LB 1126

October 18, 1993

Bob James
Pittsburgh 6

PLAINTIFF'S
EXHIBIT
AL-1142

Bob,

Dr. Borak asked me to give you a copy of Draft No. 3, "Aluminum and Pulmonary Fibrosis," for review in Dan's absence. Dr. Borak said you can call him directly (203-777-6611), but if you want to wait, that's okay too.

Also attached is a copy of Dr. Borak's letter to Sey Epstein regarding the Rockette/Gitelman Study.

I'm also expecting another copy of the PCB document from Dr. Borak which he has asked me to share with you and Connie Ritzert. I'll provide you with a copy as soon as it comes in.

Bev

/bal

Attachments

cc: D. M. Jaffe, M.D.

H:\JAMES.BAL

JONATHAN BORAK & COMPANY, INC.

Specialists in Occupational & Environmental Health

ALUMINUM and PULMONARY FIBROSIS

(DRAFT #3)

Prepared for Daniel Jaffe, MD
Director, Corporate Health Services
Aluminum Company of America

October 18, 1993

An association between inhalation of aluminum compounds (such metallic aluminum, aluminum hydroxide, pyropowder and certain aluminum abrasives) and pulmonary fibrosis, a chronic lung disease, has been researched and debated for nearly 60 years. Against the association are reports consistently indicating that, with only one historical exception ("pyropowder"), aluminum workers do not have increased risk of such disease. However, a handful of anecdotal reports have described a small number of individuals who developed characteristic pulmonary fibrosis following work-related aluminum exposures.

It is now clear that the association is not a simple one. Under rare circumstances, inhalation of certain aluminum compounds can lead to pulmonary fibrosis. In nearly every setting, however, fibrosis was more likely due to inhalation of other substances, such as asbestos and silica, which contaminated the work environment.

The following discussion considers the association between inhalation of aluminum compounds and development of pulmonary fibrosis. First, there is a description and overview of pulmonary fibrosis and related lung diseases. Then, evidence linking those diseases with inhalation of aluminum compounds is reviewed. The final sections provide a summary, a glossary, and a selected reference list. To assist the nonmedical reader, the glossary defines those terms that are EMBOLDENED AND UNDERLINED in the text.

1 ABOUT PULMONARY FIBROSIS

1.1 What is Pulmonary Fibrosis?

Pulmonary fibrosis is one of a family of lung disorders known as the Interstitial Lung Diseases. (The terms "interstitial lung disease" and "pulmonary fibrosis" are sometimes used interchangeably). These diseases are characterized by primary involvement of the walls of the lungs' ALVEOLI and the tissues that surround the alveoli. A characteristic progression occurs beginning with INFLAMMATION and damage of the alveolar structures. That often leads to deposition of scar tissue consisting of COLLAGEN fibers, a process known as FIBROSIS.

As fibrosis becomes widespread, scar tissue stiffens the lungs and obliterates alveoli. As a result, patients who suffer pulmonary fibrosis become increasingly unable to breathe. Pulmonary fibrosis is a severe form of interstitial lung disease

and represents an end-stage in the progression of those diseases.

1.2 What are the Causes of Pulmonary Fibrosis?

Pulmonary fibrosis results from a large number of different lung diseases and injuries. By some accounts, more than 180 known individual diseases cause interstitial lung involvement. But the actual cause is not known or cannot be determined in nearly half of all patients diagnosed with pulmonary fibrosis.

Among the most common known causes is inhalation of inorganic dusts. The most important examples of inorganic dusts that cause pulmonary fibrosis are asbestos, coal dust and silica. Other inorganic dusts that cause pulmonary fibrosis include beryllium, talc, antimony and "hard" metals such tungsten carbide.

Other common causes of pulmonary fibrosis include inhalation of organic dusts, immunologic diseases (such as rheumatoid arthritis and systemic lupus erythematosus), exposure to certain medications, and disorders that cause pulmonary hemorrhage. It is likely that fibrosis also result from some lung infections, but exposure to tobacco smoke is generally not regarded as a cause of pulmonary fibrosis.

1.3 How is Pulmonary Fibrosis Diagnosed?

Patients with interstitial lung disease and pulmonary fibrosis often have tell a characteristic story of their illness. They typically complain of progressive shortness of breath, decreased tolerance for exertion and exercise, fatigue and dry cough. Progression is often slow: there are usually many months or years between first signs of breathlessness on exertion and the subsequent development of breathlessness at rest.

The physical examination may be initially normal, but readily recognized and characteristic physical abnormalities develop over time. Examples of these examination findings include abnormal air flow sounds in the lungs ("rales"), deformities of the finger- and toe-nails ("clubbing") and cyanosis.

Laboratory testing is important in making this diagnosis. Chest xrays usually reveal a pattern of diffusely increased markings that correspond to deposits of scar tissue within the lungs. The extent and severity of xray changes are useful in determining the stage and severity of underlying disease.

Another helpful diagnostic tool is pulmonary function testing which measures the capacity (i.e., volume) of the lungs, the rates of airflow within the lungs, and the

ability of gases to diffuse from alveoli into the blood stream. Pulmonary fibrosis is typically associated with smaller than normal lung volumes, increased rates of air flow and decreased gas diffusion.

Often, a diagnosis of pulmonary fibrosis can only be made by invasive tests. One example is bronchoscopy, in which fiberoptic tubes are passed into the lung's airways in order to visualize diseased areas and to obtain biopsy samples for microscopic analysis. Another test is bronchoalveolar lavage (BAL) which entails rinsing the lung's airways and collecting the wash fluid for microscopic analysis of its constituents. Analysis of BAL fluid is useful for evaluating the nature and severity of lung inflammation. It is sometimes necessary to obtain lung specimens by surgical biopsy so that underlying lung disease can be fully evaluated and characterized.

1.4 What is the Prognosis of Pulmonary Fibrosis?

The prognosis of pulmonary fibrosis depends in large part on its cause and the course of disease can be variable. If untreated, most patients develop progressive illness leading to disabling shortness of breath, heart failure, further clinical deterioration and death. Lung infections are common late in the course of disease and pneumonia is a frequent cause of death in these patients.

1.5 How is Pulmonary Fibrosis Treated?

The first, and most important, strategy for treating patients with interstitial lung disease and pulmonary fibrosis is removal from further exposure to the causative agent. For this reason, it is important that efforts be made to identify possible causative exposures. A careful, detailed exposure history is essential for this purpose. Removal from further exposure, however, rarely reverses the fibrotic process.

Therapy for most forms of interstitial lung disease is directed toward suppressing inflammation in the lungs. The most effective medications to reverse inflammation are steroid compounds similar to hormones secreted normally by the adrenal glands. Steroids can be administered orally, by injection or by inhalation. In some patients, lifetime use of these medications is required.

Other medications with powerful immunosuppressive activity may be of value in patients who do not respond adequately to steroids. These medications, such as cyclophosphamide, are more often used for patients with immunologic diseases such as rheumatoid arthritis.

Supportive therapy includes nonspecific therapeutic agents that do not arrest or reverse the lung disease, but which decrease symptoms and allow patients to feel better and be more active. Examples of supportive treatment include bronchodilators, which can improve airflow throughout the lungs, and supplemental oxygen.

2 ALUMINUM EXPOSURE and PULMONARY FIBROSIS

The possible association of aluminum and pulmonary fibrosis is based on animal research and rare reports of illness in exposed workers. As described below, there is difficulty in extrapolating from those animal studies to human illness. Moreover, most of the case reports of exposed workers also involved exposure to chemicals such as asbestos and crystalline silica that are known to injure the lungs and are sometimes found as workplace contaminants.

Pulmonary fibrosis in workers exposed to aluminum compounds was first reported almost 60 years ago. Since then, fibrosis has been described in a number of different aluminum-related industrial settings including production of fine aluminum metal particulates ("pyropowder") (1-3), manufacture of alumina abrasives (corundum) (4-7), aluminum polishing (8), aluminum welding (9), bauxite refining (10,11) and other alumina-related processes (12-15). As described below, in almost all of these cases aluminum was not the cause of illness. Moreover, a far greater number of reports have failed to find such abnormalities in exposed aluminum workers.

Fibrosis has also been found in animal exposed to some aluminum compounds (16-18). However, those animal studies do not generally serve as good models of worker exposure because methods of aluminum administration differed greatly from those that occur in humans. In particular, animals often received very large doses of aluminum compounds injected directly into the tracheas, rather than by inhalation into the lungs. That route of administration shares little correlation with occupational exposure.

The following discussion considers the evidence that supports the association between exposure to various aluminum compounds and pulmonary fibrosis. Because of the variety of aluminum compounds involved and the specific settings in which they were used, the discussion tends to follow an historical narrative. Ultimately, however, any explanation for the association must depend on the physical and chemical properties of those compounds. Accordingly, the discussion begins with brief consideration of the importance of particle size and aluminum reactivity in the development of lung disease.

Readers should appreciate the large clinical effects that are associated with seemingly small variations in exposure setting, particle size or the presence of contaminants. In many cases, these small variations explain the major disparities and disagreements of the scientific findings.

2.1 The Respiratory Importance of Particle Size

Particle size plays a critical role in determining the quantity and distribution of inhaled aluminum particles. Particles <1 μ in diameter are readily inhaled into the alveoli where they are deposited. Particles >7-10 μ are mostly trapped by mucus lining the nose and upper airways and very little enters the lungs. Particles of intermediate size may enter the airways, but they rarely reach the alveoli. As a consequence, exposure to very small particles results in greater lung exposure than occurs with exposure to large particles.

2.2 Aluminum Reactivity

Aluminum is highly reactive. The metal reacts avidly and rapidly with oxygen in the air to form a thin coating of aluminum oxide (Al_2O_3). That reaction also yields large amounts of heat. It is this layer of aluminum oxide that imparts aluminum's characteristic corrosion-resistance (3). Aluminum oxide is generally very stable and insoluble in the pH range of body tissues.

To prevent freshly generated aluminum particles from being oxidized, they can be shielded from ambient oxygen by coating the particles with oils or fatty substances. As described below, the choice of coating substance has contributed importantly to the subsequent development of disease in exposed individuals.

2.3 Aluminum Abrasives and Shaver's Disease

During the late 1940's, a series of publications from Canada reported a distinct and previously unrecognized lung disease among workers manufacturing alumina abrasives (4-7). That disorder, which the authors regarded as "bizarre", was named "Shaver's Disease" after the physician who first described it. The disease caused severe pulmonary fibrosis, shortness of breath, chest pain, cyanosis and recurrent lung collapse (PNEUMOTHORAX). Progression of disease was rapid (about six years from exposure onset to death) and frequently involved young men.

Affected workers had been exposed to dense fumes from electric arc furnaces in which mixtures of bauxite, iron and coke were heated to temperatures >2000°C. The fumes consisted mainly of amorphous particles of alumina (40-60%) and silica, (30-45%). The majority of particles were <0.5μ in diameter (7). Chemical

analysis of the lungs of victims found large amounts of silica and alumina, each representing about 30% of lung mineral contents.

It seems most likely that Shaver's Disease was caused by the large amounts of silica inhaled by these workers. Silica is an important and aggressive cause of pulmonary fibrosis. Moreover, subsequent studies of workers exposed only to alumina dust have failed to demonstrate pulmonary fibrosis. It is also noteworthy that Shaver's Disease has virtually disappeared from the modern workplace, presumably because of improved work conditions and better worker protection.

2.4 Fine Aluminum Dust and "Pyropowder"

Another form of pulmonary fibrosis was associated with exposure to fine ($<1\ \mu$) aluminum dust used in explosives and pyrotechnics. First reported in Germany following World War II, it was later described in England (1,2) but has never been described in North America. Affected workers developed complaints much like those of Shaver's Disease with progressive fibrosis, breathlessness, chest pain, pneumothorax leading to death in some cases.

This disorder is related to the methods by which fine aluminum powder is manufactured. For more than 100 years, aluminum has been processed into flakes and powders of different sizes by stamping, grinding or ball milling. Particle size and shape vary according to manufacturing process and intended use. For example, particles used for metallic pigment, "bronzing powder", are flattened flakes about 60 μ. By contrast, the most desirable size for pyrotechnics particles is $<1\ \mu$ because as the size of aluminum particles decreases, they become pyrophoric (i.e., spontaneously ignite in air) (3).

During manufacture, a lubricant is added to the flakes to prevent impact welding and to minimize pyrophoricity (that is, spontaneous oxidation is minimized by coating the particles to prevent contact with oxygen). The traditional lubricant used for this purpose was stearic acid, a fatty acid which reacts with the aluminum to form stable aluminum stearate.

In retrospect, pulmonary fibrosis developed only in "pyropowder" workers who worked at a time when mineral oil replaced stearic acid as the process lubricant. Unlike stearic acid, mineral oil coats particles, but does not react with them and can be readily removed. The change to mineral acid occurred in Germany due to shortages of stearic acid. After the war, English companies changed their production methods in an effort to emulate German processes. Mineral oil was apparently never used for this purpose in North America.

It is understood that very small (i.e., <1 μ) aluminum particles are inhaled and transported to the alveoli where they are ingested (PHAGOCYTOSIS) by alveolar cells called macrophages. Stearate-coated particles and aluminum oxide-coated particles are inert and do not react within the macrophages. But following phagocytosis, it is hypothesized that the oil is removed from mineral oil-coated particles and the exposed aluminum reactively oxidizes within the macrophages. That process yields enough heat to cause tissue damage (18,19). Pulmonary fibrosis develops in response to that damage.

In other words, inhalation of aluminum pyropowder can lead to pulmonary fibrosis if they are first coated with a lubricant, such as mineral oil, that initially prevents oxidation, but which is removed following phagocytosis. Pulmonary fibrosis has been reported in only one worker exposed to stearate-treated aluminum powder (20), and that individual suffered a very atypical disease involving both lungs and nervous system. It is difficult to attribute his particular and unusual disease to inhaled dust.

2.5 Pulmonary Fibrosis and Workplace Contaminants

Isolated cases of pulmonary fibrosis have been described in workers exposed to aluminum in a variety of settings such as aluminum polishing (8), aluminum welding (9), bauxite refining (10,11) and other alumina-related processes (12-15). In most, examination of the workplace or of specimens of lung tissue from the patients themselves demonstrated other materials that can cause fibrosis.

Among the most common causes of work-related pulmonary fibrosis is asbestos which has been used to insulate potroom and welding equipment. Another important cause of work-related pulmonary fibrosis is crystalline silica. Examination of the fibrotic lungs of aluminum workers have often been shown to contain asbestos fibers (9,12,14) or large amounts of silica (7,8). Accordingly, it is likely that development of fibrosis after such mixed exposures was due to asbestos or silica, not aluminum.

2.6 Alumina as a Nuisance Particulate

NUISANCE PARTICULATES are dusts that irritate the airways when inhaled, but cause few adverse lung effects and do not produce significant disease. Generally, nuisance dusts are biologically inert and do not react chemically with lung tissues (21). By contrast, dusts that cause pulmonary fibrosis are referred to as FIBROGENIC PARTICULATES.

Alumina and bauxite are usually regarded as nuisance dusts. In most studies of

aluminum industry workers, there has been no evidence of pulmonary fibrosis or other changes due to aluminum compound exposure (22,23). There is also a well documented history of "therapeutic" aluminum inhalation ("McIntyre Powder" consisting of particles $<5\ \mu$, 80% aluminum oxide and 20% aluminum) administered daily to prevent silica-induced pulmonary fibrosis in Canadian miners (24). Total lung doses of more than 1.5 g were apparently harmless.

However, there is some evidence that prolonged exposure to alumina (as with other nuisance particulates) can provoke low-grade inflammation of the airways leading to decreased ventilatory capacity (25). Studies of large numbers of workers at a bauxite refinery and alumina-based chemical plant found that exposed workers had small, but significant decrements in lung function compared to nonexposed workers (10). However, these effects were only observed among workers exposed to excessive air concentrations.

2.7 Alumina as a Fibrogenic Particulate

There is no indication that inhalation of alumina by man leads to pulmonary fibrosis. Experimental administration of alumina to animals by routes other than inhalation, such as direct instillation into the trachea, has under some conditions caused fibrosis. The actual response, however, seems to depend on the actual form of alumina used.

Alumina names a compound of constant chemical composition (aluminum oxide, Al_2O_3), but of variable structures and form. These various forms of alumina have different properties and are known by differing names (for example, activated alumina and metal grade alumina). During the manufacturing process that turns bauxite ore into aluminum, a variety of different alumina can be formed.

Sources of differences among the forms of alumina include chemical purity (the presence of contaminants), hydration (the presence of water or hydroxyl groups) and crystal structure. From a biological perspective, two important differences among alumina are particle size and surface area. Large variations can occur.

For example, a recent study comparing alumina samples found that particles in some were all $<1\ \mu$, while in others the particles were $>7.5\ \mu$. (In effect, one sample consisted entirely of particles that could be inhaled into the alveoli, while the other contained few particles that could even enter the lungs). Likewise, the specific surface areas of samples varied from 0.5 to 110 m^2/g (26). A direct association also existed between surface area and catalytic activity (28).

When alumina were experimentally administered to rats, biological response was

correlated to particle size, surface area and catalytic activity. Only the smallest particles with the largest surface areas and the greatest catalytic activity caused pulmonary fibrosis (27).

3 SUMMARY

There is no evidence that alumina and other aluminum compounds other than pyropowder are able to cause fibrosis in the lungs of exposed workers. Occasional reports of pulmonary fibrosis associated with aluminum compounds were most often due to concomitant exposure to asbestos or crystalline silica. In most situations aluminum and alumina particles act only as nuisance dusts.

4 GLOSSARY

ALVEOLI: Small, sac-like dilatations at the ends of the lungs' airways where gas exchange takes place.

COLLAGEN: A protein that is the basic building block of connective tissue including scar tissue. Collage is secreted as fibers by connective tissue cells.

FIBROGENIC PARTICULATES: Dust particles that cause fibrosis when inhaled into the lungs. Examples of fibrogenic particles include asbestos, silica and carbon.

FIBROSIS: The formation of fibrous connective tissue (i.e., scar tissue), usually as a result of the body's response to inflammation. In fibrosis, connective tissue cells secrete increased amounts of collage fibers.

INFLAMMATION: A nonspecific reaction to injury characterized by increased movement of blood, fluids and inflammatory cells to the injury site. Inflammatory cells can release biologically active chemicals that can damage lung cells and connective tissue.

NUISANCE PARTICULATES: Dust particles that irritate the airways when inhaled, but cause few adverse lung effects and do not produce significant disease.

PHAGOCYTOSIS: The engulfing of foreign particles, microorganisms or other cells by specialized cells such as macrophage. Phagocytosis provides an important means for the removal of foreign particles from the body cavities.

PNEUMOTHORAX: A abnormal condition in which a lung collapses as a result of

air accumulation between the lung and the chest wall. Such air accumulation may result from spontaneous air leaks from damaged parts of lung, as occurs in emphysema and pulmonary fibrosis. Pneumothorax may be complete or partial.

5 REFERENCES

1. Mitchell J, Manning GB, Molyneux M, et al: Pulmonary fibrosis in workers exposed to finely powdered aluminium. Br J Ind Med 18:10-20, 1961.

2. Jordan JW: Pulmonary fibrosis in a worker using an aluminum powder. Br J Ind Med 18:21-23, 1961.

3. Dinman BD: Aluminum in the lung: the pyropowder conundrum. J Occup Med 29:869-876, 1987.

4. Shaver CG, Riddell AR: Lung changes associated with the manufacture of alumina abrasives. J Indust Hyg Toxicol 29:145-157, 1947.

5. Shaver CG: Pulmonary changes encountered in employees engaged in the manufacture of alumina abrasives. Occup Med 5:718-728, 1948.

6. Riddell AR: Pulmonary changes encountered in employees engaged in the manufacture of alumina abrasives. Occup Med 5:710-717, 1948.

7. Wyatt JP, Riddell CR: The morphology of bauxite-fume pneumoconiosis. Am J Pathol 25:447-465, 1949.

8. de Vuyst P, Dumortier P, Rickaert F, et al: Occupational lung fibrosis in an aluminium polisher. Eur J Respir Dis 68:131-140, 1986.

9. Herbert A, Sterling G, Abraham J, et al: Desquamative interstitial pneumonia in an aluminum welder. Hum Pathol 13:694-699, 1982.

10. Townsend MC, Enterline PE, Sussman NB, et al: Pulmonary function in relation to total dust exposure at a bauxite refinery and alumina-based chemical products plant. Am Rev Respir Dis 132:1174-1180, 1985.

11. Townsend MC, Sussman NB, Enterline PE, et al: Radiographic abnormalities in relation to total dust exposure at a bauxite refinery and alumina-based chemical products plant. Am Rev Respir Dis 138:90-95, 1988.

12. Jederlinic PJ, Abraham JL, Churg A, et al: Pulmonary fibrosis in aluminum oxide workers. Am Rev Respir Dis 142:1179-1184, 1990.

13. Gilks B, Churg A: Aluminum-induced pulmonary fibrosis: do fibers play a role? Am Rev Respir Dis 136:176-179, 1987.

14. Kilburn KH, Warshaw RH: Irregular opacities in the lung, occupational asthma, and airways dysfunction in aluminum workers. Am J Ind Med 21:845-853, 1992.

15. Miller RR, Churg AM, Hutcheon M, et al: Pulmonary alveolar proteinosis and aluminum dust exposure. Am Rev Respir Dis 130:312-315, 1984.

16. Stacy BD, King EJ, Harrison CV: Tissue changes in rats' lungs caused by hydroxides, oxides and phosphates of aluminium and iron. J Pathol Bacteriol 77:417-426, 1959.

17. King EJ, Harrison CV, Mohanty GP, et al: The effect of various forms of alumina on the lungs of rats. J Pathol Bacteriol 69:81-93, 1955.

18. Corrin B: Aluminium pneumoconiosis I. In vitro comparison of stamped aluminium powders containing different lubricating agents and a granular aluminium powder. Br J Ind Med 20:264-267, 1963.

19. Corrin B: Aluminum pneumoconiosis. II. Effect on the rat lung of intratracheal injections of stamped aluminium powders containing different lubricating agents and of a granular aluminium powder. Br J Ind Med 20:268-276, 1963.

20. McLaughlin AIG, Kazantzis G, King E, et al: Pulmonary fibrosis and encephalopathy associated with the inhalation of aluminum dust. Br J Ind Med 19:253-263, 1962.

21. Documentation of the Threshold Limit Values and Biological Exposure Indices (6th Edition). Cincinnati: American Conference of Governmental Industrial Hygienists, 1991.

22. Kilburn KH: Pulmonary and Neurologic Effects of Aluminum. In: Environmental and Occupational Medicine. Rom WN (ed). Boston: Little, Brown, p.465-473, 1992.

23. Abramson MJ, Wlodarczyk JH, Saunders NA, et al: Does aluminum smelting cause lung disease? Am Rev Respir Dis 139:1042-1057, 1989.

24. Crombie DW, Blaisdell JL, MacPherson G: The treatment of silicosis by aluminum powder. Can Med Assoc J 50:318-328, 1944.

25. Morgan WKC: Industrial bronchitis and other nonspecific conditions affecting the airways. In: Occupational Lung Diseases. Morgan WKC, Seaton A (eds). Philadelphia: Saunders, p.521-540, 1986.

26. Ess SM, Steinegger A, Ruettner JR, et al: The fibrogenic potential of different types of alumina. Zurich: Swiss Federal Institute of Technology, 1993.

27. Ess SM, Steinegger A, Ess HJ, et al: Experimental study on the fibrogenic properties of different types of alumina. Am Ind Hyg Assoc J 54:360-370, 1993.

28. Dinman BD: Alumina-related pulmonary disease. J Occup Med 30:328-335, 1988.

JONATHAN BORAK & COMPANY, INC.

Specialists in Occupational & Environmental Health

October 18, 1993

Mr. Seymour Epstein
Technical Director
The Aluminum Association
900 19th Street
Washington, DC 20006

Dear Sey:

I am responding for Dan Jaffe regarding the Rockette/Gitelman paper. As we discussed by phone, I have serious concerns about the quality and implications of this work. Many of my comments on an earlier version of the manuscript were incorporated into a letter that Dan Jaffe wrote to you in late May or early June.

I think that the study was badly designed and/or poorly executed. This may not be the fault of Rockette and Gitelman, but it is now their burden! There are a number of places where shortcomings should be dealt with but, instead, the manuscript either fudges the failings or tries to ignore them.

1. Study states that there were 279 workers selected (235 exposed and 44 controls). For each, "occupational exposures were evaluated by obtaining two full-shift samples for each exposed individual during the work interval" (p.4). But, "199 workers in production areas had a measurement for total aluminum exposure and 170 had a measurement for respirable aluminum" (p.8). Worse, only "156 employees had both a total aluminum and respirable aluminum industrial hygiene measurement" (p.9).

<u>In other words, there was complete exposure data for only 55.9% of the subjects</u>.

The study implies a certain rigor, but fails to deliver. The investigators should have dropped from consideration those workers for whom complete sampling was not available. It is difficult to understand the force of the conclusions drawn in light of the fact that there were not complete data for nearly half of all study subjects.

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2. There were no measurements of respirable air for two of 15 plants. Those two plants should have been deleted from further consideration. Instead, the investigators "estimated the respirable aluminum values from their total aluminum exposures using the correlation derived from plants with both measurements" (p.10).

This was procedurally improper. To achieve a meaningful "correlation" would have required more rigorous and systematic industrial hygiene assessments than were carried out. The number of data points was too small to justify such an approach.

Moreover, the limited information provided on the correlation raises still greater concerns: "Although the two measurements [i.e., total and respirable aluminum] are highly correlated ($r=0.59$, $p<0.001$), 26% of these pairs were classified as high in one measure and low in the other". Notwithstanding the statistical significance, an "r" of 0.59 indicates that variations in total dust explain only about 35% of the variation in respirable dust. Further, 26% of the plants had apparently substantial divergence between total and respirable dust levels.

Based on these data, it seems clear that estimating respirable dust levels from measured total dust levels is (in this context) without meaning and represents a distortion and misapplication of statistical methods.

As a separate concern, these authors might want to argue that a rigorous industrial hygiene relationship exists between total and respirable dust across all aluminum plants and that such relationship allows measurement of total dust to serve as a proxy for respirable dust. That would be a testable hypothesis, but to test that hypothesis would require substantial IH data. Instead, the authors simply state that such a relationship exists. But, their own data indicts that this is not true!

3. The authors state that "workers known to be using any aluminum-containing medication were not enrolled in the study" (p.4), but later state that "although we tried to exclude individuals with a history of recent antacid use from participating in the study, the study questionnaire revealed 8.5% of the exposed workers and 7.4% of non-exposed controls had used an antacid in the preceding week" (p.12).

It is likely that many of those who had used antacid medications had ingested large quantities of aluminum (500-2000 mg/day). Inclusion of these workers was incorrect and they should have been excluded from the study and their data excluded from considerations.

Moreover, the integrity of the authors is put to question by this seeming contradiction. Their only defense is that they suspected but did not know that these workers were using aluminum-containing medications. They are sophisticated researchers in this field, and they should not plead ignorance to justify bad research methods.

4. In the "Subjects" section, the authors state that there were 44 controls. In the "Experimental Design" section they indicate that there were only 42 controls ("Twelve plants had three unexposed workers as controls, one plant had four, and one plant had two").

5. There is almost no demographic data on the subjects. We are told that 244 of 279 were males (p.4). Also, the control group had proportionately more females, a disproportion large enough to explain a significant difference in serum creatinine! But, we know nothing else about the groups. Can the authors assure that other observed group differences were not based on gender? Why is the demographic data not provided?

6. The authors regard particles less than 10μ as "respirable", but in humans that is too large for particles to enter the alveoli. They then refer to aluminum "being absorbed across airway epithelia", but it is more likely that large particles were actually swept by mucociliary clearance out of the airway and were then swallowed. The authors cannot distinguish between the effects of inhalation and ingestion in this population, but they draw sweeping conclusions about the risks of inhalation.

6. Similarly, the authors compare the measured aluminum exposure (or mostly measured exposure) with a book-derived estimate of aluminum ingestion. Based on that comparison, they draw very strong conclusions about the relative importance of inhalation versus ingestion:

> "It can be seen that the amount of change ... is more than one hundred fold greater than would be expected for a similar increase in dietary exposure. This relationship provides additional support for the present of an absorptive pathway that is exceptionally sensitive to small amounts of aluminum".

Given that no actual measurements or assessments were made of the workers' actual diets, that 8.5% had recently taken antacids, and that adequate data was available for only 56% of subjects, this is a purely hypothetical conclusion that contains no rigor. The authors' properly qualified statement should have been:

> "If aluminum particles up to 10μ were respirable (but they are not), and if we knew the actual exposures of these workers (but we only know them for about 56%) and if we knew their dietary intake (but we do not, so we have estimated that intake as 18 mg per day even though we recognize that this is an oversimplification and that least 8.5% took antacids and others may have consumed tea or processed cheeses or pickles and so forth) then we might conclude that the inhalation route is 100 fold greater ..."

In short, the conclusions and summary section contains hyperbolic statements ("the absorptive pathway that is exceptionally sensitive to small amounts of aluminum") and numerically unjustified quantitative conclusions ("one hundred fold greater than would be expected").

It is likely that inhalation is a significant route of exposure for some aluminum dusts. This study provides qualitative confirmation of that. But it does not justify the actual quantitative conclusions drawn. The empirical database in this study is inherently inadequate. The authors should include a statement recognizing the limitations of their data. I also suggest a qualifier that these findings are only preliminary and require further and more rigorous confirmation.

Yours truly,

Jonathan Borak, MD

cc: D. Jaffe

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