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Accepted 25 May 2000

## Low level exposure to cadmium and early kidney damage: the OSCAR study

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### Abstract

**Objectives**—To study the dose-response relation between cadmium dose and renal tubular damage in a population of workers and people environmentally or occupationally exposed to low concentrations of cadmium.

**Methods**—Early kidney damage in 1021 people, occupationally or environmentally exposed to cadmium, was assessed from cadmium in urine to estimate dose, and protein HC ( $\alpha_1$ -microglobulin) in urine to assess tubular proteinuria.

**Results**—There was an age and sex adjusted correlation between cadmium in urine and urinary protein HC. The prevalence of tubular proteinuria ranged from 5% among unexposed people to 50% in the most exposed group. The corresponding prevalence odds ratio was 6.0 (95% confidence interval (95% CI) 1.6 to 22) for the highest exposure group, adjusted for age and sex. Multiple logistic regression analysis showed an increasing prevalence of tubular proteinuria with urinary cadmium as well as with age. After adjustment to the mean age of the study population (53 years), the results show an increased prevalence of 10% tubular proteinuria (taking into account a background prevalence of 5%) at a urinary cadmium concentration of 1.0 nmol/mmol creatinine.

**Conclusion**—Renal tubular damage due to exposure to cadmium develops at lower levels of cadmium body burden than previously anticipated.

(Occup Environ Med 2000;57:668-672)

Keywords: cadmium; environmental; tubular damage

Exposure to cadmium may cause kidney damage.<sup>1-3</sup> The cumulative exposure to cadmium and its concentration in the kidneys can be assessed by measuring cadmium in urine.<sup>4</sup> The initial sign of cadmium induced renal lesions is tubular proteinuria, usually detected as an increased urinary excretion of low molecular weight proteins, such as  $\beta_2$ -microglobulin, retinol binding protein (RBP), protein HC ( $\alpha_1$ -microglobulin), or enzymes such as N-acetyl- $\beta$ -glucosaminidase (NAG).<sup>5-7</sup> If exposure to cadmium continues the tubular dysfunction progresses and glomerular damage with a decrease in the glomerular filtration rate (GFR) may emerge.<sup>1,7</sup> Also, secondary effects on the bone and calcium metabolism may occur causing renal stones, and in cases of severe cadmium poisoning osteoporosis and osteomalacia with the infamous itai-itai disease as the final stage.<sup>3,7,8</sup> In recent years it has been

recognised that signs of early tubular damage can develop at relatively low cumulative doses of environmental cadmium.<sup>7,9</sup>

In an extensive cross sectional study of more than 1000 people living in two communities (Fliseryd and Oskarshamn) in a region in the south of Sweden, with a range of relatively low exposures to cadmium, we have examined the association between dose of cadmium and the prevalence of early tubular damage and osteoporosis—the osteoporosis, cadmium as a risk factor (OSCAR) study. Nickel-cadmium batteries have been produced in the region since 1910. The plant in Fliseryd was closed in 1974, whereas the factory in Oskarshamn is still operating. Occupational exposure to cadmium was high during the five decades of operation at the plant, but has gradually decreased since the 1960s.<sup>10,11</sup> Environmental cadmium pollution from these plants was substantial in the past, in particular in the vicinity of the Fliseryd plant. Here we present data on cadmium and early tubular effects whereas results from measurements of bone density are reported elsewhere.<sup>11a</sup>

### Methods

The study population included all people between 16 and 80 years of age, who had lived for at least 5 years and were still living in the area close to a nickel cadmium battery plant in southern Sweden between 1910 and 1992 (n=1259). A group of separately selected battery workers (n=242), was also included in the study population. A further group (n=206), matched by age and sex to the population who had lived close to the plant, was randomly selected from a general practice register in a nearby area. This group was initially intended as a reference population, but it was later discovered that there was great overlap in exposure between the two non-occupational groups, and thus these groups were merged into one environmentally exposed group (n=1465). All subjects in the study population were asked to participate. Of the environmentally exposed people 904 (62%) and of the battery workers 117 (48%), agreed to take part in the examinations. Thus, a total of 1021 people (60%) agreed to participate in the OSCAR study and gave their informed consent to the investigation. A telephone survey of a random sample of 5% of the non-participants indicated that they did not differ from the participants in a systematic way for age, sex, or morbidity.

Each study subject received a questionnaire requesting information about employment, residences, smoking, and food as well as medical history, especially kidney diseases and diseases related to osteoporosis. Morning urine

Table 1 Characteristics of the population examined

Characteristics	Men		Women	
	n	mean (10th, 90th percentiles)	n	mean (10th, 90th percentiles)
Age	479	54	544	52
Urinary Cd (nmol/mmol creatinine)	471	0.82 (0.18,1.8)	533	0.66 (0.21,1.3)
Urinary protein HC (mg/mmol creatinine)	470	0.67 (0.16,1.2)	533	0.46 (0.15,0.80)

Table 2 Dose-effect relation between urinary cadmium and urinary protein HC for men (n=469) and women (n=532), adjusted for age\*

Parameter	Men†		Women‡	
	Regression coefficient	p Value	Regression coefficient	p Value
Age	0.148	0.0013	0.205	<0.0001
Urinary Cd (nmol/mmol creatinine)	0.236	<0.0001	0.130	0.0033

\*Analyses were missing for 20 workers.

†Adjusted  $r^2=0.0937$ .‡Adjusted  $r^2=0.0718$ .

was voided in acid washed polyethylene bottles and stored frozen (-20°C) until transfer to the analytical laboratory at the Department of Occupational and Environmental Medicine at Lund University Hospital. At the laboratory, the sample was thawed and 10 ml urine was poured into a polypropylene tube. After addition of 0.2 ml nitric acid, the tube was freeze stored until the measurement of cadmium. Subsamples for the measurement of protein HC were pipetted from the sampling bottle into separate tubes and freeze stored until analysis. The subsample for protein HC measurement was mixed with a preservative solution as described by Tencer *et al.*<sup>12</sup>

Cadmium in urine was measured by inductively coupled plasma mass spectrometry (ICP-MS). A quadrupole spectrometer (VG PQ2+, Fisons Elemental, Winsford, Cheshire, UK) equipped with an autosampler (Gilson 222, Gilson, Villiers, France) was used. The samples (0.50 ml urine) were diluted 10 fold with a solution containing EDTA (0.5 g/l), Triton-X100 (0.5 g/l), and ammonia (5 ml/l) in Millipore water, and 100 µl of an internal standard solution containing 50 ng of indium (In) was added. All samples were prepared in duplicate. Spiked urine samples, at three concentrations, were used for method calibration. The isotopes <sup>114</sup>Cd (and <sup>118</sup>Sn for correction of interference from <sup>114</sup>Sn) and <sup>115</sup>In were monitored in pulse counting, peak jumping mode (three points per peak). The detection limits (calculated as 3SD for reagent blanks) varied between 0.01–0.04 µg/l from day to day.

Table 3 Tubular proteinuria (defined as excreting protein HC &gt;0.8 and 0.6 mg/mmol creatinine, for men and women, respectively) in people exposed to cadmium

Urinary Cd (nmol/mmol creatinine)	Mean urinary Cd (nmol/mmol creatinine)	Environmentally exposed people cases/total (prevalence %) (missing, n=17)	Occupationally exposed people cases/total (prevalence %) (missing, n=3)	Total population cases/total (prevalence %)	OR, environmentally exposed people (95% CI) (test for trend, p<0.001)	
					OR, total (95% CI) (test for trend, p<0.001)	OR, environmentally exposed people (95% CI) (test for trend, p=0.001)
<0.3	0.21	12/252 (4.8)	1/13 (7.7)	13/265 (4.9)	1.0	1.0
0.3–<0.5	0.38	33/243 (14)	4/30 (13)	37/273 (14)	1.8 (0.9 to 3.5)	2.5 (1.1 to 5.5)
0.5–<1	0.69	60/232 (26)	8/66 (12)	68/298 (23)	2.7 (1.4 to 5.3)	4.3 (1.9 to 11)
1–<2	1.4	22/53 (42)	10/55 (18)	32/108 (30)	3.6 (1.7 to 7.6)	7.5 (3.5 to 44)
2–<3	2.5	1/1 (100)	7/23 (30)	8/24 (33)	4.0 (1.4 to 12)	—
3–<5	3.8	0/1 (0)	7/20 (35)	7/21 (33)	4.7 (1.6 to 14)	—
≥5	6.8	— (—)	6/12 (50)	6/12 (50)	6.0 (1.6 to 22)	—

Analyses were missing for 20 people.

The precision of the method, calculated as the coefficient of variation for the duplicate measurements, was 8%. The method accuracy was checked by including commercial reference urine samples (Seronorm, Nycomed, Oslo, Norway) in each analytical series. The results agreed well with the recommended values in both low and high ranges of urinary cadmium concentrations and there were no time trends in the recoveries. Adjustments for variation in urinary concentrations between people were made by dividing the urinary cadmium values by the creatinine concentrations.<sup>4</sup>

Urinary protein HC ( $\alpha_1$ -microglobulin) was used to detect early renal damage with single radial immunodiffusion for the measurements. The sensitivity of the method was 1.7 mg/l and its total analytical imprecision (within + between assay variation) 6%. The analyses were made at the Department of Clinical Chemistry at Lund University Hospital. The cut off points used for tubular proteinuria were 0.8 mg protein HC/mmol creatinine for men and 0.6 for women, which reflects the upper 95% limit in a Swedish reference population.<sup>13</sup>

#### STATISTICAL METHODS

Data were analysed with standard statistical methods, with STATISTICA software. Odds ratios (ORs) and 95 percent confidence intervals (95% CIs) were computed with stratified analyses and multiple logistic regression by EGRET software.

#### UNITS

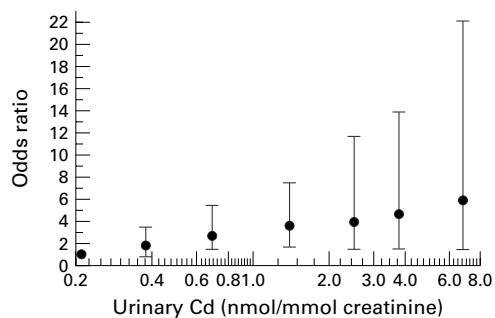
For cadmium in urine 1 nmol/mmol creatinine=1 µg/g creatinine.

#### Results

Age and sex as well as urinary excretion of cadmium and protein HC in the study population are shown in table 1.

A positive, highly significant, linear relation was found between dose (cadmium in urine) and effect (urinary protein HC) after adjustment for age for both sexes (table 2). The table shows the regression coefficients for the independent variables age and urinary cadmium, with protein HC as the dependent variable.

A total of 171 people had increased protein HC concentrations in urine with a clear dose-response relation between urinary cadmium and the prevalence of increased protein HC in urine as shown in table 3. During the course of investigation it was discovered that



Odds ratios (95% CIs) for prevalence of tubular proteinuria related to urinary cadmium in Swedish people exposed to low concentrations of cadmium.

several (n=105) environmentally exposed people also had worked in the battery plant. These people were therefore transferred to the occupationally exposed group, which thus increased to 222 people.

The dose-response relation remained even when the occupationally exposed people were excluded. The figure shows the ORs for increased urinary protein HC relative to increasing urinary cadmium after adjustment for age and sex.

Multiple logistic regression analysis, including age and urinary cadmium as independent variables and normal or increased urinary protein HC as the dependent variable was used to establish dose response relations at different ages. Given the mean age of the study population (53 years) an increased prevalence of tubular proteinuria of 10% was calculated to occur at a urinary cadmium concentration of 1.0 nmol/mmol creatinine. Here we have accounted for a normal background prevalence of increased urinary HC of around 5%, and thus the total measured prevalence of tubular proteinuria at a urinary cadmium concentration of 1.0 nmol/mmol creatinine would be 15%.

## Discussion

The present study shows that tubular proteinuria occurs in environmentally exposed people at lower concentrations of cumulative cadmium doses than was previously realised. People with cadmium in urine of around 1 nmol/mmol creatinine (which is in the upper part of the normal range) had a threefold increase in risk of having increased urinary protein HC (figure). The OR for increased urine HC is increased more than fivefold at urinary cadmium concentrations above 5 nmol Cd/mmol creatinine, which has been recommended as a health based limit by an expert group within the World Health Organisation (WHO).

Both age and urinary cadmium affect urinary protein HC excretion (table 2) and therefore age should be considered when dose-effect and dose-response relations are being analysed. Based on our data, a 10% increase in urinary protein HC would be expected in a population, with a mean age of 53, at a cadmium concentration in urine of 1.6 nmol/mmol creatinine.

One strength of our study is that we have been able to collect and analyse urine samples,

with sensitive methods, from a large population with exposures to cadmium close to the normal range. In most countries the normal urinary excretion of cadmium is in the range 0.1–0.6 nmol/mmol creatinine.<sup>1–7</sup> When more sensitive methods for detecting tubular damage are used, early and subtle effects from the accumulation of cadmium are shown.<sup>14</sup> When a very sensitive biomarker of effect (such as protein HC) is used, the clinical implication of increased urinary excretion is limited. However, as will be discussed later, subtle tubular damage is the beginning of a pathological process, which may end up in renal failure and secondary manifestations on the bone and mineral metabolism.<sup>7</sup>

Most previous studies have used  $\beta_2$ -microglobulin as the marker of tubular dysfunction. A major problem with  $\beta_2$ -microglobulin as a biomarker in large epidemiological studies is the instability of the protein in acidic urine. More sensitive markers have, however, been found. In particular, protein HC has been shown to be a sensitive and reliable marker of early tubular damage.<sup>15–17</sup> In a recent European collaborative study aimed at identifying early indicators of cadmium toxicity, the most sensitive indicators of nephrotoxicity were found to be protein HC, NAG, thromboxane B2, and RBP.<sup>18</sup> The cut off points for tubular dysfunction were taken from a rather limited reference material, based on a population living in a region not far from the study area.<sup>13</sup> It should be noted that the cut off points correspond to the 95th percentile in the reference population, and thus 5% of the study population should be expected to have values exceeding the cut off point. This has been taken into consideration in the interpretation of the results.

To obtain a wide range of cadmium exposures (facilitating the dose-response analyses) we included environmentally as well as occupationally exposed people. However, as shown in table 3, exclusion of all people with previous occupational exposure did neither affect the overall results nor their interpretation. The lower response rate among the battery plant workers might have introduced a bias, if the non-participants had different characteristics than the participants. However, as noted in the methods section, a survey of a random sample of the non-participants gave no indication that they differed from the participants in a systematic way for age, sex, or morbidity. Furthermore, the ORs for the environmentally exposed group were similar to those obtained when the occupationally exposed workers were included in the analysis (table 3).

In other parts of the world, where cadmium has contaminated the environment, increased concentrations of cadmium in urine and renal tubular effects have been recorded among residents.<sup>1–3, 7</sup> During the past decade, several studies of both occupationally and environmentally exposed populations have shown that tubular proteinuria occurs at doses of urinary cadmium of 2–4 nmol/mmol creatinine.<sup>9, 11, 19, 20</sup> In a large study on environmentally exposed people in Belgium a 10% prevalence of tubular



proteinuria was found at 2 nmol Cd/mmol creatinine, not adjusting for age.<sup>9</sup> The present study is in agreement with these findings with a 10% prevalence of tubular proteinuria at 1.6 nmol Cd/mmol creatinine adjusted to the mean age of the study population.

Kidney function, at least glomerular filtration, normally deteriorates with age<sup>21</sup> and pathological changes of the renal vessels, nephron, and the interstitium become more prevalent with increasing age.<sup>22</sup> Cadmium accumulates in the kidney with increasing age, and age may thus constitute an important effect modifier when examining long term health effects of cadmium exposure. The effect of aging itself on normal urinary excretion of  $\beta_2$ -microglobulin, however, seems to be limited.<sup>23</sup> The covariance between age and urinary cadmium in protein HC excretion (table 2) nevertheless suggests an increased vulnerability to cadmium in elderly people. Probably, normal degenerative changes of the renal tubuli in elderly people cause an increased sensitivity to cadmium.

Most studies of exposure to cadmium and renal tubular function have been performed on male workers. The present study showed only minor differences in tubular dysfunction between men and women, in accordance with a previous Japanese study of environmentally exposed people.<sup>24</sup>

All studies of exposure to cadmium and tubular dysfunction have been cross sectional. The tubular damage may have occurred a long time before the study was performed. If the concentration of urinary cadmium at the time of onset of tubular damage was higher, the dose-response curve would shift to the left in subsequent studies.<sup>17</sup> This problem, with a variable shape of the dose-response curve, is probably less relevant for environmentally exposed people, who have a continuous relatively low level of exposure compared with workers who have experienced high exposure to airborne cadmium in the past.<sup>17</sup>

It is, therefore, particularly noteworthy that tubular proteinuria occurs at relatively low concentrations of cadmium in urine and in the environmentally exposed group, in which the tubular damage appears at even lower concentrations than in the occupationally exposed group. It may well be that the occupationally exposed group comprises a selection of relatively healthy people, whereas the general population also includes more susceptible people. Furthermore, the group of environmentally exposed people also includes some who were very young when the exposure started and therefore are perhaps more susceptible to cadmium. In view of the relatively stable and low exposure to cadmium in the population examined, we think that the dose-response data presented here are valid and may be used to develop risk estimates in other environmentally exposed populations.

Research on health effects from cadmium has focused on the tubular damage, which from a health point of view may have limited importance, as the tubular proteinuria in itself does not give rise to any subjective symptoms or manifestations of disease.<sup>16, 14</sup> It has recently

been argued that the subclinical renal effects found in people with an increased cadmium body burden are not associated with progressive renal dysfunction, and that these early renal effects may even be reversible.<sup>25</sup> It has been shown, however, that the cadmium induced tubular damage is irreversible in most cases even if exposure ends.<sup>7</sup> Instead the tubular damage may become worse and glomerular damage with a drop in the GFR occurs. This has been seen among occupationally exposed workers as well as in people environmentally exposed to cadmium.<sup>7</sup>

Uraemia was common among Japanese farmers with itai-itai disease and end stage renal disease has been observed in workers heavily exposed to cadmium.<sup>3</sup> An overall increased mortality among residents with cadmium induced tubular damage in areas of Japan polluted with cadmium has been reported, indicating that serious health consequences may eventually result from the tubular damage.<sup>3, 7</sup>

Cadmium accumulation in the kidney is also related to negative health effects on the bone and mineral metabolism.<sup>1, 3, 7</sup> An increased prevalence of kidney stones in workers exposed to cadmium has been noted by several investigators.<sup>7</sup> Possibly this is related to the increased urinary excretion of calcium, secondary to tubular damage. A recent follow up of a large population of environmentally exposed people in Belgium suggests that cadmium accumulation increases the risk of development of osteoporosis.<sup>26</sup> This is in agreement with the findings of the OSCAR study, in which we found age adjusted negative correlations between urinary cadmium, or urinary protein HC, and bone density.<sup>11a</sup>

In conclusion, the results from the present study indicate that renal tubular damage due to exposure to cadmium may develop at lower concentrations than previously anticipated. Even if the tubular dysfunction in itself is a benign condition, it is an indicator of a renal effect that eventually may lead to serious health consequences. Therefore, measures should be taken to reduce exposure to cadmium in the general population, including lowering of current standards for intake of cadmium in food.

The study was supported by a grant from the Swedish Environmental Protection Agency. Approval was obtained from the relevant research ethics committee. We thank Ann-Christin Palmqvist and Ann-Kristin Thunberg who collected the data and Mariette Blomberg for entering data into computer files.

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*Journal* will destroy remaining copies of the article but correspondence and reviewers' comments will be kept.

# PostScript

## LETTERS

### Mortality from cardiovascular diseases and exposure to inorganic mercury

Paolo Boffetta and his coworkers presented a comprehensive cohort study comprising 6784 male and 265 female workers from four mercury mines and mills in Spain, Slovenia, Italy, and the Ukraine.<sup>1</sup> The expected number of deaths were derived from the national rates specific for sex, age, and calendar period. Slovenia was the only country with an increased mortality of ischaemic heart disease among men (SMR 1.66, 95% CI 1.35 to 2.02). In the Slovenian mine, dust measurements showed concentrations between 30 and 70 mg/m<sup>3</sup> with 10–35% free silica in the 1960s, and about 40 mg/m<sup>3</sup> in the 1970s. An increased mortality from pneumoconiosis was present in all countries. Mortality from ischaemic heart disease was positively correlated with duration of employment but not with cumulative exposure to mercury. Smoking habits was an unlikely confounder as mortality from diseases strongly associated with tobacco smoking—such as bronchitis, emphysema, and asthma—was not increased and mortality from lung cancer showed only a small increase (SMR 1.19). The purpose of this letter is to discuss further a possible relation between silica exposure and ischaemic heart disease (IHD).

A recently published study comprised 4626 industrial sand workers exposed to crystalline silica.<sup>2</sup> The study showed a higher standardised mortality ratio regarding IHD (SMR 1.22, 95% CI 1.09 to 1.36). Smoking might hypothetically be responsible for 2–4% of this increase.

A Swedish case-control study comprised 26 847 men with myocardial infarctions; for each case, two controls were selected from the study base through random sampling, stratified by age, county, and socioeconomic group. The second highest risk was found among stonecutters and carvers (RR 1.9, 95% CI 1.1 to 3.4). This high risk could not be explained by differences in smoking habits.<sup>3</sup>

A cohort consisted of 597 miners from North Karelia in Finland employed for at least

three years in a copper mine or a zinc mine.<sup>4</sup> The excess mortality was mainly due to IHD; 44 were observed, the expected number was 22.1 based on the general male population, and the North Karelian expected number was 31.2 ( $p < 0.05$ ).

A cohort of 3971 white South African gold miners was followed from the beginning of 1970. Most of the miners worked that year and the age of the workers was 39–54 years. The participants of the study were followed for nine years. A case-referent analysis was conducted comprising the miners who had had at least 85% of their service in gold mines. Ten years of underground mining was associated with a risk ratio of 1.5 ( $p = 0.004$ ) regarding IHD after adjustment for smoking, blood pressure, and body mass index.<sup>5</sup>

A large cohort comprised 68 241 miners as well as pottery workers from south central China.<sup>6</sup> The participants were employed between 1972 and 1974 and followed until 1989. There was an increased mortality due to IHD (SMR 1.25, 95% CI 1.05 to 1.45). Smoking habit was unlikely to be responsible for this risk as the mortality from lung cancer was lower than expected (SMR 0.8, 95% CI 0.7 to 0.9). There was no significant trend regarding mortality due to IHD when medium and high dust exposed workers (RR 1.16) were compared with low dust exposed workers (RR 0.65). Silicotics did not have an increased mortality due to IHD (RR 1.1, 95% CI 0.7 to 1.8).

A general hypothesis about exposure to inhaled particles and the occurrence of IHD can be expressed in the following way. Long term inhalation of particles retained in the lungs will create a low grade inflammation associated with an increase in plasma fibrinogen. The high concentration of fibrinogen will increase the likelihood for blood clotting and thereby the risk for myocardial infarction and IHD.<sup>7–9</sup> A high concentration of fibrinogen in plasma is an established risk factor for IHD.<sup>9</sup> An increased concentration of fibrinogen has been observed among tunnel construction workers after a workshift with a dust exposure of less than 2 mg/m<sup>3</sup>.<sup>10</sup> Thus dust exposure in general and silica exposure in particular could be interesting to discuss in relation to ischaemic heart disease in this study by Boffetta and coworkers.<sup>1</sup>

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### Joint action of smoking and asbestos exposure on lung cancer

This subject has long been bedevilled by unwarrantable assumption and circular argument. Why should there be only two possible hypotheses of interaction (additive and multiplicative)? Theory expects multiplicativity; epidemiology can seldom reject this hypothesis; so theory is “accepted”, and deviations from multiplicativity must be explained away. Resolution is made especially difficult because the nature of the data imposes very large error; also it has to be assumed that the exposed smoked as many cigarettes as the unexposed, and that smokers and non-smokers were exposed equally.

Thus the “comprehensive” review by Lee<sup>1</sup> was to be welcomed. However, discrepancies, particularly with another review,<sup>2</sup> demanded discussion: this letter is the result.

From almost 40 “results” in 25 reports, Lee makes two selections to confirm the well known facts that asbestos can increase lung cancer risk in non-smokers and that the additive theory (of independent action) does not explain many of the data. Then, for 16 results, Lee calculates a statistic  $V$ ; for an observed multiplicative interaction,  $V = 1$ . The weighted average  $V = 0.90$  (95% CI: 0.67 to 1.20) leads to Lee’s conclusion.<sup>1</sup> Repair of (acknowledged) imperfections (one misquoted result; two incorrect omissions) reduced  $V$  only slightly, to 0.83 (95% CI: 0.63 to 1.08); for nine cohorts and nine case-referent studies, respectively,  $V = 0.63$  and 1.08, a “significant” difference ( $p = 0.049$ ).

There are, however, other imperfections: two cohorts<sup>3,4</sup> broke the rule of independence; in another,<sup>5</sup> asbestos had a minuscule (protective) effect on lung cancer in both non-smokers and smokers (that is, no action, so no interaction); and in a Chinese cohort,<sup>6</sup> risks from cigarette smoke were dramatically lower than in the West. After exclusion, the cohorts’  $V = 0.54$  (95% CI: 0.35–0.82), and the difference between types is much wider ( $p = 0.017$ ).

Problems with case-referent designs are well known; here they are compounded by impure definitions of non-smokers and by retrospective assessment of exposure. It is clear from personal experience over five

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decades that, unless obtained from employers' records, job histories can be quite unreliable, even in basic facts, especially when reported by proxies. The assumption that the interactions between smoking and exposure to asbestos plus other carcinogens and between smoking and asbestos alone take the same form is untested and so indefensible. Thus, Lee's grounds for his unprecedented incorporation of the Italian study in which all concerned were exposed to PAHs,<sup>7</sup> namely, that subjects in many studies would have been exposed to "other" carcinogens, far from justifying inclusion, provide strong additional reasons for excluding all such studies, the majority of the case-referent studies in particular. It becomes obvious that inferences from the latter cannot overthrow conclusions from the cohorts.

The potential risks from dusty coal reinforce the need to exclude the Chinese cohort.<sup>5</sup> Undoubtedly, the North American insulation workers were not exposed only to 4–12 fibres/ml of chrysotile,<sup>8</sup> so there is a good case for discarding this result, although it forms a cornerstone of the evidence for multiplicativity. On the other hand, the study of crocidolite miners<sup>9</sup> might be taken into account, despite faults.<sup>2</sup> The resultant is  $V = 0.47$  (95% CI: 0.29 to 0.75).

Lee proceeds from  $V = 0.83$  (for 18 studies), noting that the significance of the difference between study types is not great, and "is removed" by an (admittedly dubious) adjustment of the lowest  $V$ . He "sides with other reviewers" and includes all data, concluding that "they do not clearly allow rejection of the simple multiplicative relationship".

Despite some doubt about the "best" estimate of  $V$  from cohort studies, most

reasonable people would accept that it is  $< 1$ , as shown even by Lee's  $V = 0.63$ , with  $p = 0.018$ .

Therefore, the multiplicative hypothesis is not generally satisfactory. Nor, of course, is the additive hypothesis, although it does fit some data sets very well.<sup>10</sup>

Evidently, interaction takes several forms.

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## Author's reply

Having read Liddell's paper<sup>1</sup> and the comments he expressed in his letter and at a recent meeting, it is useful to clarify where we agree and disagree. Originally I included estimates 1–16 shown in table 1, and estimated  $V$ , the ratio of the asbestos relative risk in smokers to that in non-smokers, as 0.90 (95% CI: 0.67 to 1.20). Omitting estimate 18 was an unfortunate error, and I also agree with Liddell that it is better to include estimate 17 and replace estimate 13 by estimate 19. Accounting for this reduces  $V$  to 0.83 (95% CI: 0.63 to 1.08).

Liddell also suggests excluding estimates 4, 11, 12, and 14, but for reasons I consider unconvincing. He would exclude estimate 4 as the population was exposed to PAHs. However, virtually all populations have exposure to carcinogens other than asbestos or tobacco smoke and anyway exposure to other carcinogens may simply multiply risk by about the same factor in each of the four groups being studied, little affecting the nature of the joint relation of asbestos and smoking to lung cancer. He would exclude estimate 11 because of low smoking risks, but these are typical of China<sup>2</sup> and do not invalidate the study. He would exclude estimate 12 as no asbestos effect was seen, but doing so based on

**Table 1** Assessing the multiplicative relationship of smoking and asbestos in lung cancer risk

Estimate*	Study type	V (95% CI)	Heterogeneity $\chi^2$	Degrees of freedom
1. DeKlerk	CC	1.25 (0.19 to 8.08)		
2. Martischinig	CC	2.89 (0.87 to 9.62)		
3. Pastorino, no PAH	CC	0.64 (0.10 to 4.06)		
4. Pastorino, PAH	CC	1.01 (0.13 to 7.94)		
5. Bovenzi	CC	0.86 (0.31 to 2.39)		
6. Kjuus	CC	1.52 (0.39 to 5.93)		
7. Blot, Georgia	CC	1.26 (0.54 to 2.93)		
8. Blot, Virginia	CC	0.84 (0.39 to 1.81)		
9. Blot, Florida	CC	0.72 (0.22 to 2.36)		
10. McDonald	P	0.61 (0.25 to 1.49)		
11. Zhu	P	1.60 (0.43 to 5.90)		
12. Meurman	P	1.19 (0.07 to 20.4)		
13. Berry, 1960–70 M+F	P	0.61 (0.10 to 25.7)		
14. Selikoff and Hammond	P	1.22 (0.32 to 10.4)		
15. Selikoff	P	0.19 (0.07 to 0.61)		
16. Hammond	P	0.95 (0.47 to 2.21)		
17. Berry, 1971–80 M+F	P	0.33 (0.13 to 1.25)		
18. Liddell <sup>1</sup>	P	0.56 (0.20 to 1.56)		
19. Berry, 1960–70 F	P	1.47 (0.22 to 50.0)		
<i>Original analysis</i>				
Estimates 1–16	All	0.90 (0.67 to 1.20)	14.88	15
<i>Revised analysis</i>				
Estimates 1–12, 14–19	All	0.83 (0.63 to 1.08)	18.39	17
Estimates 1–9	CC	1.08 (0.74 to 1.59)	4.33	8
Estimates 10–12, 14–19	P	0.63 (0.43 to 0.92)	10.17	8
<i>Revised analysis with exclusions</i>				
Estimates 1–3, 5–10, 15–19	All	0.79 (0.59 to 1.05)	17.00	13
Estimates 1–3, 5–9	CC	1.09 (0.74 to 1.60)	4.33	7
Estimates 10, 15–19	P	0.54 (0.35 to 0.82)	6.95	5

\*References and fuller details given elsewhere<sup>4</sup> except where stated. C, case-control; P, prospective.

V is the ratio of the asbestos relative risk in smokers to that in non-smokers.



observed results can cause bias. He would exclude estimate 14 as the study population is a subset of that for estimate 15. However, the follow up period was much longer for estimate 14 (1943–74) than for estimate 15 (1967–76), so omitting it would have lost data. Anyway, omitting estimates 4, 11, 12, and 14 only has a minor effect,  $V$  reducing to 0.79 (95% CI: 0.59 to 1.05) (table 1).

At face value, the combined data appear reasonably homogeneous and compatible with the multiplicative model. However, as Liddell notes, estimates for prospective and case-control studies differ. Using my revised analysis, prospective studies give  $V = 0.63$  (95% CI: 0.43 to 0.92) and case-control studies  $V = 1.08$  (95% CI: 0.74 to 1.59), a statistically significant difference ( $p = 0.049$ ). With Liddell's four suggested exclusions,  $V = 0.54$  (95% CI: 0.35 to 0.82) for prospective studies and  $V = 1.09$  (95% CI: 0.74 to 1.60) for case-control studies, with  $p = 0.017$ .

He stresses this significant difference, rejects the case-control data due to data unreliability, use of proxies, and inclusion of ex or light smokers in the reference group and argues that inferences should be drawn only from the prospective studies. I regard these arguments as dubious. The significance of the difference is not great and is removed ( $p = 0.089$  for the revised data) if the estimate of  $V$  for the one study (estimate 15) showing a very low value is revised based on "best available evidence" rather than on death certificate diagnosis (though this revision is itself questionable). Prospective studies may be limited by failure to record changes in smoking status after follow up starts. The Quebec prospective study<sup>7</sup> obtained data from proxies; many case-control studies did not. While data on accuracy of exposure is no doubt better in prospective studies, I side with other reviewers in considering the whole data.

The asbestos relative risk may be somewhat lower in smokers than non-smokers, but the available data do not clearly reject the simple multiplicative relation. More complex models of joint action might indeed fit the data better, but in view of the general problems with the data, it seems doubtful whether more detailed statistical analysis would shed any greater insight.

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### Occupational exposure to magnetic fields

While Savitz's point of view expressed in the editorial<sup>1</sup> that epidemiological methodology faces its limits when the risk is small, exposure assessment is poor, and biological insight is lacking, must be reinforced, it is not

so clear whether or not this view is applicable to the field of exposure to extremely low frequency electromagnetic fields (ELF EMF). Unfortunately some of the studies that could contribute to an evaluation of the relation between ELF EMF exposure and cancer have serious deficits. This is apparently also the case for the paper by Sorahan and colleagues.<sup>2</sup> First it has to be stressed that there is no such diagnostic entity as "brain tumour". Brain tumours comprise a heterogeneous group of both malign and benign neoplasms generating from different tissues, with different growth rates and other essentially different features (for an overview see Black<sup>3</sup>). The authors do not even mention the number of cases of different tumour types, let alone discuss why they feel that all these completely different entities could be affected by a single cause.

Another crucial point is latency. The only essential criterion of causation in the assessment of epidemiological evidence is "temporal relation". It is crucial that provisions are made to allow for biologically reasonable latencies. Instead the authors report on estimates based on the most recent (!) five years of exposure, thus choosing an exposure metric that has nothing to do with the vast majority of brain tumours that have latencies of at least five (but many 20 or more) years (for example, Strojan *et al.*<sup>4</sup>). Most of the brain tumours will have been already initiated before the point in time the exposure was accumulated to give the indicator the authors have chosen. At least the last 10 years prior to diagnosis of the tumour have to be truncated in computation of the exposure metric and all cases occurring earlier than 10 years after onset of exposure have to be omitted.

To choose Tesla-years as the exposure variable is also questionable because we do not know whether or not risk is cumulative. A more sophisticated exploitation of information on exposure could be expected from the authors. For example, time spent under peak exposures (e.g. exceeding 10% of the exposure limit) would be a meaningful surrogate. Tesla-years introduces an equivalence that has never shown to be meaningful: that exposure duration and intensity are commutative (that is, 10 years exposure to 1  $\mu$ T is equivalent to one year exposure to 10  $\mu$ T).

Overall the study in its presented form cannot be considered to contribute to the assessment of a relation between ELF EMF exposure and brain tumours.

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#### Authors' reply

Professor Kundi implies that, in our analyses of brain tumour risks and magnetic field

exposure, we only considered exposures occurring in the most recent five years. We did not. Analyses of total cumulative exposures to magnetic fields in relation to mortality risks from primary brain tumours were reported in table 3, and analyses of the potential role of recent exposures were reported in table 4.<sup>1</sup> Confirmation of diagnosis had also been sought from cancer registration particulars. These analyses were planned in advance as tests of the main hypotheses of interest. These hypotheses had been derived from a review of the current literature, and for neither analysis was there any suggestion of magnetic field exposure being implicated in mortality risks for brain tumours. The ICD codes we used to define the health outcome and the use of micro-Tesla years as the unit of magnetic field exposure enabled our study findings to be compared to other reports. Their use appears, at least to us, to be eminently sensible. We remain open to the possibility that other exposure metrics may come to be appreciated as more biologically relevant but we doubt whether the proposal of Prof. Kundi (time spent exceeding an arbitrary percentage of a contemporaneous exposure limit) will gain favour.

We hope our study makes a useful contribution to the practice of occupational health and that employees in the UK electricity supply and transmission industry treat the findings as good news.

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## BOOK REVIEW



### Innovation in Chinese Medicine

Elisabeth Hsu (pp 426; £55) 2001. Cambridge: Cambridge University Press. ISBN 0 521 80068 4

With increasing popularity of Chinese medicine in the West, there has been an increasing number of books published in this field. Some of them have dealt with the philosophical aspect of Chinese medicine, and others concentrated on the diagnosis and treatments. All of them referred to ancient texts such as the *Yellow Emperor's Inner Cannon* and used terminology from them. The uses of



these ancient concepts and terminology have led many to consider Chinese medicine as primitive, ritualistic, and unchanging. Such negative connotations have deterred many from studying Chinese medicine. Even if they did they felt they had to forego its theories and use the Western scientific paradigm to explain their treatment.

Elisabeth Hsu and the other authors in this book aimed to challenge this stereotype of Chinese medicine. They did so using selected examples to explain how evolution occurred in different aspects of Chinese medicine over time and the factors which motivated these changes. They showed that such changes could be brought about by the prevailing cosmological theories at the time, such as the incorporation of the system of five circulatory phases and six seasonal influences around the tenth century. Some changes were brought about by the political ideology at the time, such as the development of the new *acumoxa* theory in early communist China. But many are down to individuals' intuition, such as the new system of cataloguing natural pharmaceuticals by Li Shizhen in *Bencao gangmu* compiled in the sixteenth century. Many of the examples were chosen because they had far reaching consequences but some, notably one that was brought about for the sake of political correctness, did not have any sustainable influence.

The style of writing used in this book is one of its strengths. The reference text from which main arguments were based is cited both in Chinese and in English to avoid quoting out of context. Detailed footnote and extensive cross referencing underpin and expand the author's line of argument. Readers with scientific and medical background will appreciate such "evidence based" approach.

Its method of translation deserves to be noted separately. Chinese medicine terms have been notoriously difficult to have a standard translation, partly because they represent abstract concepts and their meaning can be different, depending on the context. Hsu used the official transcription system *pinyin* and Chinese characters alongside the English translation. These minimise confusion and allow readers to cross reference these terms with texts from other sources.

As well as achieving the author's objective, this book shows that Chinese medicine is not illusive and does not defy investigation. The author has shown how this could be done and her approach is different and innovative. The logical arguments in this book will appeal to professionals within the scientific community and can be a useful way to evaluate Chinese medicine.

**Gilbert Shia**

## CORRECTIONS

We apologise for the following errors.

In the paper "Low level cadmium exposure and kidney damage—the OSCAR study" (Järup *et al*) published in 2000 (*Occup Environ Med* 2000;57:668–72) the following errors were made:

(1) In the second paragraph, page 670, and at the fourth row, page 671, the text reads "1.6 nmol/mmol creatinine". It should read "1.0 nmol/mmol creatinine" at both places.

(2) In Table 1, "n" for age for the women should be 542 and not 544.

In the paper "Upper airway inflammation and respiratory symptoms in domestic waste collectors" (Wouters *et al*) published in February 2002 (*Occup Environ Med* 2002;59:106–12), the following errors were made:

(1) On page 108, right hand column, lines 5–7, part of the sentence was omitted. It should have read: "Estimated **within and between subjects variance components of exposure concentrations** were 0.51 and 0.34 for dust, 1.08 and 0.22 for endotoxin, and 1.49 and 0.14 for glucan."

(2) Table 2 heading: "from microbial agents" should have been omitted.