



## Exposure to Metal Fume and Infectious Pneumonia

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To test the hypothesis that inhalation of metal fume reversibly increases susceptibility to pneumonia, the authors conducted a case-control study. Men aged 20–64 years, admitted to 11 hospitals in West Midlands, England, with community-acquired pneumonia during 1996–1999 were interviewed about their lifetime occupational history, exposure to metal fume, and potential confounding factors. Similar information was collected from controls admitted to the same hospitals with nonrespiratory illness. For cases, exposures were timed relative to the onset of their illness (on average, 6 months before interview). Exposure histories for controls were censored 6 months before interview. Interviews were completed by 525 cases and 1,122 controls (response rates of 74% and 99%). Pneumonia was associated with reported occupational exposure to metal fume in the previous year (adjusted odds ratio (OR) = 1.6, 95% confidence interval (CI): 1.1, 2.4) but not in earlier periods (OR = 1.1). The risk was highest for lobar pneumonia and recent exposure to ferrous fume (OR = 2.3, 95% CI: 1.2, 4.3). The association was not specific to any one microorganism. These findings support the hypothesis that ferrous and possibly other metal fumes reversibly predispose to infectious pneumonia. Research should now focus on the underlying mechanisms and prevention.

ferrous compounds; occupational exposure; pneumonia; welding

Abbreviations: CI, confidence interval; OR, odds ratio.

National analyses of occupational mortality for England and Wales have repeatedly demonstrated increased death rates from pneumonia in welders. During 1949–1953, 70 deaths were observed with 31 expected (1); in 1959–1963, 101 deaths as compared with 54.9 expected (2); and in 1970–1972, 66 deaths with 42.0 expected (3). Most recently, an analysis covering the period 1979–1980 and 1982–1990 confirmed the association and showed that the excess was attributable largely to deaths from pneumonias other than bronchopneumonia (principally lobar pneumonia) (4). Moreover, the elevation of mortality was limited to men below the normal retirement age of 65 years (55 deaths from lobar pneumonia observed, 21.6 expected), and a similar pattern was apparent for several other occupations entailing

exposure to metal fume, such as furnacemen, molders, and coremakers (workers who make molds and cores for casting metal and pour molten metal into dies by hand) in foundries.

Taken together, these findings strongly suggest that inhalation of metal fume increases susceptibility to infectious pneumonia, and that the effect is reversible following cessation of exposure. It is not clear, however, whether the additional risk applies to all categories of pneumonia or only to those caused by certain specific microorganisms, whether it is the same for all types of metal, and whether the effect is on the incidence of infections or on their fatality. To address these questions, we conducted a hospital-based case-control study.

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## MATERIALS AND METHODS

The study population comprised approximately 650,000 men aged 20–64 years who were resident in five metropolitan districts (Sandwell, Dudley, Walsall, Wolverhampton, and Birmingham) of the English county of West Midlands. This area was chosen because it has a relatively high prevalence of metalworking occupations. The cases were members of the study population who were admitted to any of 11 hospitals providing acute medical services to the area, during November 1996 through May 1999, with community-acquired pneumonia. The diagnostic criteria for pneumonia were as follows: 1) new or recently worsened lower respiratory tract symptoms (cough, sputum, dyspnea, or pleurisy) plus 2) shadowing on a chest radiograph, taken within 48 hours of admission, that was previously unrecorded and 3) evidence of an infective illness (e.g., peak temperature of  $\geq 37.8^{\circ}\text{C}$  in the first 48 hours after admission; history of rigors, chills, or shakes; white cell count of  $>12,000$ ; or a response to antibiotics) (5). Patients were excluded if their illness was associated with lung cancer, human immunodeficiency virus infection, bronchial obstruction distal to a foreign body, or pulmonary tuberculosis; if they had been admitted from a nursing home or chronic care facility; or if they had acquired their infection in the hospital or within 10 days of an earlier discharge from the hospital. Potential cases were identified principally from the hospitals' computerized discharge records, and their case notes and chest radiographs were then reviewed to determine whether they were eligible for inclusion in the study. In addition, over the course of the study, we made regular visits to the wards that admitted medical emergencies in order to recruit controls (see below), and any eligible cases of pneumonia who were on the ward at the time of a visit were invited to participate while still in the hospital.

The controls were men admitted acutely to the hospital under the same medical teams as the cases with nonrespiratory illnesses other than attempted suicide. They were group matched to the cases for age. Exclusion criteria were the same as for the cases, except that we also rejected men who had been unemployed 6 months before coming into the hospital as a consequence of the disorder that had subsequently led to their admission. The controls were identified by regular (at least weekly) visits to admission wards at each of the hospitals, in a predefined, rotating sequence. At each visit, the clinical records of all potential controls were reviewed, and those who were eligible and available for interview were invited to participate.

Cases and controls who agreed to take part in the study were interviewed by one of four research assistants, using a structured questionnaire. This covered all jobs held for a year or longer (coded according to the *Standard Occupational Classification 1990*) (6) and whether they involved exposure to metal fume or other specified respiratory hazards; more detailed information about jobs and occupational exposure to metal fume in the 18 months before admission (including the types of metal giving rise to fume); whether the patient had ever carried out certain activities (either at work or elsewhere) that would be expected to entail exposure to metal

**TABLE 1. Distribution of potential nonoccupational risk factors in men with pneumonia and controls, West Midlands, England, 1996–1999\***

Variable	Men with pneumonia (n = 525)		Controls (n = 1,122)	
	No.	%†	No.	%‡
Race				
Caucasian	452	86	968	86
Other	73	14	152	14
Employed				
Yes	360	69	724	65
No	165	31	398	35
Social class‡				
Nonmanual	118	22	322	29
Manual	407	78	800	71
Smoking				
Never	131	25	314	28
Former	151	29	374	33
Current	243	46	433	39
Alcohol§				
None or light	282	54	644	57
Moderate or heavy	192	37	372	33
Declined to answer	51	10	106	9
Diabetes				
No	486	93	931	83
Yes	39	7	191	17
Chronic obstructive airways disease¶				
No	447	85	1,010	90
Yes	78	15	112	10
Childhood pneumonia				
Never	507	97	1,094	98
Ever	18	3	28	2
Previous history of tuberculosis				
Never	513	98	1,100	98
Ever	12	2	18	2
Spleen removed				
Never	513	98	1,102	98
Ever	1	0	7	1
Flu vaccination in past 12 months				
No	425	81	828	74
Yes	99	19	294	26
Oral or parenteral steroids in past 3 months				
None	492	94	1,079	96
Any	29	6	43	4

\* The timings of all exposures were assessed relative to the effective date (i.e., for cases, the day on which they had fallen ill, and for controls, 6 months before the day of their admission).

† Percentages may not total 100 because of rounding errors or missing values.

‡ Nonmanual = social classes I, II, and IIINM; manual = IIIM, IV, and V (Registrar General's classification for England and Wales) (2, p. 5).

§ None or light = 0–10 units/week; moderate or heavy  $\geq 11$  units/week.

¶ Chronic sputum production and breathlessness on effort.

fume (welding, flame cutting or burning, flame gouging, metal spraying, use of a plasma arc, or pouring and casting

**TABLE 2. Association between pneumonia and occupational exposure to metal fume, West Midlands, England, 1996–1999**

Timing of exposure	Men with pneumonia ( <i>n</i> = 525)		Controls ( <i>n</i> = 1,122)		All (no.)	Adjusted* OR†	95% CI‡
	No.	%	No.	%			
Never exposed	325	61.9	742	66.1	1,067	1	
Last exposed more than 1 year before the effective date‡	142	27.0	309	27.5	451	1.1	0.8, 1.4
Last exposed from 8 days to 1 year before the effective date	11	2.1	12	1.1	23	1.8	0.8, 4.2
Last exposed within 7 days of the effective date	47	9.0	59	5.3	106	1.6	1.0, 2.4

\* Odds ratios were adjusted for age (in five bands), hospital center, smoking history, history of chronic airways disease, diabetes, childhood pneumonia, steroids in 3 months before the effective date, and influenza vaccination in the year before the effective date.

† OR, odds ratio; CI, confidence interval.

‡ Timings of all exposures were assessed relative to the effective date, that is, for cases, the day on which they had fallen ill; for controls, 6 months before the day of their admission.

molten metal); and various nonoccupational factors that might confound associations between pneumonia and metal fume.

For cases, the timing of exposures to metal fume and other risk factors, including potential confounders, was assessed relative to the day on which they had fallen ill (the “effective date”). Most cases were interviewed at home, on average approximately 6 months after entry to the hospital. Therefore, to ensure comparability of recall, for controls, all of whom were interviewed while still in the hospital, the effective date was set at 6 months before the day of admission and the most recent exposure history was censored.

For participating cases, additional information was abstracted from the medical records on any microbiologic findings. In addition, the chest radiograph on admission was reviewed by a trained physician (K. T. P.). Where present, the appearance of radiologic shadowing was scored using a standardized schedule as homogeneous and affecting the whole of one or more lobes (lobar), segmental, or multifocal and scattered (bronchopneumonia). The medical records and radiographs were examined without knowledge of the subject’s history of employment or exposure to metal fume.

Associations between pneumonia and metal fume were assessed by unconditional logistic regression, with adjustment for age, hospital, and other potential confounders (generally as dichotomous outcomes), and summarized as odds ratios with 95 percent confidence intervals. To explore the possibility of recall bias and to test the specificity of the findings, we compared the associations with those for other reported occupational exposures (to metal dust, wood dust, cement dust, asbestos, man-made mineral fibers, coal dust, and oil mists). We also assessed the relation of pneumonia to three occupations (welder; molder, coremaker, or die caster; and foundry furnaceman) in which exposure to metal fume was considered likely a priori and that had previously been found to have high mortality from the disease (4, 7).

## RESULTS

A total of 1,293 potential cases were identified, but for 81 of these the diagnosis could not be confirmed—either because no technically adequate radiograph was taken (*n* =

45) or because the radiographs or records were untraceable (*n* = 36). A further 504 men were excluded according to predefined criteria, the main reasons being no new radiologic changes on the chest radiograph (*n* = 173), pneumonia hospital acquired (*n* = 106), discharge from the hospital within the previous 10 days or admission from a nursing home (*n* = 52), and associated lung cancer (*n* = 72). This left 708 cases fulfilling the inclusion criteria, 574 of whom were identified from discharge records, 71 from visits to admission wards, and 63 from both sources. Among the 71 cases who were ascertained only from ward visits, many had a computerized discharge diagnosis of “chest infection” or exacerbation of obstructive airways disease without mention of pneumonia. From the eligible cases, 525 (74 percent) completed interviews. The nonresponders comprised 38 men who had died and 33 who had moved away before they could be interviewed, 74 who declined to participate, and 38 who did not respond despite several invitations.

Altogether, 1,188 men were approached to serve as controls, but of these 52 were excluded, either because their current illness had rendered them unemployed 6 months previously (*n* = 42) or because they fulfilled the exclusion criteria applied to the cases (*n* = 10). This left 1,136 eligible controls, of whom 1,122 were successfully interviewed (response rate, 99 percent). Among those interviewed, the most frequent reasons for admission were ischemic heart disease (*n* = 343); other cardiovascular diseases, including heart failure and venous thrombosis (*n* = 161); gastrointestinal disease, including hemorrhage and inflammatory bowel disease (*n* = 181); neurologic diseases, including stroke and epilepsy (*n* = 152); and diabetes (*n* = 68).

The cases and controls both had a mean age of 46 years with a range of 20–64 years. Table 1 compares the distribution of other potential confounding factors between cases and controls. No important differences were found in race, employment status at the effective date, or past history of pulmonary tuberculosis, and few subjects had undergone splenectomy. However, cases and controls differed in their smoking habits, use of corticosteroids during the 3 months before the effective date, and history of chronic airways disease, childhood pneumonia, diabetes, and influenza vaccination. Therefore, in subsequent analyses adjustment

**TABLE 3. Associations with other occupational exposures in the year before the effective date, West Midlands, England, 1996–1999**

Job held in the year before the effective date with exposure to one of the following below	Cases		Controls		Partially adjusted* OR†	95% CI†	Fully adjusted‡ OR	95% CI
	No.	%	No.	%				
Metal fume	58	11.0	71	6.3	1.6	1.1, 2.4	1.4	0.8, 2.3
Metal dust	75	14.3	110	9.8	1.4	1.0, 2.0	1.2	0.7, 1.8
Wood dust	38	7.2	82	7.3	0.9	0.6, 1.3	0.8	0.5, 1.4
Cement dust	46	8.8	88	7.8	1.0	0.7, 1.5	1.1	0.7, 1.9
Coal dust	5	1.0	12	1.1	0.8	0.3, 2.3	0.8	0.3, 2.4
Man-made mineral fibers	44	8.4	99	8.8	0.9	0.6, 1.3	0.9	0.5, 1.3
Oil mists	45	8.6	62	5.5	1.6	1.0, 2.4	1.3	0.8, 2.1
Asbestos	26	5.0	46	4.1	1.2	0.7, 1.9	1.2	0.7, 2.1

\* Odds ratios were adjusted for age (in five bands), hospital, smoking history, history of chronic airways disease, diabetes, childhood pneumonia, intake of steroids in the 3 months before the effective date, and influenza vaccination in the year before the effective date.

† OR, odds ratio; CI, confidence interval.

‡ Adjusted as above and also for the other exposures in the table.

was made for these six variables (as defined in table 1) as well as for age and hospital.

Altogether, 200 cases (38 percent) and 380 controls (34 percent) reported occupational exposure to metal fume at some stage during their working careers (either in the year leading up to the effective date or before that in a job held for a year or longer). Among these were 47 cases and 59 controls with exposure in the week before the effective date (odds ratio (OR) = 1.6, 95 percent confidence interval (CI): 1.0, 2.4) and 11 cases and 12 controls who were last exposed from 8 days to 1 year earlier (OR = 1.8, 95 percent CI: 0.8, 4.2) (table 2). In contrast, no elevation of risk was apparent for men last exposed more than a year before the effective date (OR = 1.1, 95 percent CI: 0.8, 1.4). The relation between metal fume and pneumonia was found to be similar in current smokers and lifetime nonsmokers to that in all workers (results not reported). Among the subjects who reported exposure in the year leading up to the effective date, the most common occupations were welder ( $n = 26$ ) and molder, coremaker, or die caster ( $n = 14$ ).

Table 3 compares the relation of pneumonia to metal fume and other respiratory hazards in the workplace. No association was found with recent occupational exposure to wood dust, cement dust, coal dust, man-made mineral fibers, or asbestos, but risk was elevated in men exposed to metal dust and oil mists, as well as in those who worked with metal fume. These last three exposures often occurred in the same individuals, and when the risk estimates were mutually adjusted, they all decreased. The highest odds ratios in the mutually adjusted analysis were for metal fume (OR = 1.4) and oil mists (OR = 1.3).

For the 129 men who had worked with metal fume in the year before the effective date, additional information was obtained on the metals that gave rise to the fumes. The predominant exposure was to iron or steel, either alone (52 men) or in combination with other metals or alloys (40 men). A few men were exposed only to other metals or alloys (27 in total, including seven to zinc, four to aluminum, and seven

to other metals), and for 10 no information was provided on the type of metal.

Table 4 shows the association of pneumonia with recent occupational exposure to metal fume according to the type of metal and also the radiologic pattern of disease. Among the cases were 158 men whose chest radiographs showed confluent shadowing affecting the whole of one or more lobes (classic lobar pneumonia), 142 with homogeneous shadowing in a segmental or subsegmental distribution, and 225 with shadowing suggestive of bronchopneumonia. Overall, risks were significantly elevated for lobar and segmental pneumonia (ORs = 1.8) but less marked for bronchopneumonia (OR = 1.3). Exposures that involved iron or steel carried a higher risk of pneumonia (OR = 2.0) than those that were limited to nonferrous metals or alloys (OR = 0.8), and in men exposed to ferrous fumes, higher risks were again seen for lobar and segmental patterns of disease (OR = 2.3 compared with OR = 1.6 for bronchopneumonia).

In 43 cases, the pneumonia was shown to be pneumococcal (diagnosed by recovery of the organism from blood ( $n = 30$ ), sputum ( $n = 8$ ), or both ( $n = 5$ )), while another specific microbiologic diagnosis was made in 88 men (including 22 with *Legionella*, 12 with *Mycoplasma*, and 12 with *Haemophilus influenzae*). Both of these diagnostic subgroups were associated with occupational exposure to metal fume in the year before the effective date (OR = 1.8, 95 percent CI: 0.6, 5.2 for *Streptococcus pneumoniae*; OR = 2.0, 95 percent CI: 1.0, 4.3 for other organisms) and more specifically with exposure to ferrous fumes (OR = 3.1, 95 percent CI: 1.0, 9.5 for *S. pneumoniae*; OR = 2.1, 95 percent CI: 0.9, 5.3 for other organisms).

During the year before the effective date, 22 cases (4 percent) and 21 controls (2 percent) had worked as a welder, molder, coremaker, die caster, or foundry furnaceman (OR = 1.9, 95 percent CI: 1.0, 3.6).

Among the subjects who did not report any occupational exposure to metal fume, 20 cases and 56 controls indicated that they had welded, cast metal, or used hot metal-cutting

**TABLE 4. Association with occupational exposure to metal fume in the year before the effective date according to the radiologic pattern of pneumonia, West Midlands, England, 1996–1999\***

Exposure relative to the effective date	No. of controls (n = 1,122)	All men with pneumonia (n = 525)			Lobar pneumonia (n = 158)			Segmental/ subsegmental pneumonia (n = 142)			Bronchopneumonia (n = 225)		
		No.	OR†,‡	95% CI‡	No.	OR	95% CI	No.	OR	95% CI	No.	OR	95% CI
Never exposed to metal fume	742	325	1.0		97	1.0		89	1.0		139	1.0	
Exposed to metal fume in the year before the effective date													
Any metal	71	58	1.6	1.1, 2.4	20	1.8	1.0, 3.3	18	1.8	1.0, 3.3	20	1.3	0.8, 2.3
Ferrous metal with or without other metals/alloys	46	46	2.0	1.3, 3.1	17	2.3	1.2, 4.3	14	2.4	1.2, 4.7	15	1.6	0.8, 3.0
Ferrous metal but not other metals/alloys	24	28	2.2	1.2, 4.0	12	3.0	1.4, 6.7	8	2.4	1.0, 5.9	8	1.6	0.7, 3.7
Other metals or alloys but not ferrous metal	19	8	0.8	0.4, 2.0	2	0.7	0.2, 3.2	2	0.7	0.2, 3.2	4	1.0	0.3, 3.2

\* Ten men did not provide information on the type of metal giving rise to fumes.

† Odds ratios were adjusted for age (in five bands), hospital, smoking history, history of chronic airways disease, diabetes, childhood pneumonia, steroid intake in the 3 months before the effective date, and influenza vaccination in the year before the effective date.

‡ OR, odds ratio; CI, confidence interval.

techniques on at least one occasion in the year leading up to the effective date (OR = 0.8, 95 percent CI: 0.5, 1.4).

## DISCUSSION

The findings of this case-control investigation support our hypothesis based on earlier analyses of occupational mortality. They suggest that occupational exposure to metal fume increases susceptibility to infectious pneumonia, especially lobar pneumonia; that the effect is not limited to fatal cases; and that the risk is reversible following cessation of exposure. It appears that the hazard applies to pneumococcal infections but also extends to other infectious agents, and that it can occur with exposure to ferrous fume. Whether other types of metal fume also carry a risk is unclear.

To ensure that our ascertainment of cases was as complete as possible, we not only searched the computerized discharge records of participating hospitals but also recruited cases opportunistically when visiting admission wards to interview controls. A substantial minority of the patients identified from this supplementary source were not subsequently picked up through the computer search. In some cases, although pneumonia was documented in the case notes, the recorded discharge diagnosis was less specific. In others, an error may have occurred in coding. Whatever the explanation, the discrepancy suggests that we did not detect all of the cases that occurred in the study population over the course of the investigation, nor did we manage to interview all of the cases whom we did identify. Some 26 percent were lost because they had died, could not be contacted, or declined to participate. It seems unlikely, however, that our failure to include all eligible cases would have seriously biased risk estimates for occupational exposures. In particular, there is no reason to expect that it would have produced a spurious association with recent occupational exposure to metal fume but not with earlier exposures or with recent exposure to other respiratory hazards.

The control group included patients with a wide range of diagnoses, and the response from those approached was almost complete. Moreover, we excluded men admitted

because of a chronic illness that might have affected their employment during the relevant time period. For these reasons, we would expect the occupational exposures of the controls to be adequately representative of those in the study population.

Another possible source of error was biased recall of exposures. Ideally, cases and controls would have been interviewed in similar circumstances (home or hospital) and without knowledge of their case or control status. This was not practical, but to reduce bias, we did not inform the interviewers of the hypotheses on which the investigation was based. Moreover, in the course of the interview, we asked first about the jobs that subjects had held and about a range of possible exposures in each job. Only later did we go into detail about metal fume and metalworking activities specifically. Again, therefore, the absence of associations with other respiratory hazards argues against important bias. Furthermore, an increased risk was found for occupations that were expected a priori to entail exposure to metal fume. Errors are less likely in the recall of job title than of detailed occupational exposures.

Various nonoccupational exposures are known or suspected risk factors for pneumonia and, where their prevalence differed importantly between cases and controls, we adjusted for these variables in the regression analyses to minimize any possible confounding. In addition, it is unlikely that the association with metal fume can be explained by a confounding effect of concomitant occupational exposures. There was a correlation between exposure to metal fume and oil mists that made it difficult to resolve their independent influences in a regression model, but an elevated risk of pneumonia was clearly apparent in welders, molders, coremakers, and die casters—occupations that would not be expected to entail heavy exposure to oil mists.

The association could not be explained by concomitant exposure to other noxious agents in welding fume (e.g., ozone and oxides of nitrogen). Most cases and controls who reported occupational exposure to metal fume in the year before the effective date (103 of the 129 subjects) did not weld, and in these subjects the relation between pneumonia

and metal fume was similar to that in all subjects (data not shown).

Occupational exposure to metal fume sometimes causes a chemical pneumonitis, and exposure to oil mists has been linked with hypersensitivity pneumonitis (extrinsic allergic alveolitis), both of which may mimic pneumonia. However, misdiagnosis is unlikely to explain associations that were also apparent for microbiologically confirmed cases of disease and for clinical patterns of disease not normally observed in patients with pneumonitis (such as homogeneous lobar shadowing). Moreover, in our earlier study of mortality (4), in which many cases went to necropsy, the postmortem findings indicated infectious pneumonia rather than pneumonitis as the underlying cause of death.

Our findings suggest that the increased susceptibility to pneumonia from inhalation of metal fume persists for longer than a week, although probably not for more than a few years. More precise conclusions about its duration are not possible because there were too few cases with a reported last exposure in the critical time window. An elevated risk was observed in men who worked only with ferrous metal, but the numbers with exposures solely to nonferrous metals and alloys were insufficient to exclude a hazard also from these other sources. The lack of association with nonoccupational metalworking activities suggests that risk is importantly increased with only relatively heavy exposures. Although a clear elevation of risk was seen for pneumococcal infections and with lobar pneumonia (in which *S. pneumoniae* is the usual organism implicated), other types of infection appeared to be affected also.

At least two pathogenic mechanisms could explain this pattern of observations. First, it is possible that metal fume (ferrous and perhaps some other types of metal) causes oxidative damage to the lung's immune defenses. This is similar to the mechanism of free-radical injury at the bronchioalveolar level that has been postulated to underlie the toxicity of fine particulate pollution in the general environment of cities (8–10). It is known that free iron, iron released from ferritin, and other transition metals can catalyze the generation of reactive hydroxyl radicals (11–13) and that free radicals can impair the function of lymphocytes and normal immune responses, such as the migration of macrophages (14). Furthermore, there is direct evidence that fine particles of metal and of metal-coated carbon are cytotoxic to macrophages (15).

Alternatively, it may be that free iron serves as a nutrient for microorganisms and promotes their growth. This would be consistent with the observation that, in patients with sickle cell disease, iron released during hemolytic crises may increase susceptibility to pneumonia and pneumococcal infection (16, 17). In addition, there is some evidence to suggest that iron may enhance bacterial pathogenicity if the host's ability to withhold iron from the invading organism is reduced (7, 18).

With either of these two proposed mechanisms, the increased risk of pneumonia would only be temporary, disappearing once the excess of free iron in the lung had been bound to transferrin and any damage to immune cells had been repaired or compensated.

Research now needs to focus more closely on the mechanism by which metal fumes promote pneumonic infection. A first step might be to establish 1) whether exposure to metal fume provokes a generalized inflammatory reaction (such as a rise in white cell count or C-reactive protein), 2) whether free iron is more abundant and pulmonary macrophages are more iron loaded and impaired in function in exposed workers as compared with controls, and 3) whether an oxidant effect of transitional metals potentiates bacterial multiplication locally. If relevant biomarkers could be established in this way, they might provide a means of assessing the relation of risk to exposure with greater accuracy than is possible from retrospective case-control studies and thereby enable controls on exposure to be set at an appropriate level.

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