# DOES OCCUPATIONAL EXPOSURE TO IRON

# PROMOTE INFECTION?

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# Abstract

Siderosis, the accumulation of ferric oxide particles in the lung, was first described by Zenker over a century ago1. Enquiries subsequently focused on the effect of this pneumoconiotic process on lung function, generally concluding that it was benign2,3. More recently however, it has become apparent that iron influences bacterial virulence and has a role in host defence against infection. The evidence accrued is sufficient to trigger a reappraisal of health risks in iron-exposed occupational groups. This paper reviews some of the evidence linking iron with infection, and considers what information exists on risk in the occupational setting.

**Introduction**

## Iron in biological systems

Fifty years ago Schade and Caroline discovered that iron binding proteins, present in blood and the whites of eggs, could inhibit bacterial growth *in vitro*4,5. They hypothesised that the proteins they had discovered bound iron so tightly that bacteria could not obtain enough of it to support growth - an effect they were able to abolish by adding extra iron. Later on, others showed that animals injected with iron were more susceptible to infection than untreated controls, and that the well known antibacterial effects of body fluids could be abolished *in vitro* by adding iron6-8.

As Schade and Caroline suggested, a check is placed on growth of pathogens because the amount of free iron available to them in the body fluids of humans and animals is extremely limited. Most of the body’s iron stores are intracellular - in ferritin, haemosiderin or haem; and the extracellular fraction is bound to high affinity iron binding proteins - transferrin in serum and lactoferrin in external secretions9. These proteins have large association constants, and are only partially saturated under normal circumstances (30 to 40% in the case of serum transferrin), so the concentration of free iron in equilibrium with iron binding proteins is believed to be as low as 10-18 M10.

This arrangement makes sense. The ease with which iron undergoes changes in its oxidative state by electron transfer makes it an ideal biological catalyst, essential in the life processes of prokaryotes, eukaryotes, anaerobic, photosynthetic and nitrogen-fixing life forms11, but also a focus for potentially injurious free radical formation. Under physiological conditions ferric iron tends to oxidise, hydrolyse and polymerise, forming relatively insoluble ferric hydroxide and oxyhydroxide polymers10. The absorption, transfer and delivery of iron is tightly controlled at every stage, to ensure it remains available in a soluble, non toxic form. Commensal micro-organisms and microbial pathogens are therefore believed to exist in an iron restricted environment.

## The battle for free iron

There is evidence that pathogens adapt in a variety of ways to obtain the iron they need - for example, by producing their own low molecular weight iron chelators, by modifications to their outer membrane proteins and by the elaboration of haemolysins which liberate iron from   
haem12. Host organisms counter this by restricting iron availability during infection. Additional iron binding capacity may be recruited in inflammatory exudate, as polymorphonuclear leucocytes degranulate, releasing lactoferrin13,14; while the amount of iron bound to serum transferrin falls (“the hypoferraemia of infection”) by a mechanism that may entail lactoferrin release, macrophage sequestration of Fe3+-transferrin complexes and increased synthesis of ferritin15. Dietary iron assimilation is suppressed by as much as 80%; and iron eflux from macrophages that have digested effete red blood cells is reduced by as much as 70%16.

Other interactions between organism and host may also operate, including the host’s immune response to foreign iron-sequestering proteins, and the proteolytic cleavage of transferrin and lactoferrin by certain bacteria16. The essential point is that a critical balance exists between commensal/pathogen and host in the fight for available iron. The normal flora of the respiratory tract reflect in part the nutrient-limited balance so achieved. In situations where the balance is disturbed, as for example when exogenous or endogenous supplies of iron exceed the capacity of the iron binding protein system, overgrowth of organisms may be encouraged.

Similar considerations may apply in viral infection: although viruses do not require iron, the host cells they infect need iron before viral replication can occur, and the hypoferraemia of infection has been observed in children infected with mumps and chickenpox17.

***Other mechanisms of action***

Apart from its role as a nutrient for pathogens, there are other possible ways in which iron could promote infection, especially respiratory tract infection. Iron may be implicated through a mechanism of free radical injury: *in vivo* iron-dependent reduction of hydrogen peroxide generates hydroxyl radicals, whose toxic properties have recently been reviewed18. Studies have shown that metal particles, or carbon coated with metals, can be cytotoxic to macrophages19,20, and short-term inhalation experiments in animals have produced a cytotoxic response at ambient concentrations down to 0.1 mg/m3 19. Factors that interfere with the efficiency of phagocytosis are liable to render the host more susceptible to infection, independent of any effect on the nutrient status of the pathogen.

***Excess iron in vivo***

Observations on iron overload *in vivo* are generally consistent with the *in vitro* experimental data. In clinical situations where the availability of free iron is increased, a propensity to infection has been described - for example:

* patients with sickle cell disease who release free iron in haemolytic crises, appear to be more susceptible to infection, particularly pneumonia21 and pneumoccocal infection 22
* patients with haemochromatosis, who absorb excessive quantities of iron from dietary sources are prone to infection with *Vibrio* species23
* in case reports, accidental iron overdose has been linked with bacterial septicaemia24 and meningitis25
* low levels of unsaturated transferrin have been associated with high fatality in pneumoccocal pneumonia26
* and lactoferrin deficiency has been described in the polymorph granules of a patient with repeated deep seated abscesses27.

These and other clinical consequences of excess iron have been reviewed recently28.

# Occupational Exposure To Iron

***Sources of exposure***

Occupational exposure to iron arises mainly from work that generates metal fume or metal dust. Occupations in the former category include: gas and electric welders, cutters and braziers; furnacemen in foundries and iron and steel production; and foundry moulders and core makers, who in smaller foundries also pour and cast molten metals. Metal fume exposure may also occur, although to a lesser extent, in foundry and steel-mill labourers; and in sheet metal workers, who sometimes cut metal sheets using welding apparatus. Occupations that may incur exposure to iron dust include: fettlers, metal polishers, boiler scalers and workers engaged in the mining, crushing, milling and mixing of iron ores.

The occurrence of siderosis in a number of these groups, such as welders, fettlers, dressers, boiler scalers, and iron ore miners3 attests to significant degrees of iron exposure. In 1955-60 the prevalence of siderosis among welders and burners in the fettling and grinding shops of a Sheffield foundry was found to be 17.6%29; others too have reported its frequent occurrence.

Commonly the occupational exposure is to ferric oxide, although in the case of welding the fume is more complex (20-90% is crystalline, especially as Fe3O4, but it also contains other compounds, including fluorides of sodium and calcium, carbonates of sodium and potassium, magnesium oxide and MnFe2O4). In metal mining the main ores are haematite and magnetite.

***Lung responses to iron overload***

The lung’s response to excessive iron may include the liberation of iron-binding protein, extra macrophage uptake and ferritin formation. Interestingly, simulated welding exercises provoke a marked increase in the polymorphonuclear count in bronchoalveolar lavage fluid, together with a release of cytokines, including TNF, IL-1 and IL-630. Perhaps this inflammatory cellular response leads to the release of lactoferrin and the sequestration of free iron, as the IL-1 response in infection has been linked with the hypoferraemia of infection28.

In any case, the response is not always complete or adequate. In siderosis ferric oxide particles have been found extravascularly, in the alveolar walls and spaces. Some of the iron is stored as ferritin, and so stains with Perl’s Prussian blue, but much of it does not2. This confirms a situation of iron overload. It should be noted in this context that even a partial increase in iron saturation may make iron more freely available to some well adapted pathogens28.

What factors are likely to determine the type and magnitude of effect? As in other occupational exposures, dose is important, but the relative importance of intensity and duration of exposure is not clear. Perhaps brief peaks of exposure matter in relation to short-term adaptive responses in the host, while the outcome of long term exposure depends upon the lung’s adaptive reserves.

Particle size may influence local dose and delivery site. Two different methods of particle generation are in operation occupationally - condensation of heated metal fume to produce very fine particulate metal oxides, and abrasion and dispersion of iron-bearing materials to produce somewhat larger iron laden dusts. It might be supposed that these mechanisms result in different patterns of deposition and different clinical effects. In practice, however, there is overlap: metal oxide condensates in metal fume tend to aggregate and grow and to deposit in large as well as small airways, while the occurrence of siderosis and alveolar iron in the dust generating professions confirms that these actvities can also produce significant numbers of fine particles.

The effect may also depend on host susceptibility and a multiplicity of host defence factors - some related to iron (including differences in iron body stores and iron-binding capacity) and some not. Constitutional factors, nutrition, pre-existing disease, and cigarette and alcohol intake are all likely to play a part. Finally, the outcome may depend upon the resident microbial population. For example, workers with chronic bronchitis who have a permanent reservoir of pathogens in their bronchi may be at different risk from other healthier workers.

To date interest has mainly focused on the role of endogenous and dietary iron in infection, but some occupational data exist that provide information on the relationship between exogenous respirable iron and infective illness.

# Epidemiology

## Occupational Mortality

Direct evidence that occupational exposure to iron increases susceptibility to infection comes mainly from routinely published analyses of occupational mortality. Coggon et al31 recently conducted an analysis of mortality from pneumonia in metal-exposed populations, with data abstracted from the Registrar General’s Decennial Supplements for the periods 1959-6332 and 1970-7233; and information provided by the Office of Population, Censuses and Surveys (OPCS) on deaths among men aged 20-74 in England and Wales during 1979-80 and 1980-9034.

In the Decennial Supplements, expected numbers of deaths for each occupation in men of working age were calculated by applying five year age-specific death rates for pneumonia in the general population to an estimate of the occupational population derived from national census in the mid year of the study period (1961 or 1971). The relation of observed to expected deaths was expressed as a standardised mortality ratio (SMR). The report for 1970-72 also presented proportional mortality ratios (PMRs) for the age range 65-74 years, with expected numbers of deaths derived by applying age-specific proportions of death from pneumonia in the general population to the total number of deaths at each age in the occupational population. Death reports for 1979-80 and 1982-90 were used to derive PMRs for pneumonia by occupation, standardised for age in five year strata and for social class (SMRs could not be calculated as the population denominators for this period were not available).

The analysis revealed a consistently elevated mortality from pneumonia in occupations involving exposure to metal fume, and particularly in welders and moulders and coremakers. The largest excess of deaths was for lobar pneumonia, but increases were also observed for other subcategories with the exception of bronchopneumonia. Moreover, the higher risk was restricted to men below retirement age, suggesting a short-term, reversible effect of exposure.

Table 1 extends these observations with addition of data derived from the Registrar General’s Supplements for 1930-3235 and 1949-5336. Only SMRs were published for this period. In table 1 we have grouped occupations with potential exposure to metal fume into those where exposure is ‘definite’ (welders, moulders and coremakers, and foundry furnacemen), and those where it is ‘possible’ (foundry labourers, sheet-metal workers, tin platers and galvanisers); included a group of workers with ‘definite’ metal dust exposure (metal polishers and fettlers); and examined influenza and bronchitis as other causes of death that might also be influenced by iron exposure. The data for 1979-80 and 1981-90 have been standardised for age and social class, and those for earlier periods standardised for age, and adjusted for social class by multiplying the expected numbers of deaths by the corresponding cause- and social class-specific PMR or SMR.

As in previous analyses, occupations with potential exposure to metal fume, and particularly welders, moulders and coremakers and furnacemen, had significantly elevated mortality from pneumonia. Excesses were also apparent for metal grinders and polishers, although they were less marked. The pattern for influenza (deaths from which may result from secondary bacterial pneumonia37,38) was broadly similar, although by the 1980s there were too few deaths observed and expected for meaningful interpretation. Occupations entailing exposure to metal fume and dust also tended to have elevated mortality from bronchitis and again the highest rates were in welders, moulders and coremakers and furnacemen.

As previously noted, the excess mortality from pneumonia in occupations with exposure to metal fume has been confined to men of working age. This makes confounding by smoking and other non-occupational factors an unlikely explanation. In further support of this, the occupations do not have comparable excesses of lung cancer (Table 2), nor is their mortality from non-respiratory infections elevated.

These findings support the hypothesis that inhalation of metal fume and dustpromotes respiratory infection, but they do not indicate whether the effect is specific to iron. A test of this is provided by data from 1930-32 and 1949-53 when (in contrast to later reports) workers in ferrous foundries were distinguished from foundrymen working other metals, and iron ore miners from miners of tin, copper and other metalliferous ores (Table 3). The elevation of mortality from pneumonia and influenza was generally more marked in those working with ferrous metal, but no consistent differences were apparent in mortality from bronchitis. Similarly, in 1910-2 the risk of death from pneumonia in iron founders was twice that in brass founders, and that in iron miners and quarriers was 50% greater than in lead miners; but there was no corresponding excess mortality riskfrombronchitis39. Generally, the pattern is compatible with a specific hazard from iron, possibly superimposed on a second hazard from metal fume more generally.

**Other studies**

Published cohort studies of mortality in workers exposed to metal fume or dust from iron ore shed little extra light on the topic. In general these have not looked specifically at infective risk, and have lacked sufficient statistical power to address this particular question. Where excess mortality from respiratory disease has been described, often the data have not been broken down by cause40,41, although in two large studies excesses of pneumonia were apparent, with SMRs of 185 and 167 amongst welders in the North East of England and in Seattle, USA42,43. An association has also been described between work in ferrous foundries and death from chronic bronchitis44. By contrast a large European study of 11,000 welders failed to demonstrate an excess of pneumonia, or of bronchitis, emphysema and asthma45, and no excesses were found in a cohort of iron ore miners from Minnesota46.

Morbidity from infective illness in metal workers has been studied even less than mortality. An analysis of hospital admissions among American shipyard workers during 1942-4547 and a cross-sectional survey of British shipyard employees48 indicated no relation between pneumonia and exposure to metal fume; but in a survey of certified sickness absence during a 10-year period, 4 of 36 welders had absences attributed to pneumonia compared with none of a similar number of controls49. A number of cross-sectional studies have failed to find an excess of chronic bronchitis in welders50,51, but many studies have identified an excess of current cough and sputum in active workers, independent of smoking48. Furthermore, a recent longitudinal study has described an enhanced deterioration in lung function in welders which was also independent of smoking52.

# Conclusions

A growing body of evidence suggests that free iron in body fluids promotes bacterial growth. In theory, therefore, occupations that entail exposure to iron fume or dust could carry an increased risk of infection. The principal data that allow a test of this come from national statistics of occupational mortality, and are subject to several well-documented biases. In particular, the derivation of SMRs depends on occupational codings for the numerator and denominator that come from different sources (death certificates and censuses respectfully); while PMRs, although derived from a single source (death certificates), may mislead if overall mortality rates in an occupation are unusually high or low. There are other limits to the data: for example, scope for exposure misclassification if the job reported for death certification is inaccurate or ill-defined; changes over time in diagnostic practice and classification; and in some analyses small numbers of observed deaths and correspondingly wide confidence intervals. Nor should the potential for confounding by non-occupational factors be ignored. Our findings have been adjusted for age and social class, and we have argued that confounding by smoking is unlikely to explain them, but the increases in relative risk in a number of analyses are comparatively modest, and vulnerable to the effects of unrecognised confounders.

Set against these concerns are the consistency and coherence of effect, apparent through several periods of analysis and for several outcomes*.* Analyses of occupational mortality indicate that workers exposed to metal fume and dust have high death rates from pneumonia, influenza and bronchitis, but not from other infections.

Risks have tended to be higher in men working with ferrous as compared with other metals, but the difference is not clear cut. Thus, the possibility of a general hazard of metal fume (for example, from impairment of macrophage function) cannot be ruled out. Nevertheless, the specific role of iron merits further investigation. An early priority is to establish whether exposure to metal fume is associated with a higher incidence of respiratory infection as well as a higher mortality, and whether the association is with all types of metal or only with iron. It would also help to know more about the fate of inhaled iron fume, and particularly what proportion remains unbound, for how long, and at what sites in the lung.

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