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LUNG PATHOLOGY AND MINERALOGY ASSOCIATED WITH HIGH PULMONARY BURDEN OF METAL PARTICLES: Fe, Ti, Al AND Cr IN A PNEUMOCONIOSIS DATABASE

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INTRODUCTION

The inhalation of respirable inorganic particles at low levels is a commonplace everyday occurrence. Typically, the types of particulates which are inhaled and variably retained in the lungs, are those commonly present in ambient aerosols. Much of the particulate matter is aeolian crustal material (deflationary soil) and anthropogenerated material (combustion emissions, construction products). This low or "background" level of exposure is usually orders of magnitude lower than the levels of exposure in occupational settings giving rise to lung disease. We have been studying the human lung burden of retained inorganic particulates for many years (Abraham and Burnett, 1983) and have developed an ever-expanding database (Abraham *et al.*, 1991) of information on the lung burden in currently over 700 analyses of over 600 lungs. The database contains mostly data from persons with known or suspected aerosol particulate exposures of one kind or another; it also contains data from histologically normal lungs and lungs from persons with lung disease but not known occupational or environmental exposures.

Previous studies have examined the relationship of concentrations of a few specific particles to pathologic reactions in patients with specific exposures and/or diseases, such as: sandblasters with silicosis; beryllium ceramics workers with and without chronic beryllium disease; cemented tungsten carbide workers with the unusual pathologic reaction; GIP (giant cell interstitial pneumonia); granulomatous and fibrotic lung disease in persons exposed to metals such as titanium, zirconium or aluminium; and welders. In addition, with the ongoing interest in the relationship of fine particulate aerosols in air pollution to health effects several studies have investigated the potential toxicity of various metals, especially the transition metals, Fe, Ni, V, Cu, Mn and Zn in materials such as residual oil fly ash (ROFA). The higher prevalence of such metals as V in ROFA than in particulates identified in, or recovered from lungs, is consistent with the importance of soluble metals from such particulates. Factors such as particle diameter, surface area, roughness and the presence of surface species are also likely to play critical roles. Metal particulate exposures are also of increasing interest in the etiology and pathogenesis of interstitial lung disease which might otherwise be termed "idiopathic" pulmonary fibrosis/"cryptogenic" fibrosing alveolitis (Kennedy and Chan-Yeung, 1996). Several years ago evidence of metal particulate exposure was found in a number of cases of DIP (desquamative intersitial pneumonia) (Abraham and Hertzberg, 1981). The above supports the need for further research into metal particulate exposures and lung disease.

In this study we investigate the four most commonly occurring metallic elements in the lung burden database, namely: Fe, Ti, Al and Cr. Previously, we have reported the aggregate findings in our database (Abraham *et al.*, 1991) and several groups of cases and individual cases have been investigated with comparison of the findings in selected cases to those in the database. Our aim here is to determine whether the elevated frequency of occurrence of Fe, Ti, Al and Cr is of particular significance. Furthermore, examining the cases with the highest concentrations of these metals may reveal hitherto unrecognized associations of exposures to diseases.

BACKGROUND AND METHODS

For each analysed case, an *in situ* quantitative analysis of particulates using SEM and EDXA yields total concentration as well as specific concentrations of particle types (Abraham and Burnett, 1983). The morphometric analytical technique yields concentrations in volumetric terms, numbers of particles per cubic centimeter of lung tissue. The three major groupings of particles are: silica (containing only Si), aluminium silicates (containing Si and Al at least) and metals (containing metallic elements and not containing Si). Among the metal-containing particles, the concentrations and frequencies of detection vary greatly. A summary of this data is shown in Table 1. The overall distribution of inorganic particle concentrations is log-normally distributed (Fig. 1).

Metal particulates form a diverse group. They are quite different from the silica and aluminium silicate particle groups in that the metal group includes, potentially, at least, virtually any metallic element. Nearly one-third of the elements in the periodic table have been detected in lungs in the database (Abraham *et al.*, 1991). What is difficult to present in detail is the complexity of the metal associations. Since the SEM/EDXA method permits analysis of individual particles and reveals simultaneously all those elements with atomic number greater than 9 (Na and higher) and their relative abundance (with a detection limit of approximately 1% by weight in that particle) the permutations of possible specific particle types with several different elements in the same particle (and multiple possible ratios of one element to the other(s) are practically innumerable. Therefore, initially, for the sake of manageability, the individual cases with concentrations of any of the four most prevalent metals ranked in the top 3% of all analyses were selected for study. This includes the 22 cases each ranked highest by concentrations of Fe, Ti, Al or Cr.

RESULTS AND DISCUSSION

When the top-ranked cases for Fe, Ti, Cr and Al particulate concentrations are tabulated, it becomes apparent that these metals do not always occur in isolation, and are not the result of independent exposures. Table 2 presents the 16 possible combinations of these four elements. It reveals that only a few cases contain high

Table 1. Frequency of various metal particles in 690 tissue section analyses

Metal	Number (and %) of cases where metal identified
Fe	610 (88.41%)
Ti	555 (80.43%)
Al	397 (57.53%)
Cr	315 (45.65%)
Ni	209 (30.29%)
Zn	175 (25.46%)
Sn	162 (23.48%)
Cu	146 (21.16%)
W	126 (18.26%)
Mn	120 (17.39%)
Pb	114 (16.52%)
Ba	89 (12.90%)
Zr	73 (10.58%)
Ce	73 (10.58%)
Ag	60 (8.70%)
V	51 (7.39%)
Au	41 (5.94%)
Co	34 (4.93%)
Hg	31 (4.49%)
Ta	27 (3.91%)
Sb	26 (3.77%)
Bi	25 (3.62%)
La	14 (2.03%)
Nd	14 (2.03%)
Cd	8 (1.16%)
Mo	7 (1.01%)
Br	5 (0.72%)
Nb	5 (0.72%)
Se	4 (0.58%)
Os	2 (0.29%)
As	2 (0.29%)
Ru	1 (0.14%)

concentrations of only one of these elements. Much more common are high concentrations of more than one of the four metals. Moreover, for these "frequently occurring" metals the occurrence of high concentrations of specific metal associations appears to be related to particular exposures. This is reflected in the coding of the individual cases by occupation. For example, it is easy to recognize certain combinations, such as Fe with Cr from steel working operations such as welding or grinding or foundry work. Some additional elements, not the subject of this report, may also be important in distinguishing different types of exposures and pathologic reactions. For instance, Ni is also found in many particles which contain Fe and Cr (indicating a stainless steel type of source). Although there were potentially 88 cases when the top 22 (3%) cases were tabulated by concentration for each of four elements, only 46 individual cases result, since many of the cases show increases of more than one of these elements. The median diameter for metal particles was 0.4 μm. In the analyses for which the particular metal was detected, the median concentrations (in millions of particles per cm^3 of tissue) were: Fe, 10.3; Ti, 7.5; Al, 5.6; and Cr, 3.4.

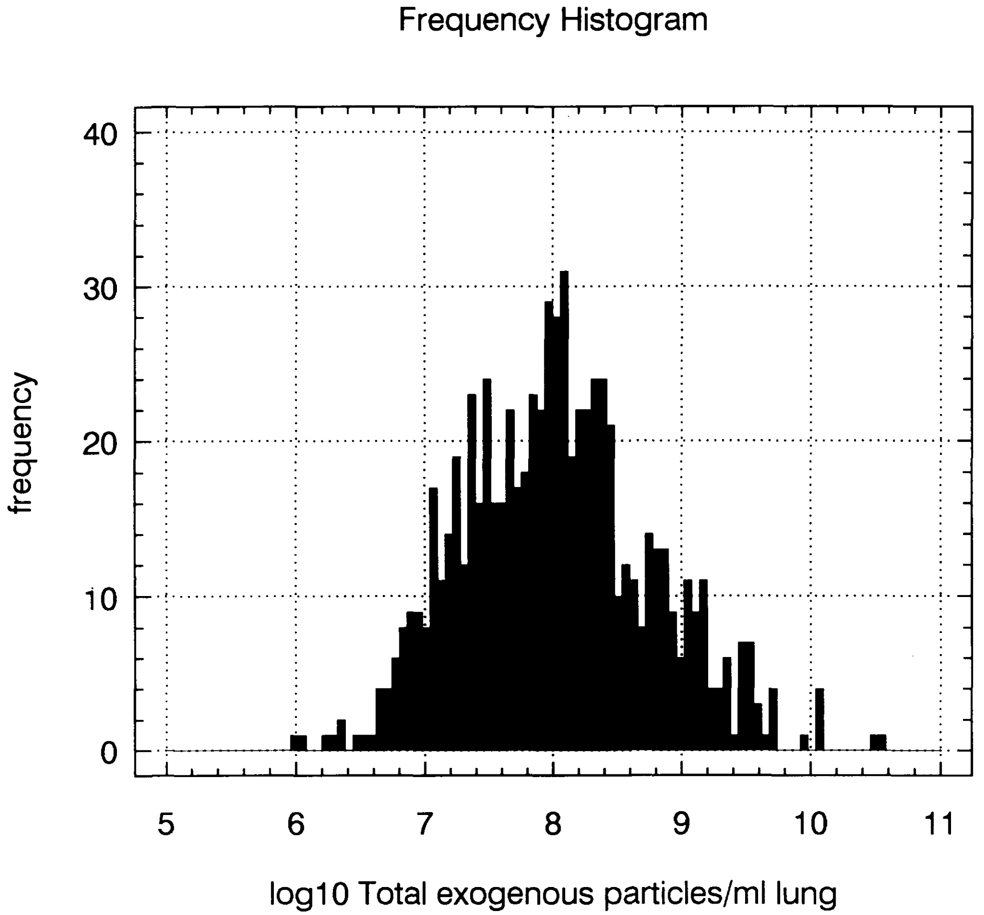

Fig. 1. Histogram showing frequency of cases by concentration of all non-fibrous inorganic particles in pneumoconiosis database. Logarithmic (base 10) scale for concentrations in particles cm^{-3} lung.

Iron

There were five cases showing high Fe but not high Ti, Al or Cr. These cases had histories of metal working and pathology revealed extensive siderosis, some with arc welder's pneumoconiosis, others with mixed dust pneumoconiosis. The other high Fe cases also had elevation of one or more of the other three major metals reported here. The most common association with Fe with Cr (12 cases) and Fe with Ti (11 cases). The histories associated with these cases included metal working and sandblasting and the pathology did not appear specific.

Titanium

There were five cases showing high Ti but not high Fe, Al or Cr. These cases had histories of spray painting and pathology revealed deposits of fine opaque, birefringent dust typical of titanium dioxide. One case had hypersensitivity pneumonitis, shown to be most likely related to toluene di-isocyanate exposure (Redline *et al.*, 1986). The other high Ti cases also had elevation of one or more of

Table 2. Cases with combinations of metals where Cr, Al, Ti, Fe concentrations singly or combined are in the top 3% of all cases

Case (occupation)	Cr Al Ti Fe	Cr Al Ti	Cr Al Fe	Cr Ti Fe	Cr Al	Cr Ti	Cr Fe	Cr	Al Fe Ti	Al Ti	Al Fe	Al	Fe Ti	Fe	Ti
1 (MW) [a]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
2 (SB) [b]	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
3 (SB)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
4 (SB)	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
5 (SB)		√			√	√		√		√		√			√
6 (SB)			√		√		√	√			√	√		√	
7 (MW)			√		√		√	√			√	√		√	
8 (SB)				√		√	√	√					√	√	√
9 (MW)				√		√	√	√					√	√	√
10 (MW)				√		√	√	√					√	√	√
11 (SB)						√		√							√
12 (F) [c]						√		√							√
13 (?) [d]						√		√							√
14 (SB)							√	√						√	
15 (MW)							√	√						√	
16 (MW)							√	√						√	
17 (MW)								√							
18 (SB)								√							
19 (SB)								√							
20 (SB)								√							
21 (SB)								√							
22 (?)								√							
23 (DT) [e]								√							
24 (AlW) [f]									√	√	√	√	√	√	√
25 (AlW)										√		√			√
26 (MW)											√	√		√	
27 (BeC) [g]												√			
28 (BeC)												√			
29 (BeC)												√			
30 (AlW)												√			
31 (AlW)												√			

continued

Table 2. *continued*

Case (occupation)	Cr Al Ti Fe	Cr Al Ti	Cr Al Fe	Cr Ti Fe	Cr Al	Cr Ti	Cr Fe	Cr	Al Fe Ti	Al Ti	Al Fe	Al	Fe Ti	Fe	Ti
32 (ECP) [h]												√			
33 (HM) [i]												√			
34 (HM)													√	√	√
35 (HM)													√	√	√
36 (MW)													√	√	√
37 (MW)														√	
38 (MW)														√	
39 (MW)														√	
40 (MW)														√	
41 (NiR) [j]														√	
42 (HM)															√
43 (Con) [k]															√
44 (?)															√
45 (P) [l]															√
46 (P)															√

(a) Metal working occupations (welding, grinding, cutting, foundry work). (b) Sand blaster. (c) Farmer. (d) Occupation unknown. (e) Dental technician. (f) A1 industry/product worker. (g) Beryllium ceramic worker. (h) Electronic components polisher. (i) Hard metal (cemented tungsten carbide) worker. (j) Nickel refinery worker. (k) Construction worker. (l) Painter.

Table 3. Case (occupations), pathology and metal concentrations where Cr, Al, Ti, Fe concentrations singly or in combination are in the top 3% of all cases

Case (occupation)	Pathology	Cr conc.	Al conc.	Fe conc.	Ti conc.	Metals as % of Total
1 (MW)	MD	1079	1174	1084	200	37
2 (SB)	AcS	158	436	1160	828	27
3 (SB)	AcS	433	208	364	455	25
4 (SB)	AcS	276	281	276	241	33
5 (SB)	AcS	64	257	119	484	80
6 (SB)	AcS	380	266	251	143	17
7 (MW)	GR; MD	346	520	476	54	62
8 (SB)	AcS	335	134	328	485	21
9 (MW)	ARC; ASB	191	0	255	168	32
10 (MW)	ARC	977	122	1128	940	99
11 (SB)	AcS	431	0	21	173	21
12 (F)	MD	205	0	10	234	9
13 (?)	MD; ASB	146	142	57	329	43
14 (SB)	AcS	110	0	296	142	21
15 (MW)	MD	191	71	284	6	61
16 (MW)	MD; ASB	362	0	562	2	100
17 (MW)	GR; HSP?	157	37	167	53	60
18 (SB)	AcS	181	140	135	116	50
19 (SB)	AcS	242	0	156	154	30
20 (SB)	AcS	123	52	26	89	28
21 (SB)	AcS	152	29	34	162	24
22 (?)	MD	174	0	57	0	16
23 (DT)	AcS; MD	235	15	185	95	31
24 (AlW)	GR	8	528	327	178	61
25 (AlW)	IF	0	1239	20	378	89
26 (MW)	GR; ARC	0	1235	625	87	47
27 (BeC)	GR	0	458	9	55	45
28 (BeC)	GR	0	218	81	53	24
29 (BeC)	GR	1	213	242	1	73
30 (AlW)	IF (min)	0	1330	3	45	97
31 (AlW)	AlW	0	11 328	0	0	100
32 (ECP)	PAP; AS	0	688	0	0	31
33 (HM)	GIP	0	230	156	102	83
34 (HM)	GIP	0	167	425	821	97
35 (HM)	GIP	0	0	765	650	100
36 (MW)	MD	0	0	430	377	27
37 (MW)	ARC; ASB	0	0	286	29	30
38 (MW)	ARC; ASB	0	0	610	46	97
39 (MW)	ARC	0	14	738	89	100
40 (MW)	ARC	0	0	11 489	0	100
41 (NiR)	MD; ASB	79	9	296	36	70
42 (HM)	GIP	27	27	142	406	11
43 (Con)	MD	0	24	5	178	48
44 (?)	MD	0	80	40	180	74
45 (P)	MD (min)	14	0	20	313	64
46 (P)	MD (min)	2	0	143	226	81

Concentrations in millions of particles cm^{-3} lung; percentages = total metal/total exogenous particle concentration.
Legend for occupation: see Table 2.
Legend for pathology: AcS = accelerated silicosis; MD = mixed dust pneumoconiosis; GR = granulomatous disease; ARC = arc welder's pneumoconiosis (siderosis); GIP = hard metal disease (giant cell interstitial pneumonia); PAP = pulmonary alveolar proteinosis (AS = acute silico-proteinosis); IF = interstitial fibrosis; ASB = asbestos bodies found; AlW = aluminum arc welder's lung; HSP = hypersensitivity pneumonitis; min = minimal.

the other three major metals reported here. The most common association was Ti with Fe (see Fe, above).

Aluminum

There were eight cases showing high Al but not high Ti, Fe or Cr. These cases had histories of aluminum work or beryllium ceramics work. Their pathology revealed interstitial pneumonitis and fibrosis or granulomatous disease. The other high Al cases also had elevation of one or more of the other three major metals reported here. The most common association was Al with Ti (see Ti above). Several of these cases included a series of beryllium ceramics workers (in whose lungs Zr was also found frequently) (Abraham *et al.*, 1995).

Chromium

There were seven cases showing high Cr but not high Ti, Al or Fe. These cases had histories of sandblasting (Wiesenfeld and Abraham, 1995), metal working and dental technician work; pathology revealed mixed dust pneumoconiosis in most. The other high Cr cases also had elevation of one or more of the other three major metals reported here. The most common association with Cr was Fe (see Fe above). Also, other dusty occupations resulted in high concentrations of silica and/or aluminium silicates in some of the cases and with Ni in cases exposed to stainless steel welding, Ni refinery work.

CONCLUSIONS

These preliminary observations further extend the study of inorganic particulates in the lung and illustrate some of the types of questions which a large database of this type can begin to ask. The complexity of the data precludes many definitive conclusions except in cases with high concentrations of single specific types of particles. There is a wide range of pathologic reactions associated with inhalation of metal particulates, very few of which are specific for a single type of exposure, with perhaps the exception of giant cell interstitial pneumonia and arc welder's pneumoconiosis. These findings of a number of granulomatous reactions and non-specific interstitial inflammatory and fibrotic processes also may indicate the need for further study of metal exposures in all such cases. It must be kept in mind that the exposures demonstrated by tissue microanalysis may reveal particles which are only markers of a more complex environment, such as the finding of tungsten in hard metal disease when cobalt is the most suspect agent (Abraham *et al.*, 1991), or similarly, metal fume particles found and toxic gases suspected in welding (Stern *et al.*, 1983). However, we can begin to recognize associations of unusual combinations of metallic elements with certain patterns of occupations and diseases.

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