Longitudinal studies of exposure to cadmium

R Armstrong, D R Chettle, M C Scott, M Blindt, H J Mason

Abstract

Measurements of urinary proteins, blood and urinary cadmium, and in vivo kidney and liver cadmium have been made for a group of workers at several times between 1981 and 1990. The possibility of the introduction of measurement artifacts due to the use of different in vivo measurement systems has been assessed and is considered to be small. Changes in cadmium body burden with time have been studied in relation to kidney function. The results suggest several interesting patterns, although more data are needed to elucidate these further. They do, however, show the effectiveness of good hygiene in the workplace.

The toxic effects of cadmium have been acknowledged for decades.¹ Of special interest in chronic occupational exposure are its nephrotoxic effects,^{2,4} particularly tubular damage that is characterised by the excess excretion of low molecular weight proteins such as β_2 -microglobulin and retinol binding protein.⁵⁻⁷ Cadmium accumulates mainly in the kidneys and the liver, these organs alone accounting for roughly 70% of the total body burden.⁸ In vivo measurement of concentrations in these organs therefore provides a good estimate of body burden. These, along with biochemical measurements such as urinary proteins and blood and urinary cadmium concentrations may then be used to assess the health of the worker with respect to cadmium. Many such studies of the accumulation and toxicology of cadmium have been reported. These have mainly been of

a cross sectional nature (at one point in time),⁹⁻¹³ with few studies including measurements over a period.¹⁴ The last are of particular interest as they provide information on changes in cadmium stores, and relate these to the onset of toxic effects in some members of the workforce.

The opportunity has been provided to make additional in vivo and biochemical measurements on a group of workers exposed to cadmium fume in the process of producing cadmium silver alloy. Previous measurements on these workers have already been reported.^{15,16} In this paper we present further conclusions from this longitudinal study.

Subjects and methods

In the overall study, four sets of measurements have been carried out to date. The initial measurements were made in December 1981, with subsequent measurements in March 1983, January 1986, and April 1990. At each survey, with the exception of 1983, measurements were made of urinary proteins, blood cadmium and urinary cadmium concentrations and in vivo kidney and liver cadmium burdens. In 1983, no in vivo data were collected. The original study group consisted of 37 male workers who were exposed to cadmium and silver fumes, along with, to a lesser extent, other metal fumes such as those of lead, zinc, copper, and arsenic for various periods. Twenty eight of these presented for further measurements in 1983, 21 in 1986 (although only 16 kidney measurements were available for analysis), and 18 in 1990. Of those measured in 1986, all but five had blood and urinary measurements made in 1983 and, of those in 1990, four were not measured in 1983 and two were not measured in 1986. The table shows the measurement pattern.

Throughout the study, urinary β_2 -microglobulin concentration was measured with a commercial immunoassay.¹⁷ Retinol binding protein was measured with an assay developed by the Health and Safety Executive.¹⁸ Blood cadmium and urinary cadmium concentrations were measured using graphite furnace atomic absorption spectrometry.^{19,20} The in vivo measurements were made by prompt γ -ray neutron activation analysis,²¹ using different versions of transportable kidney and liver measurement systems.

As the measurement systems have been repeatedly

Medical Physics Group, School of Physics and Space Research, University of Birmingham, Birmingham B15 2TT, England

R Armstrong, D R Chettle, M C Scott

Gleadless Medical Centre, Sheffield, England

M Blindt

Occupational Medicine and Hygiene Laboratories, Health and Safety Executive, London, England

H J Mason

Present address for R Armstrong: **Department of Physics, University of Warwick, Coventry CV4 7AL, England**

Present address for D R Chettle: **Department of Physics, McMaster University, Hamilton, Ontario L8S 4M1, Canada**

In vivo measurement pattern for workers

Subject Number	December 1981	March 1983	January 1986	April 1990	Subject Number	December 1981	March 1983	January 1986	April 1990
1	✓	✓		✓	20	✓	✓		
2	✓				21	✓		✓	✓
3	✓	✓	✓*	✓	22	✓	✓	✓*	✓
4	✓	✓			23	✓	✓		
5	✓	✓	✓*	✓	24	✓		✓	✓
6	✓	✓	✓		25	✓	✓		
7	✓				26	✓	✓	✓	✓
8	✓	✓			27	✓	✓	✓	
9	✓				28	✓	✓	✓	✓
10	✓	✓	✓	✓	29	✓	✓	✓	
11	✓	✓		✓	30	✓	✓	✓	
12	✓	✓		✓	31	✓	✓		✓
13	✓		✓	✓	32	✓			
14	✓	✓			33	✓	✓		
15	✓	✓	✓	✓	34	✓		✓*	✓
16	✓	✓	✓	✓	35	✓	✓	✓	✓
17	✓	✓			36	✓		✓	
18	✓	✓	✓*	✓	37	✓	✓	✓	✓
19	✓	✓							

*Indicates those workers with no 1986 measurements of kidney cadmium.

modified over the years, it is important to eliminate the possibility of artifacts due to differences in the systems. Although some features have changed, the basic design and geometry of the systems have remained the same. The main differences lie in the type of material used as a neutron shield and as a neutron reflector. In 1981, neutrons from the $^{238}\text{Pu}/\text{Be}$ sources (used in all measurements) were shielded with borated water filled tanks, and reflected forward towards the subject by graphite used as the source holder, in both the kidney and liver systems.²² The lower limit of detection (LLD) (2 SDs of the peak area) obtained was 8 mg for the kidney system, and 20 $\mu\text{g/g}$ for the liver. In 1986 the neutron shielding was changed to boric oxide powder and the neutron sources were placed in an iron holder, again for both systems,²³ giving detection limits of 6.4 mg and 6.5 $\mu\text{g/g}$.²⁴ In 1990 the kidney system alone had been redesigned changing the neutron shielding to iron and polythene.²⁵ An LLD of 4.8 mg was obtained. The liver system used in these measurements was the same as that used in 1986. The LLD for both kidney and liver measurements has decreased for each new system introduced, reflecting the increased precision of the measurements arising from the improvement in counting statistics. The precision of the measurements also depends on any error introduced due to mispositioning of the subject. In all the kidney measurements and the last two sets of liver measurements, ultrasound was used to locate the organ, with an estimated measurement uncertainty of ± 5 mm. In practice, the reproducibility of kidney depth estimates for subjects with repeated measurements was ± 5.5 mm even over this nine year interval, supporting the estimated precision. This 5 mm uncertainty in the kidney depth results in a cadmium measurement uncertainty of the order of

7%. For the liver measurements, the corresponding uncertainty is less than 1%.

In each survey, extensive phantom measurements have been carried out. The method of making the phantoms has not changed throughout the measurement period and the same phantoms were used in 1986 as in 1990. The error introduced in mispositioning any phantom is well within 5% but, in any case, in each survey, sets of phantom results were used for calibration, decreasing the importance of mispositioning any individual phantom. The above factors would seem to suggest that the likelihood of the introduction of appreciable artifacts is small.

Results

In reporting the original results taken in 1981, the population was divided into groups according to their duration of exposure to cadmium at that time. The first group had been exposed for periods of up to 10 years. Of these workers nine had complete in vivo measurements made in both 1986 and 1990 (subjects 15, 16, 21, 24, 26, 28, 31, 35, and 37), from which body burden was calculated as:

$$\text{body burden} = \frac{1.8 \times \text{liver Cd} + 2 \times \text{kidney Cd}}{0.16 + 0.53} \text{ mg}$$

For this subgroup, the inverse variance weighted mean and associated error of the body burden fell from 115.1 ± 9.48 mg in 1981, to 108.8 ± 7.35 mg in 1986, to 81.5 ± 4.05 mg in 1990. Four of these workers retired between 1983 and 1984; their body burdens fell from 110.3 ± 14.45 mg in 1981 to 68.0 ± 10.94 mg in 1986, and to 66.3 ± 5.89 mg in 1990. The other five workers are still employed in the cadmium melting shop in the factory. Their inverse variance weighted mean body burdens changed from

118.6 $\pm$ 12.57 mg in 1981 to 142.5 $\pm$ 9.93 mg in 1986 and to 79.4 $\pm$ 5.59 mg in 1990. This, at first sight, indicates an increase in exposure from 1981 to 1986. One subject in this group, however, had a substantial increase in body burden in 1986, and when the weighted means of the other four workers who are still employed were calculated they gave values of 123.0 $\pm$ 13.52 mg in 1981, 96.4 $\pm$ 10.94 mg in 1986, and 90.3 $\pm$ 5.98 mg in 1990.

The one subject in this group (24) who exhibited an unusual pattern in accumulation of cadmium had a dramatic increase in body burden in 1986 to a value of 358.7 $\pm$ 23.7 mg from 91.0 $\pm$ 15.7 mg in 1981. In 1990, the body burden had fallen to 128.4 $\pm$ 15.7 mg. This pattern is mimicked, although not to the same extent, in the blood and urinary cadmium measurements, which were slightly raised in 1983 and 1986. The liver and kidney cadmium levels in 1986 were 56.4 $\pm$ 4.3 μ g/g and 73.0 $\pm$ 7.2 mg.

It should be noted that, in determining body burden from the *in vivo* measurements, the liver cadmium concentration was calculated assuming a standard liver size of 1.8 kg,²⁶ and both kidneys were assumed to have the same content of cadmium. The denominator in the equation indicates the fractional body burden attributed to each organ: 0.16 for the liver and 0.53 for the kidneys.⁸

In 1983 six members of the group with the shortest exposure (subjects 3, 4, 5, 26, 28, and 31) were identified as having sufficiently high body burdens to suggest that kidney damage, although not present at that time, might well occur. In 1983, all the subjects were remeasured, in 1986, three were remeasured, and in 1990 five were remeasured. At no time was there evidence from the biochemical data that renal damage had occurred. The weighted mean body burdens for the three subjects who had complete *in vivo* measurement records fell from 265.5 $\pm$ 16.90 mg in 1981, to 137.2 $\pm$ 12.19 mg in 1986, and to 117.2 $\pm$ 7.41 mg in 1990.

Two workers (10 and 13), who have complete *in vivo* records, can be identified from the beginning of the study, as having kidney damage as assessed by urinary excretion of the low molecular weight proteins β_2 -microglobulin and retinol binding protein. Both showed similar patterns of distribution of cadmium between the liver and kidney during the time period studied. The liver cadmium concentrations appeared to decrease in 1986 only to rise again in 1990. The kidney cadmium burdens, however, showed the opposite trend, increasing in 1986 and falling in 1990. The body burdens, within errors, did not change appreciably.

Discussion

Although the workers studied in these surveys have

had exposure to toxic metal fumes other than cadmium, this exposure has been well within current safety limits.²⁷ It therefore seems reasonable to attribute the changes in renal function found in some of the workers to cadmium alone.

For the subgroup of nine workers, body burden decreased significantly between 1981 and 1990, for both the retired workers and the workers still employed. This suggests a decrease in accumulation of cadmium in this period, compared with that before 1981. This is easily explained for the retired workers, assuming environmental cadmium levels to be less than occupational levels. The decreased accumulation in the workers still employed is substantiated by factory records, which indicate a decrease in exposure to cadmium due to the use of more effective extraction techniques, and to the decrease in cadmium content of the alloys produced by the factory; these measures having been introduced after the initial measurements in 1981.

The one worker who had a large increase in body burden in 1986 has not, according to factory records, increased his exposure significantly in the study period and, indeed, is considered to be a very careful worker. This large increase is not believed to be a result of measurement error, and no explanation of it can be offered at this time. It should be noted, however, that despite this increase in body burden, especially the large kidney cadmium level, this worker does not, from the biochemical measurements, appear to have developed cadmium induced nephropathy.

The liver and kidney cadmium levels in the two workers with signs of kidney damage exhibit an interesting yet puzzling pattern of redistribution. Unfortunately, the numbers do not make it possible to study this in depth, but this pattern has been seen in similar workers from another factory.

An important finding of the original study on this population,¹⁵ was the existence of a group of workers with a short period of exposure and increased body burdens who had not developed cadmium induced nephropathy. From subsequent biochemical measurements it is evident that this is still the case. Of this group, three had retired in 1983; the others are still employed to date in the melting shop. All subjects (apart from one, for whom only one set of *in vivo* measurements was available) showed the same change in cadmium distribution from 1981 to 1990—namely a decrease in liver cadmium, an increase in kidney cadmium and an overall decrease in body burden. It is also interesting that the mean decrease in body burden from 1981 to 1990 for the retired workers was 200.8 $\pm$ 21.90 mg and for those still employed was 119.3 $\pm$ 18.82 mg suggesting that although exposure to cadmium in the factory has been appreciably reduced, it is, not surprisingly, still greater than that found in the environment. The

important point to note from this group is, however, that despite their large initial body burdens, they have not developed kidney damage. One interpretation of this is that the accumulation of cadmium in the kidneys, resulting from transfer from the liver, has not at any time been sufficient to cause renal damage. A decrease in exposure such as has happened in this factory may, therefore, be beneficial in preventing renal effects by limiting the accumulation in these organs.

This longitudinal study has brought to light several interesting patterns of change of cadmium body burden. Despite the large number of workers measured during this longitudinal study, it has been difficult to follow more than a few throughout the entire study period. This limits the interpretation of the data, and the conclusions which can be drawn, and supports the case for collaboration between researchers with similar data. Nevertheless, in this factory, the results indicate the importance and beneficial effects of good occupational hygiene practice.

We gratefully acknowledge the help of Mr Paul Tear of Thessco Ltd, without whom these measurements would not have been possible. We are also grateful to the Health and Safety Executive for financial support for two of us (RA and DRC), and for general input and helpful discussion.

Requests for reprints to: Dr R Armstrong, Department of Physics, University of Warwick, Coventry CV4 7AL, England.

- 1 Friberg L. Proteinuria and kidney injury among workmen exposed to cadmium and metal dust. *Journal of Industrial Hygiene and Toxicology* 1948;30:32-6.
- 2 Nordberg GF, ed. *Effects and dose-response relationships of toxic metals*. Amsterdam: Elsevier, 1976.
- 3 World Health Organisation. Environmental health criteria for cadmium. *Ambio* 1977;6:287-90.
- 4 Hutton M. *Evaluation of the relationship between cadmium exposure and indices of kidney function*. London: University of London, 1983. (Technical report No 29, 1983, Monitoring and Assessment Research Centre.)
- 5 Friberg L. Cadmium and the kidney. *Environ Health Perspect* 1984;54:1-11.
- 6 Herber RFM. Beta-2-microglobulin and other urinary proteins as an index of cadmium-nephrotoxicity. *Pure and Applied Chemistry* 1984;56:957-65.
- 7 Friberg L, Elinder C-G, Kjellström T, Nordberg GF, eds. *Cadmium and health: a toxicological and epidemiological appraisal, Vol II. Effects and response*. Boca Raton, Florida: CRC Press Inc, 1986.
- 8 Friberg L, Elinder C-G, Kjellström T, Nordberg GF, eds. *Cadmium and health: a toxicological and epidemiological appraisal, Vol I. Exposure, dose and metabolism*. Boca Raton, Florida: CRC Press Inc, 1985.
- 9 Roels HA, Lauwerys RR, Buchet J-P, et al. *In vivo* measurement of liver and kidney cadmium in workers exposed to this metal: Its significance with respect to cadmium in blood and urine. *Environ Res* 1981;26:217-40.
- 10 Webb MAH, Chettle DR, Al-Haddad IK, Downey SPMJ, Harvey TC. Measurement of cadmium in liver and kidney using *in vivo* techniques. *Ann Occup Hyg* 1982;25:33-7.
- 11 McNeill KG, McLellan JS, Mohammad Amin AK, Vohra K, Marnagh JR. Measurement of cadmium *in vivo* in industrial workers. *Journal of Radioanalytical Chemistry* 1982;71:573-80.
- 12 Ellis KJ, Yuen K, Yasumura S, Cohn SH. Dose-response analysis of cadmium in man: body burden vs kidney dysfunction. *Environ Res* 1984;33:216-26.
- 13 Mason HJ, Davison AG, Wright AL, et al. Relationships between liver cadmium, cumulative exposure, and renal function in cadmium alloy workers. *Br J Ind Med* 1988;45:793-802.
- 14 Roels H, Lauwerys R, Buchet JP, Bernard A, Alfons V, Oversteyns M. *A prospective study of proteinuria in cadmium workers. Nephrotoxicity: in vitro to in vivo, animals to man*. New York: Plenum Press, 1989.
- 15 Gompertz D, Chettle DR, Fletcher JG, et al. Renal dysfunction in cadmium smelters: relationship to *in vivo* liver and kidney cadmium concentrations. *Lancet* 1983;i:1185-7.
- 16 Guthrie CJG, Franklin DM, Scott MC, et al. A longitudinal study of exposure to cadmium fume—preliminary findings from *in vivo* body burden measurements. In: Ellis KJ, Yasumura S, Morgan WD, eds. *In vivo body composition studies*. London: Institute of Physical Sciences in Medicine, IPSM3, 1987.
- 17 Kjellström T, Piscator M. Beta-2-microglobulin in urine induced by cadmium. 'Phadebos No. 1' diagnostic communications. Uppsala, Sweden: Pharmacia Diagnostics AB, 1977.
- 18 Topping MD, Forster HW, Dolman C, Luczynska CM, Bernard AM. Measurement of urinary retinol binding protein by enzyme linked immunosorbent assay and its application to the detection of tubular proteinuria. *Clin Chem* 1986;32:1863-6.
- 19 Delves HT, Woodward J. Determination of low levels of cadmium in blood by electrothermal atomisation and atomic absorption spectrophotometry. *Atomic Spectroscopy* 1981;2:65.
- 20 McAughy JJ, Smith NJ. The direct determination of cadmium in urine by electrothermal atomic absorption spectrometry with the L'vov platform. *Anal Chim Acta* 1984;156:129-37.
- 21 Chettle DR, Fremlin JH. Techniques of *in vivo* neutron activation analysis. *Phys Med Biol* 1984;29:1011-43.
- 22 Fletcher JG. *The in vivo measurement of iron and cadmium—methods and results*. Birmingham: Department of Physics, University of Birmingham, 1987. (PhD thesis.)
- 23 Franklin DM. *Studies relating to the in vivo measurement of liver and kidney cadmium burdens*. Birmingham: Department of Physics, University of Birmingham, 1986. (PhD thesis.)
- 24 Guthrie CJG. *The statistical analysis of survey measurements made from workers exposed to cadmium*. Birmingham: Department of Physics, University of Birmingham, 1987. (MSc thesis.)
- 25 Franklin DM, Armstrong R, Chettle DR, Scott MC. An improved *in vivo* neutron activation system for measuring kidney cadmium. *Phys Med Biol* 1990;35:1397-408.
- 26 ICRP 23. Report of the task group on reference man. New York: Pergamon Press, 1975.
- 27 Triger DR, Crowe W, Ellis MJ, Herbert JP, McDonnell CE, Argent BB. Trace element levels in the blood of workers in two steel works and a non-ferrous plant handling lead and cadmium compared with a non-exposed population. *Science of the Total Environment* 1989;78:241-61.

Accepted 11 November 1991