems. Gaps exist in the literature to date concerning the mechanisms of action with regard to both the essential function of Al and its toxic reactions at the extracellular, cellular, subcellular and enzymatic levels. Some information is available with regard to the interaction of Al at the molecular level, but much more is needed.

Of particular need, in this regard, are animal studies of the molecular interaction of Al and components of the central nervous system which give rise to pathological changes similar to those seen in Alzheimer's disease. These animal studies have been done with injections of Al compounds into the CNS which have no correlation with human exposure. However, with the reports that senile humans have markedly elevated blood and brain Al levels, the results obtained with injection into the CNS may be significant with regard to this disease process. Although it has been suggested that Al may be the etiologic agent, accumulation in the brain may in fact be the result of other environmental agents which allow the transportation of large quantities of Al across the blood-brain barrier. Alternatively, environmental agents which cause a deficit of other essential metals in the brain may in this way allow the accumulation of Al. This is still another area where additional work is needed with regard to the effects of Al on all forms of life.

Concerning the effects of Al on lower forms of life, there is a growing interest with regard to water and soil pollutants and their effect on aquatic and soil organisms. Although various forms of aquatic life and soil microorganisms require Al for metabolism, the effects of excess Al may be as harmful to them as it has been observed with higher forms of life. Mechanisms of actions of both toxic and beneficial effects are

of interest because of the concern for our environment.

Aluminum-containing compounds continue to be used medicinally as antacids, adjuvants, dispersants, and antihyperphosphatemic agents in the management of renal disease. In this regard, the use of  $\text{Al}(\text{OH})_3$  in the prophylaxis of hyperphosphatemia is believed to be safe as long as hypophosphatemia is avoided. In addition, Al and its oxide, when inhaled by workers exposed to silica, appears to be effective in the prevention of silicosis but has no effect in reversing established silicotic disease. The incidence of silicosis has been dramatically decreased in gold mining and ceramic industries; however, more work concerning the treatment and prevention of this pulmonary disease is needed. Alternatives to the use of this dust, which increases the dust load of the lung, are being sought, both with regard to prophylaxis and treatment. Perhaps future work will be done to add to the information concerning the mechanism of action of Al in the prevention of silicosis and also lead to a better understanding of alternative approaches to therapy of this disease. Aluminum compounds have also received some attention with regard to the prevention of fluorosis in animals due to increased ingestion of F. Compounds of Al may also find use in the prevention of dental caries and therapeutically in tissue repair processes.

In summary, the literature since the mid-fifties on the biology and toxicology of Al has revealed that absorption and retention or accumulation in humans occurs at lower levels of intake than had been assumed formerly. However, levels of 5 to 50 times the daily intake failed to interfere with phosphorus metabolism. The adverse effects of Al reported in the more recent years resulted from the inhalation or ingestion of Al in concentrations many times greater than the amounts present under normal circumstances. Despite the apparent wider use of Al in the processing and storage of foods and beverages, the levels of daily human intake are no higher than those reported earlier. If anything, they are lower, probably attributable to the method generally used. As in the past, there is still no need for concern by the public or producers of Al or its products concerning hazards to human health derived from well es-

established and extensively used products. This has been expressed by a number of toxicologists such as Ondreicka, Browning, Furst, and others. Finally, as in the past, there have been no reports of either acute or chronic poisoning from the use of Al and its compounds in the processing of foods and beverages.

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