Correspondence

Cancer mortality of cadmium workers

SIR—In their paper on cancer mortality in cadmium workers Elinder *et al* summarised the “mortality and incidence data” for cancer of the prostate in six studies and the mortality data for lung cancer in five studies.¹ The latest follow up data were combined to yield 28 observed and 17.2 expected cases of prostate cancer with an SMR of 162 and a two tailed $p = 0.02$. For lung cancer, there were 195 observed and 161.4 expected deaths with an SMR of 121 and a two tailed $p = 0.008$. Based on this pooling of results, the authors concluded that “there is a clear impression of an increased incidence of these cancers among cadmium workers compared with the expected figures from the general population.”

Doll has drawn attention to an error committed by an international workshop on the carcinogenicity of metals in 1981.² The data available at that time for prostatic cancer in four series of cadmium workers were combined to yield 14 observed versus 5.6 expected cases with a one tailed $p = 0.002$. The conclusion of the workshop was that “exposure to cadmium had contributed to the development of prostatic cancer.” The inclusion of the first set of data must be regarded as hypothesis forming and should be excluded from subsequent analysis to check the unexpected finding of excess prostatic cancer in cadmium workers. If the first British series³ with four observed cases and 0.6 expected is excluded there would be 10 cases observed versus 5.1 expected with a one tailed $p = 0.04$ and a two tailed $p > 0.05$ (our calculation). Doll then concluded that “there is no logical reason to suggest that cadmium can cause prostatic cancer . . . and it should not now be regarded as a human carcinogen.”

The calculation by Elinder *et al* also included the first British series. When these data are excluded, there are only 24 observed versus 16.6 expected cases with an SMR of 145 (one tailed $p > 0.05$ and two tailed $p > 0.10$) which is statistically not significant.

As for lung cancer, since the earliest statistically significant observation of an excess mortality in cadmium workers was derived from the study by Lemen *et al* with 12 observed and 5.1 expected deaths,⁴ this series should then be regarded as hypothesis forming and should be excluded as well. Excluding these data, there are 183 deaths observed versus 156.3 expected with an SMR of 117 and a two tailed $p < 0.05$ which reaches statistical significance.

Based on the above calculation by the procedure of excluding the hypothesis forming data advocated by Doll, we find the statement by Elinder *et al* that their “new analysis suggests that long term, high level exposure to cadmium is associated with an increased risk of cancer” not valid for prostatic cancer and inconclusive for lung cancer.

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Dr Elinder replies:

The interpretation of conjoined epidemiological data is difficult. We have recently made one attempt¹ concerning cancer risks and cadmium which is not supported by Lam and Kazantzis. They are of the opinion that the first, “hypothesis generating” data from each site should be excluded from the analysis. They also, however, point out that the tendency towards an increased mortality in lung and prostatic cancer also remains after the exclusion of these cases first reported. Furthermore, the hypothesis of cadmium carcinogenicity had to some extent been generated from experimental work rather than from field observations.

Another, and perhaps more important, factor to consider when interpreting data from epidemiological studies is to what extent the examined group is comprised of people who have experienced significant exposure. In the extensive study by Armstrong and Kazantzis only 2.8% of the workers belonged to the

high exposure group.² An increased mortality restricted to a high exposure group might be difficult to identify when the high exposure group is diluted by large and relatively low exposed groups. In the Swedish¹ and in the recent American³ cohorts an increased cancer mortality was seen only among workers who had been exposed to high concentrations of cadmium ($>0.1 \text{ mg Cd/m}^3$) for at least two years.

Even though we agree with Lam and Kazantzis that the epidemiological data on cadmium are not conclusive, we are of the opinion that the combined epidemiological and experimental⁴ evidence speaks in favour of cadmium as a potential occupational carcinogen. History has shown that it may take many years from the first suspicion of an occupational carcinogen until it becomes a recognised occupational hazard and action is taken to decrease the industrial exposure.⁵ Until additional epidemiological studies on cadmium exposed workers have been made available, from a preventive health point of view, we think that cadmium should remain on the list of chemicals which are regarded as probably carcinogenic to man.⁶

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Are hazard warnings sufficient?

SIR,—A 50 year old man presented with blurred vision and unsteadiness. He was drowsy, hyperventilating, and had dilated pupils that reacted poorly to light. Initial investigations showed a profound metabolic acidosis pH 6.95, standard bicarbonate 5.9 mmol/l (mEq/l). Further investigations showed a significant methanol level 15.5 mmol/l (500 mg/l); ethanol was not detected. He was treated with intravenous sodium bicarbonate 1000 mmol (mEq), haemodialysis, and a nasogastric infusion of ethanol. On recovering consciousness, he developed delirium tremens that responded to diazepam.

The full story then emerged. Fifteen years previously, after the breakdown of his first marriage, he had drunk heavily. In recent years he had been drinking two bottles of spirits a week, concealing this from his wife. On occasions he had stolen and drunk methylated spirits from another department at work. Unbeknown to him, however, his employers changed from using methylated spirits to methanol, using standard hazard warnings. Two days later he took some to drink, with tragic consequences. He now has permanent optic nerve damage and is registered as blind, only being able to count fingers.

There is no legal requirement for methylated spirits or methanol to be kept under lock and key. Therefore unauthorised members of the workforce may have access. The hazard symbols and risk and safety phrases differ: for methylated spirits *highly flammable*, and for methanol *highly flammable, toxic by inhalation and if swallowed*.^{1 2} These differences, however, might not be appreciated by a worker without a scientific training who was accustomed to taking quickly a little from a bottle in a particular cupboard. They are both colourless liquids (industrial methylated spirits is not dyed with methyl violet³). The odour of methylated spirits is slightly stronger.

The ingestion of 15 ml of 40% methanol has been reported to cause death, while the highest reported dose for a survivor is 500–600 ml.⁴ In survivors the most common physical sequelae are optic nerve damage and permanent blindness.

Industrial methylated spirits is 95% ethanol and 5% methanol³; both are metabolised by hepatic alcohol dehydrogenase. Toxicity arises from the metabolic products. The relatively high concentration of ethanol in methylated spirits leads to competitive inhibition of the metabolism of methanol so any toxic effects are usually those of ethanol alone.

It is probably relatively common for employees to take methylated spirits or ethanol for their own consumption. Therefore, if a change is made to methanol I suggest that all employees who might have access should be verbally informed of the potential dangers as standard hazard warnings may not be sufficient. In this way, repetition of this sad case might be avoided.

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