Reduced Cadmium Levels in Human Kidney Cortex in Sweden

Lennart Friis, Lars Petersson, and Christer Edling

1Department of Occupational and Environmental Medicine, University Hospital, Uppsala, Sweden; 2Department of Chemistry, National Veterinary Institute, Uppsala, Sweden

Environmental pollution with the nephrotoxic metal cadmium is considered a potential health risk for the general population. In 1976 it was reported that the cadmium concentration in human kidney cortex in Sweden had increased in parallel with increasing levels in soil and grain during the twentieth century. Since the cadmium concentration in farming lands is still increasing, the present study was undertaken to further elucidate whether the cadmium concentration in the kidney is still increasing. Kidney cortex biopsies were collected at 171 autopsies of victims to sudden and accidental death during 1995 and 1996, and the cadmium concentrations were determined and compared with previously published Swedish data obtained from forensic autopsies. The geometric mean cadmium concentration in kidney cortex in subjects 40 years of age and younger was about 40% of the concentration found in the 1970s, while the reduction was less pronounced among older people. The highest individual concentration of cadmium was 41.5 μg/g wet weight (ww). The geometric mean concentration was less than 14 μg/g ww at ages around 50 years of age, when the cadmium concentration in kidney cortex is highest, as compared with approximately 20 μg/g ww in the 1970s. There was also a reduction in cadmium concentrations among nonsmokers; thus, a decrease in tobacco smoking in Sweden during the last decades is not the only explanation for the reduction of cadmium in the kidney cortex. Other reasons for this reduction could be changes in dietary habits and reduced cadmium contamination from Swedish industries. Key words: autopsy, cadmium, human, kidney cortex, Sweden. Environ Health Perspect 106:175–178 (1998). [Online 26 February 1998] http://ehpnet1.nihes.nih.gov/docs/1998/106p175-178friis/abstract.html

Environmental cadmium was recognized as a public health hazard in the late 1960s after the Japanese studies of Itai-Itai disease in an extremely cadmium-polluted area. This bone disease was considered to be secondary to a chronic cadmium intoxication of the kidneys, although other contributing factors have been discussed (1). The continued discussions about cadmium as an environmental pollutant of public health interest has recently been strengthened after reports from Belgium about an increased prevalence of kidney dysfunction—leakage of small proteins with the urine (tubular proteinuria) (2). The increased prevalence of this early marker of chronic cadmium toxicity was reported in a population living in an area with industrial pollution by cadmium. The critical level of cadmium in kidney cortex, the level at which tubular proteinuria first appears, has been estimated to be 200 μg/g wet weight (ww), but there are data suggesting that the critical level might be lower (3). Ingestion is the major route for cadmium exposure among nonsmokers in the general population (4). Cadmium is a normal constituent of most food, but certain food items such as liver, kidney, shellfish, mushrooms, vegetables, and cereals may contain especially high levels (5). Tobacco smokers also have a considerable contribution to their cadmium intake through inhalation because tobacco plants accumulate cadmium in the leaves. A heavy smoker may absorb more cadmium by inhalation than from food (6).

The environmental levels of cadmium have been rising worldwide since the beginning of the twentieth century, when the industrial use of the metal accelerated (7). The cadmium concentration in human kidney cortex has increased in Sweden during the twentieth century in parallel with increasing levels in soil and grain (5–7). Although the emissions of cadmium in Sweden have been reduced during the last decades, the level of cadmium in arable land is still increasing because of continued use and spreading of phosphorus fertilizers containing cadmium (8). This has caused concern about a continued increase of the exposure to cadmium in the Swedish population.

In 1976, Elinder et al. (9) presented data about cadmium in kidney cortex from forensic autopsies performed in Stockholm. They found the highest cadmium concentrations in kidney cortex from subjects 40 to 60 years of age, with geometric means around 20 μg/g ww. Some individuals had levels around 100 μg/g ww. Given the small safety margin for the levels described 20 years ago and the increasing environmental burden, a new survey was warranted. We have therefore analyzed the cadmium concentration in samples of kidney cortex collected at forensic autopsies performed in Uppsala, Sweden, and compared them with the Swedish data from 1976. Our hypothesis was that the cadmium concentration in human kidney cortex should have increased in parallel with the increased concentrations in the environment since the 1970s. The ethics committee of the Faculty of Medicine, Uppsala University, approved this study.

Methods

Biological samples. The present study was a cross-sectional analysis of the concentration of cadmium in samples of kidney cortex from victims of sudden and accidental deaths examined at the Department of Forensic Medicine in Uppsala, Sweden, from August 1995 to June 1996. A sample of kidney cortex from the caudal pole of the right kidney was obtained from 173 subjects and stored dry in airtight cadmium-free containers (Cerbo, Trollhättan, Sweden) at -20°C until analysis. Two of the collected samples were destroyed before the analysis on request from relatives. Of the remaining samples, 161 were from residents in four counties in central Sweden (Dalarna, Gävleborg, Uppsala, and Västmanland), and 10 were from other parts of Sweden.

Chemical analysis. Five grams (ww) of kidney cortex was weighed in a filter paper (OOH 7.0 cm; Munktell Filter AB, Grycksbo, Sweden) and placed in an ashing tube of borosilicate glass. Oxidizing acid mixture (15 ml) containing 65% nitric acid and 70% perchloric acid (7:3, by volume; analytical grade) was added and the sample was digested overnight according to a standard digestion program (10,11), using an electrically heated aluminum block connected to a programmable microprocessor for control of temperature and time (Tecator Digestion System, Model 40; Tecator AB, Höganäs, Sweden) (10,11). After digestion was completed, the solution was evaporated to dryness and dissolved in ionic buffer (12).

Cadmium was determined using an inductively coupled plasma emission spectrometer, (ICP-AES model JY 50 P; Instruments S.A., division of Jobin Yvon, Longjumeau, France).

Address correspondence to L. Friis, Department of Occupational and Environmental Medicine, University Hospital, S-751 85 Uppsala, Sweden. The County Council of Uppsala funded this project. Received 10 September 1997; accepted 13 November 1997.
with setup and conditions according to the manufacturer (13). The analytical method was checked by analyzing a certified standard reference material [National Institute of Standards and Technology (NIST)]. The cadmium concentration [mean ± standard deviation (SD)] obtained in NIST SRM 1577b bovine liver (n = 4), with the certified concentration 0.50 ± 0.03 μg/g dry weight (dw), was 0.49 ± 0.01 μg/g dw.

Validation of the sample preparation. To exclude the possibility of false low cadmium levels due to remaining kidney medulla in the tissue samples, a random subsample of 18 kidneys was reanalyzed. A pathologist, assisted by an experienced laboratory technologist, performed these new preparations. The absence of medulla in the preparations was microscopically confirmed on cryosectioned tissue slides. The new cadmium concentrations obtained from this subsample (geometric mean ± geometric SD, 7.82 ± 2.29 μg/g ww) did not differ significantly (p = 0.52 in a paired t-test on logarithm-transformed data) from the previously determined concentrations in the same kidneys (7.65 ± 2.30 μg/g ww). A certified standard reference was included also in this analysis: 0.52 μg/g dw was measured in NIST SRM 1577b bovine liver with the certified concentration 0.50 ± 0.03 μg/g dw.

**Questionnaire.** A questionnaire about tobacco smoking and occupational history regarding jobs that may have involved cadmium exposure was sent to one next of kin of 166 subjects 6 months after the death. Nonresponders were contacted by telephone a few months later. In seven cases we were either not able to find any next of kin (from autopsy reports and from population registries) or we judged it unethical to approach the relatives. The questionnaire was eventually completed by 152 (88%) relatives of subjects. Two subjects were excluded from the study on request from their relatives.

Sixty subjects were smokers until their deaths or had quit smoking during the last year of life, 33 were habitual smokers who had quit smoking before the last year of life (ex-smokers), and 58 had never smoked tobacco. Based on job titles, 10 had held jobs with potential cadmium exposure.

**Statistical analysis.** Two-by-two table statistics were used to compare proportions. The distribution of the kidney cortex cadmium concentration was tested for normality with Lilliefors test [SPSS (14)] and normalized by a logarithmic transformation. The logarithms of the geometric means and SDs published by Elinder et al. (9) were used for comparison with the data from this study using the Student’s t-test. The level of significance was set at p<0.05 (two-tailed) in all comparisons.

**Results**

The individual cadmium concentrations in kidney cortex are presented in Figure 1. The highest cadmium concentration was 41.5 μg/g ww. Three of 29 subjects with a cadmium concentration over 20 μg/g ww had worked in jobs with potential cadmium exposure, whereas 7 among the remaining 142 had been in such jobs (p = 0.4). Women had higher cadmium concentrations than men (p = 0.01), and smokers had higher concentrations than nonsmokers (p = 0.001; Table 1). The geometric mean cadmium concentrations in kidney cortex in 10-year age groups are shown in Table 2. There has been a statistically significant decrease in cadmium concentrations since 1976 in most age groups under 70 years of age, and the decrease is more pronounced in the younger age groups. In the youngest groups, the concentrations were 40% of concentrations in the same groups in the 1970s.

**Discussion**

This study shows a reduction of the cadmium concentration in human kidney cortex in Sweden since the 1970s. The concentration is at least half of the 1976 value in people under 40 years of age, whereas the reduction is less pronounced among older people. This reduction is in contrast to the increased environmental burden of cadmium during the same period (8).

One might question the comparability of two measurements as complicated as these two studies represent. Our view is that it is always possible to compare two separate measurements of the same phenomenon, in spite of possible shortcomings, as long as these are acknowledged and discussed to the best of one’s ability. The two studies we compared are the best available, with information about cadmium exposure of the human kidney in Sweden during the last decades; possible trends in these data are of importance for the evaluation of the public health impact of cadmium pollution.

Differences in the collection and processing of the tissue samples that affect cadmium concentrations could invalidate the comparisons between the two studies. The validation of our sampling and preparation indicates that the data obtained for this study do at least not suffer of two obvious possible errors: underestimation of the cadmium levels because of contamination of the samples with kidney medulla (with lower cadmium concentrations than the cortex) or overestimation due to drying of

![Figure 1. Cadmium concentrations in human kidney cortex in Sweden, based on smoking status. WW, wet weight.](image-url)
the samples during the processing. The observed differences in cadmium levels could also depend on poor laboratory standards. However, the two laboratories involved in the compared studies are both well known and have good reputations. Elinder et al. (9) used duplicate samples to check the analytical precision, and our analyses were checked by use of standard reference material as well as duplicate samples. There is no indication that either of these two studies has suffered from severe errors in the analyses. The almost-equal cadmium levels in the highest age groups support the conclusion that no serious error has been made in sampling, preparation, or analysis that affects the comparisons. Considering the long half-life of cadmium in the kidney cortex, this conclusion is biologically plausible because the oldest subjects in both studies do, in part, reflect the same exposures during some decades before the mid-1970s. Therefore, by analogous reasoning, we find the reduced cadmium concentrations in younger people even more compelling.

Because the comparison with the 20-year-old Swedish data presented in 1976 by Elinder et al. (9) was the main objective of this study, we essentially used their design with tissue samples from forensic autopsies. However, among people who die suddenly and unexpectedly, one might expect an overrepresentation of life styles that are less common than the general population. On the other hand, choosing forensic autopsies as the source for the samples does increase the ratio of young people and people without chronic diseases, when compared with sampling from clinical autopsies; this probably gives a more representative sample in these respects. It is important to control for the influence of tobacco smoking and some occupational exposures when analyzing cadmium levels in humans in relation to environmental exposures. The questionnaire to the relatives, supplemented by telephone interviews, had a high response rate. We asked relatives if the subject had ever smoked tobacco, when he or she started smoking, and if and when the subject quit. We refrained from collecting information about daily tobacco consumption, because such data supplied by relatives can be anticipated to be insufficient. At least for the older subjects, there was also uncertainty about when the subjects had started smoking. Therefore, we did not estimate any lifetime smoking dose. Forty percent of our study group were smokers, compared with approximately 25% of the Swedish general population (15). Thus, we believe that the cadmium concentrations we report for the total group are higher than the actual concentrations in the Swedish general population.

A reduced occupational cadmium exposure is probably not the reason for reduced cadmium concentrations in human kidney cortex on a population level. During the last two decades, there has been a decrease in tobacco smoking in the Swedish population. In 1995, 23.6% of men and 26.0% of women were daily smokers (16–74 years of age), compared to 1977 when the corresponding figures were 42.4% and 33.4%, respectively (16). This might explain, at least partially, the reduced cadmium burden. The reduced cadmium levels in the smokers could be an indication of reduced consumption of tobacco in this subgroup.

### Table 1. The distribution of sex and smoking with the kidney cortex cadmium concentrations dichotomized at 20 μg/g wet weight (ww)

|                | ≤20 μg/g ww | >20 μg/g ww | p-Value |
|----------------|-------------|-------------|---------|
| Women          | 36          | 14          | 0.01    |
| Men            | 106         | 15          |         |
| Smokers + ex-smokers | 71      | 22          | 0.001   |
| Nonsmokers     | 56          | 2           |         |

### Table 2. Cadmium in human kidney cortex (micrograms per gram wet weight) in Sweden

| Subjects       | Year | 0–9 | 10–19 | 20–29 | 30–39 | 40–49 | 50–59 | 60–69 | 70–79 | 80–89 | 90–99 |
|----------------|------|-----|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| All            | Mean | 0.47| 2.48  | 4.22  | 7.52  | 13.2  | 13.6  | 10.1  | 9.35  | 5.93  | 5.63  |
|                | SD   | 1.46| 1.47  | 1.83  | 2.24  | 1.90  | 1.98  | 2.24  | 1.80  | 2.00  | 1.69  |
|                | n    | 1   | 1     | 4     | 1     | 2     | 2     | 1     | 3     | 1     | 2     |
|                | p-Value | <0.01| <0.01| <0.01| <0.01| <0.01| <0.01| <0.01| <0.01| <0.01| <0.01|
| Women          | Mean | 4.30 | 7.69  | 17.2  | 16.2  | 27.5  | 11.4  | 6.06  |       |       |       |
|                | SD   | 1.97 | 1.93  | 1.81  | 1.94  | 1.91  | 2.82  | 2.03  |       |       |       |
|                | n    | 0   | 0     | 6     | 5     | 6     | 12    | 8     | 0     | 0     | 0     |
|                | p-Value | 0.003| 0.009| 0.1   | 0.3   | 0.9   | 0.9   |       |       |       |       |
| Men            | Mean | 0.47 | 2.48  | 3.95  | 7.47  | 12.0  | 12.5  | 9.58  | 8.36  | 5.76  | 5.63  |
|                | SD   | 1.46 | 1.47  | 1.83  | 2.24  | 1.90  | 1.98  | 2.24  | 1.80  | 2.00  | 1.69  |
|                | n    | 1   | 1     | 4     | 1     | 2     | 2     | 1     | 3     | 1     | 2     |
|                | p-Value | <0.01| <0.01| <0.01| <0.01| <0.01| <0.01| <0.01| <0.01| <0.01| <0.01|
| Nonsmokers     | Mean | 2.48 | 3.87  | 5.52  | 6.82  | 6.92  | 6.17  | 4.92  | 6.31  | 6.25  | 6.25  |
|                | SD   | 1.59 | 1.57  | 1.57  | 1.54  | 1.54  | 1.55  | 1.29  | 2.29  | 1.96  | 1.96  |
|                | n    | 0   | 3     | 9     | 6     | 4     | 8     | 7     | 12    | 9     | 9     |
|                | p-Value | 0.03 | 0.01 | 0.06 | 0.02 | 0.02 | 0.06 | 0.02 |       |       |       |
| Smokers        | Mean | 5.13 | 8.49  | 19.1  | 18.9  | 17.8  | 18.3  | 8.16  |       |       |       |
|                | SD   | 1.44 | 1.94  | 1.55  | 1.54  | 1.61  | 1.61  | 1.41  |       |       |       |
|                | n    | 0   | 0     | 1     | 5     | 6     | 3     | 5     |       |       |       |
|                | p-Value | 0.005| 0.03 | 0.3   | 0.3   | 0.3   | 0.4   | 0     |       |       |       |
| Ex-smokers     | Mean | 4.52 | 6.23  | 7.38  | 10.7  | 10.6  | 11.1  | 5.30  | 3.88  |       |       |
|                | SD   | 1.59 | 1.57  | 1.57  | 1.54  | 1.54  | 1.55  | 1.29  | 2.29  | 1.96  | 1.96  |
|                | n    | 0   | 1     | 1     | 5     | 6     | 3     | 5     |       |       |       |

Geometric means and standard deviations (SD) are shown. Data from 1976 are from Elinder et al. (9). The p-values were from a Student’s t-test on log-transformed data.
Elinder et al.'s (9) classification of smokers included some that we have preferred to call ex-smokers. Therefore, our comparison may in fact have underestimated the reduction of cadmium concentration in smokers because the ex-smokers had lower concentrations. Also, the nonsmokers showed a tendency toward reduced cadmium concentrations, although this not as convincing. The changed behavior of Swedish smokers has reduced the general exposure for environmental tobacco smoke during the last decades; however, passive smoking does not seem to be an important source for cadmium accumulation in the human kidneys and its associated potential health risks.

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