Smoking, cadmium, and emphysema

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Does cadmium contribute to the development of smoking induced emphysema?

Most respiratory physicians recognise that chronic exposure to respirable cadmium in the workplace may lead to emphysema. What may come as a surprise is that cadmium is a constituent of tobacco and hence cigarette smoke, and so is inhaled outside the workplace by all smokers. The question arises whether inhaled cadmium may contribute to, or even be the principal cause of, smoking induced emphysema.

Mannino and colleagues have taken advantage of the Third US National Health and Nutritional Examination Survey (NHANES III) to investigate the matter, since it allowed them to compare creatinine adjusted urinary cadmium levels with spirometric measurements in as many as 16 024 subjects, representative of the adult US population. Their findings are presented in this issue of *Thorax*.[1] Not only was there an increasing trend in urinary cadmium levels from never, through former, to current smokers, but among the current and former smokers (though not the never smokers) urinary cadmium was correlated negatively with forced expiratory volume in 1 second (FEV_1) and the ratio of FEV_1 to forced vital capacity (FVC) after adjustments for potential confounders. They concluded that cadmium might indeed contribute importantly to tobacco related lung disease.

Is this plausible? If so, is it likely? Neither question can be answered easily, and there is a possible alternative explanation for the observed association. Urinary cadmium may simply be a marker of cumulative exposure to tobacco smoke.

CADMIUM SOURCES, UPTAKE, AND METABOLISM

Cadmium occurs within zinc, copper, and lead ores and its concentration in soil varies widely (typically 0.01–7.0 ppm). This influences the amount in local drinking water and the amount delivered into tobacco leaves and other plants. In the absence of occupational exposure, cadmium enters the body in trace amounts within drinking water and foodstuffs, and within tobacco smoke. Food intake of cadmium averages 10–25 μg/day, but may exceed this considerably if shellfish is prominent in the diet. Up to 30 μg of cadmium contaminates a pack of cigarettes. However, only a small proportion of this (median 2.74 μg per pack in one study, as Mannino and colleagues point out) is transferred to mainstream smoke, and only 20–50% of the amount inhaled is absorbed. An even smaller proportion (2–6%) of ingested cadmium is absorbed. The net outcome is that current smokers have roughly twice the body burden of never smokers.

Cadmium entering the blood is retained chiefly within the liver and kidneys, where most becomes complexed with metallothionein. This makes it relatively innocuous, but that which is not complexed is potentially toxic—especially to the kidneys, but also to the lungs and other organs. The complexed cadmium has a long half life (many years) and the body's store generally increases until late middle age to a normal total of 10–30 mg. The little that is re-released into the blood may become re-absorbed temporarily within tubular cells of the kidney and then dissociated, allowing the potential for delayed and ongoing toxicity. It is unclear whether a similar mechanism operates in the lungs. The daily excretion of cadmium in urine is a useful, if crude, marker of the total body burden. Normal excretion averages 1–2 μg/day at most, but the range can be wide. By contrast, the blood cadmium level is a poor reflection of the total burden and relates more closely to recent exposure.

CADMIUM MEASUREMENTS AND THE EFFECTS OF CHRONIC LOW LEVEL EXPOSURE

Proteinuria is usually considered the earliest sign of toxicity from chronic low level exposure to cadmium, whether by ingestion or inhalation, following which cadmium is less readily retained by the kidney. Urinary excretion is then a less reliable measure of the body burden. In a population with environmental (but not occupational) exposure living at various distances from regional zinc smelters, a small risk of perturbed renal function was noted from an initial study only when urinary cadmium levels exceeded 2–4 μg/day. When a nested cohort of 593 men and women selected to have higher than average exposures was followed for 5 years there was no indication of progressive renal damage. The mean urinary cadmium level was almost exactly 1 μg/day initially and diminished by about 15% over the 5 years.[2]

In studies of populations with respirable as well as gastrointestinal exposure, the presumed risk of proteinuria has not been increased unless urinary excretion reached 10 μg/g creatinine (men usually excrete 1–2 g creatinine daily, women a little less) or airborne levels exceeded 20–50 $\mu g/m^3$. Such threshold estimates may be conservative, and in a study of 90 workers exposed to cadmium dusts for up to 20 years (average 7.5 years) of whom 75 were smokers, a mean urinary excretion of cadmium of 23 μg/g creatinine (50 times that of the NHANES III smokers) was not associated with any excess proteinuria compared with unexposed controls.[3] Up to 1996 the lowest mean airborne levels reported to cause toxicity in individuals were 88 $\mu g/m^3$ over 8.6 years in a man and 129 $\mu g/m^3$ over 20 years in a woman.[4]

Emphysema was the primary end point in a study of 99 men, mostly retired, who had worked for at least 1 year in a copper-cadmium alloy factory.[5] Lung function evidence of excess emphysema was associated with liver cadmium levels as measured by neutron activation analysis. Airborne levels of exposure measured with static and personal samplers during the relevant periods of employment (1926–83) had ranged between 600 and 34 $\mu g/m^3$. The mean liver cadmium level was calculated at 26.1 ppm, more than 40 times that of ''unexposed'' controls with similar smoking habits (0.6 ppm).

NO—CADMIUM IN TOBACCO SMOKE IS NOT A LIKELY CAUSE OF EMPHYSEMA

If cadmium is a constituent of tobacco smoke, it is to be expected that urinary cadmium levels will increase as pack years accumulate. It may simply be an innocent marker of cumulative exposure to tobacco smoke, much as expired carbon monoxide, blood carboxyhaemoglobin, serum thiocyanate, or serum/urinary/salivary cotinine are innocent markers of acute exposure.

In the NHANES III population the mean creatinine adjusted urinary cadmium levels of current and former smokers (0.46 and 0.32 μg/g creatinine, respectively) were no more than 2.0- and 1.4-fold that of the never smokers (0.23 μg/g creatinine). The level among

the smokers was thus twice that of the never smokers—and so consistent with general experience—but it was very low indeed compared with working populations exposed to cadmium, even populations without any apparent adverse effect on kidneys or lungs. If urinary cadmium provides a reliable measure of the cumulative dose of cadmium absorbed by the lungs and gut, and if cadmium delivered to the lungs through the circulation is as hazardous as cadmium delivered in inspired air, these observations imply a ''dose'' threshold for inducing emphysema that is similar to, or only marginally above, the average dose retained without apparent ill effect in the population at large from food and water. This is just plausible, but it is not likely.

An obstructive impairment of ventilatory function in the NHANES III population was correlated with urinary cadmium levels even after adjustment for pack years and cotinine level—a point in favour of cadmium being relevant independently. Although variability in puff frequency and depth of inhalation may play a role in the implicit discordance between reported pack years and urinary cadmium, the major factor could be the notorious inaccuracy with which smokers estimate their levels of consumption. If all underestimate by similar degrees, the effect on epidemiological investigation would be minor, but the likelihood is that a minority provide accurate estimates while the majority provide estimates with variable degrees of inaccuracy. In such circumstances, urinary cadmium may simply provide a more accurate reflection of cumulative tobacco consumption.

YES—CADMIUM IN TOBACCO SMOKE IS A PLAUSIBLE CAUSE OF EMPHYSEMA

Mannino and colleagues offer a different explanation for any discordance between smoking histories and urinary cadmium levels. They suggest, reasonably, that there may be important differences in the handling and metabolism of cadmium. Biological variability in absorbing and metabolising the same inhaled dose of an emphysema inducing component of tobacco smoke could well help to explain the striking variability in susceptibility that is characteristic of smoking related diseases.

There is a clear example of genetic susceptibility to emphysema. Subjects with α_1-antitrypsin deficiency are less able to protect themselves from injury from proteases generated from inflammatory insults to the lung. Curiously, of a number of trace metals investigated, cadmium appears to be the only one to reduce the serum concentration of α_1-antitrypsin and so depress trypsin inhibition.[6] In addition, it adversely affects fibroblast production of procollagen and interferes with the synthesis of proteoglycans.[7] Cadmium thus diminishes the lung's capacity to produce connective tissue proteins and so prevent the disruption characteristic of emphysema. Genetic variability in these biological functions would weaken any relation between ''dose'' and response, and an inability to allow for different degrees of susceptibility between individuals in populations exposed to hazardous agents poses a major problem in epidemiological research.

Mannino and colleagues did, of course, study a sample of a normal population, not subjects selected because they had worked with cadmium or had known COPD. The dose-response relation between cadmium and ventilatory function was necessarily focused at low dose levels, and their ability to demonstrate it undoubtedly owed much to the great power generated by so many participants. The relation could still be causal even if the actual effect at such low levels of exposure is minor and not detectable by studies of smaller populations with higher levels of exposure.

This assumes that the accumulated body burden of cadmium (and the more readily measured urinary excretion of cadmium) does reasonably reflect the risk of toxicity from inhaled and ingested sources alike. This may not be so. It is interesting that ''doses'' of zinc oxide that cause metal fume fever when inhaled have no comparable effect when administered by ingestion or intravenous injection.[8] Thus, zinc has to be inhaled to produce this particular type of toxic reaction. This might explain why Mannino and colleagues found no relation between urinary cadmium and ventilatory function in the never smokers. The small difference in urinary excretion levels between the smokers and never smokers in their study may consequently be of limited significance.

If there is considerable variability in metabolic pathways relevant to absorption, storage, injury, and repair so that some individuals are particularly susceptible even at low levels of relevant exposure, then it is plausible that cadmium plays at least a contributory role in the development of smoking induced emphysema.

Incidentally, cadmium is also recognised to cause lung cancer …

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