Renal dysfunction from cadmium contamination of irrigation water: dose–response analysis in a Chinese population

S. Cai,1 L. Yue,2 T. Jin,3 & G. Nordberg3

In a cadmium-contaminated area in China and a nearby non-contaminated area, 342 persons were selected for studies of a possible relationship between cadmium dose (i.e. total cadmium intake) and response in terms of renal dysfunction. An increase in urinary excretion of β-2-microglobulin (UB2M), adjusted for age and sex, was used as an indicator of the response. A statistically significant relationship was found between measured cadmium concentrations in whole blood (range; <3.5 to >15μg/l) and UB2M, and there was a statistically significant linear trend. Also, cadmium in urine (<4 to >16μg/g creatinine) and UB2M displayed a statistically significant positive relationship when the total data set was analysed for males and females. The relationship between a dose index (obtained from calculated cumulative absorbed doses over a lifetime) and UB2M was statistically significant. The results of this first study on dose–response relationships in a Chinese population are similar to those observed in other populations.

Introduction

Renal dysfunction is a well-established adverse effect resulting from long-term exposure to cadmium, both occupationally and from the general environment (1, 2). Such an effect from general environmental exposure was first documented in Japanese populations (e.g. 3, 4) and, in the 1980s, in reports from Belgium (5, 6). Several studies on dose–response relationships have been reported from Japan (e.g. 4, 7). Recently, reports have appeared on cadmium-related renal tubular dysfunction in China (8) and dose–response data have been presented from Belgium (9).

Because of the possibility that large population groups in different parts of the world could suffer from cadmium-related renal dysfunction, it is important to define dose–response relationships in order to evaluate existing human exposures in various countries. Such an analysis, employing some of the principles of dose estimation outlined by Kjellström & Nordberg (10, 11) and by Kjellström (12), as applied to data from China collected in 1986 by Cai et al. (8, 13, 14), is described here. In this study, analysis of β-2-microglobulin in urine (UB2M) was used to indicate the presence or absence of renal tubular dysfunction. Calculated cumulative cadmium uptake over a lifetime and measured cadmium concentrations in blood or urine were used as indicators of the absorbed dose in various dose–response analyses.

Materials and methods

Population studied. Farmers, whose age and sex distribution are given in Table 1, were selected from an area in China (Dayu County) where contaminated irrigation water had given rise to long-term cadmium exposure via food and tobacco. Details of the exposure conditions were described by Cai et al. (13), who reported an average cadmium intake in food of 299μg for females and 312μg for males, based on a dietary survey in 1986. Our control group was selected from a nearby non-contaminated area (Table 1). The individuals included in the present study were those who had been selected for measurement of both blood and urine cadmium (BCd and UCd) and urine β-2-microglobulin (UB2M).

Exposure conditions and cadmium uptake. A detailed account of the exposure conditions, including possible alternatives for calculating the cumulative uptake of cadmium from food and smoking, has been presented by Cai et al. (13). Although several estimates have been made for variations in historical cadmium levels in food and tobacco (13), in this article we have assumed that the levels found at the time of the 1986 survey were present also over the
Table 1: Age groups and sex distribution of selected subjects from Dayu County, China

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>No. of subjects in polluted area</th>
<th>No. of subjects in control area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>25–34</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>35–44</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>45–54</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>≥55</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Total</td>
<td>219</td>
<td></td>
</tr>
</tbody>
</table>

period 1961–86. This corresponds to an average daily dietary intake of 312 μg per person irrespective of sex. As reported by Cai in 1995 (13), mining has been carried out in the study area since 1962 and even if the early mining activities probably caused only minor water pollution, it is still reasonable to estimate that cadmium intake was higher than in the control area. In 1960 mining was expanded and ore dressing plants were constructed, which caused considerable water pollution. For the period before 1960 a daily intake of 98 μg was used, which is double the lowest estimate for background exposure in the control area where cadmium intake was estimated to be 49 μg per day and unchanged over time. Details on the retrospective dose estimates are given by Cai et al. (13).

All persons included in the study had resided in the area for the whole of their life.

The cadmium uptake from food was assumed to be directly related to the rice consumption calculated for various age groups by Cai et al. (13), i.e. we assumed the weighing factor for daily intake to be 1 for ages 21–60 years; 0.41 for ages <10 years, 0.89 for ages 11–20 years, and 0.82 for ages ≥60 years.

Calculation of cadmium uptake from smoking was based on the assumption that 3% of the cadmium content in the tobacco smoked was absorbed, which is the usual estimate for cigarette smoking (13, 15). Because BCd did not increase if smokers used more than 0.5 kg of tobacco per month, the influence of tobacco usage on intake was maximized at 0.5 kg per month. Similar observations by Ikeda (16) support this assumption. Also smoking for more than 25 years was assumed to produce no additional intake (cadmium content in tobacco was probably much lower before 1960).

Urine and blood sampling and analysis. A survey of the area, including health examination of the persons selected, was carried out in 1986 by Cai et al. (13). Urine and blood samples were collected from a total of 342 persons in the present study. This is a subset of the large study in which a number of analyses were performed on these and other samples (13). We measured only the cadmium concentrations in blood and urine and UB2M from the 342 subjects whose age and sex distributions are shown in Table 1.

Cadmium in blood was determined by flameless atomic absorption spectrophotometry, while urinary cadmium was analysed with flameless atomic absorption spectrophotometry after extraction by a chelating agent dissolved in an organic solvent. The level of β-2-microglobulin in urine was determined by radiomoanoassay (RIA) using kits which were purchased from the Chinese Academy of Science. Details of the analytical procedures and information on quality control have been given by Cai et al. (13). The pH of all urine samples exceeded 6.

Criteria for β-2-microglobulinuria. β-2-Microglobulin excretion in the urine among males in the control area was related to age, persons <45 years having a lower excretion than those older than this. The mean and standard deviation (SD) of the logarithm of urinary β-2-microglobulin excretion in μg per g creatinine (log UB2M (mean)) was 2.08 (SD = 0.51) for females regardless of age, and 2.00 (SD = 0.43) for males <45 years. As cut-off level for UB2M, the 10% prevalence limits were used as obtained from these data. Because UB2M was dependent on age and sex, different cut-off levels were defined for the control group. A concentration of UB2M of 500 μg/g creatinine was thus used as an indicator of renal dysfunction in females of all ages (corresponding to 10% prevalence in the control group). For males <45 years, the corresponding cut-off level was 355 μg/g creatinine; for males ≥45 years, the distribution is still skew after logarithmic transformation, with an overrepresentation of high values. The median value for urinary β-2-microglobulin excretion in the older age group of males was 241 μg/g creatinine and the 90% cut-off limit (as estimated from computation of the cumulative percentage) was as high as 2500 μg/g creatinine.

Dose index for cadmium uptake. A dose index (lifetime total Cd uptake) was calculated as the cumulative cadmium uptake from food over the whole lifetime, taking into account the age-related weighting factor derived from rice consumption (cf. exposure conditions and cadmium uptake) and adding the cumulative uptake from smoking when applicable. Because of the small difference in measured cadmium intake between males and females, no differentiation of intake was made by sex. The fractional uptake (absorption) of cadmium from food was assumed to be 0.05 (13, 17). The uptake from smoking was assumed to be 3% of the amount of...
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Results

Relationship between various dose indicators. Table 2 gives BCd and UCd values for different dose-index levels. There is a clear statistically significant progression of both BCd and UCd with increasing dose index (Table 2).

Relationship between blood cadmium and response. Using the cut-off levels for β-2-microglobulinuria which are adjusted for age and sex (cf. criteria for UB2M, see above), the relationship between blood cadmium and UB2M, as shown in Table 3, was obtained. There was a clear dose-related relationship in both males and females. A statistical analysis for trend gave a significant result.

Relationship between urinary cadmium and response. Table 4 gives data on the relationship between UCd and response (UB2M). There was a positive trend for UCd in both males and females; however, only for males was it statistically significant (P = 0.0484 for the x2 test and P = 0.0071 for x2 test for trend). When pooled data for males and females are considered, it is seen from Table 4 that there is an increase in UB2M by approximately 9.1% when the groups with urinary cadmium 0–4μg/g creatinine and 4–8μg/g creatinine are compared. There is an even larger difference in UB2M between the lowest and the highest UCd groups. In statistical tests significance was reached in both tests (χ2 test and χ2 test for trend).

Relationship between dose index and response. In Table 5 the relationship between dose-index categories and UB2M is given. Statistically significant differences in response occurred in dose-index categories for nonsmokers, with a clearly significant linear trend according to the χ2 test. This clearly

<table>
<thead>
<tr>
<th>Table 2: Relationship between dose index (lifetime cadmium uptake), BCd and UCd among the 342 study subjects</th>
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<tbody>
<tr>
<td>Dose index (mg)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>0–99</td>
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<tr>
<td></td>
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<td></td>
</tr>
<tr>
<td>100–149</td>
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<td></td>
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<td>150–174</td>
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<tr>
<td></td>
</tr>
<tr>
<td>≥175</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

χ2 test: 274.77 (P < 0.0001)
Linear trend: with 3.5μg/l as upper value; χ2 test = 233.007 (P < 0.0001)

χ2 test: 151.13 (P < 0.0001)
Linear trend: with 4μg/g creatinine as upper value; χ2 test = 105.487 (P < 0.0001)

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Table 3: Prevalence of β-2-microglobulinuria for various levels of blood cadmium concentrations

| BCd level (μg/l) | Males | | | | Females | | | | Total | | |
|------------------|-------|---|---|---|-------|---|---|---|---|---|---|---|
|                  | +     | -  | %  |     | +     | -  | %  |     | +     | -  | %  |     |
| 0–3.49           | 5     | 44 | 10.2 | 7    | 57   | 10.9 | 12   | 101  | 10.6 |
| 3.5–6.99         | 3     | 25 | 10.7 | 6    | 23   | 20.7 | 9    | 48   | 15.8 |
| 7–14.99          | 11    | 35 | 23.9 | 14   | 30   | 31.8 | 25   | 65   | 27.8 |
| >15              | 17    | 29 | 37.0 | 16   | 20   | 44.4 | 33   | 49   | 40.2 |

χ² test = 12.38
(P = 0.0062)
χ² test = 15.45
(P = 0.0015)
χ² test = 26.30
(P < 0.0001)

Linear trend:
χ² test = 11.79
(P = 0.0006)
χ² test = 14.913
(P = 0.0001)
χ² test = 20.556
(P = 0.00001)

* + = above UB2M cut-off level; - = below UB2M cut-off level.
Cut-off levels (UB2M in μg/g creatinine):
- males aged <45 years = >355;
- males aged >45 years = >2500; and
- females, all ages = >500.

Table 4: Prevalence of β-2-microglobulinuria for various levels of urinary cadmium concentrations

| UCd level (μg/g creatinine) | Males | | | | Females | | | | Total | | |
|-----------------------------|-------|---|---|---|-------|---|---|---|---|---|---|---|
|                             | +     | -  | %  |     | +     | -  | %  |     | +     | -  | %  |     |
| 0–3.99                      | 5     | 46 | 9.8  | 8    | 32   | 20.0 | 13   | 78   | 14.3 |
| 4–7.99                      | 7     | 30 | 18.9 | 7    | 32   | 17.9 | 14   | 62   | 18.4 |
| 8–15.99                     | 11    | 30 | 26.8 | 9    | 34   | 20.9 | 20   | 64   | 23.8 |
| >16                         | 13    | 27 | 32.5 | 19   | 32   | 37.3 | 32   | 59   | 35.2 |

χ² test = 7.89
(P = 0.0484)
χ² test = 6.05
(P = 0.109)
χ² test = 12.4
(P = 0.0061)

Linear trend:
χ² test = 7.251
(P = 0.0071)
χ² test = 4.902
(P = 0.0268)
χ² test = 11.877
(P = 0.0006)

* + = above UB2M cut-off level; - = below UB2M cut-off level.
Cut-off levels (UB2M in μg/g creatinine):
- males aged <45 years = >355;
- males aged >45 years = >2500; and
- females, all ages = >500.

Discussion

Several studies have previously reported the occurrence of cadmium-induced renal dysfunction in human populations. Dose–response data are available from studies both of industrially exposed workers (12, 18) and of persons exposed in the general environment (3, 4, 19). Relationships between blood cadmium and UB2M have not been well established partly because of the difficulties in the past of performing reliable analyses of BCd (12) and partly because the latter is related both to recent exposure.
Table 5: Prevalence of \( \beta \)-2-microglobulinuria in different dose-index categories corresponding to lifetime cumulative uptake of cadmium

<table>
<thead>
<tr>
<th>Dose index (mg)</th>
<th>Smokers</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–99</td>
<td>+ 6</td>
<td>- 46</td>
<td>11.5</td>
<td>7</td>
<td>64</td>
<td>9.9</td>
<td>13</td>
</tr>
<tr>
<td>100–149</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>28</td>
<td>12.5</td>
<td>4</td>
</tr>
<tr>
<td>150–174</td>
<td>4</td>
<td>9</td>
<td>30.8</td>
<td>10</td>
<td>34</td>
<td>22.7</td>
<td>14</td>
</tr>
<tr>
<td>( &gt; 175 )</td>
<td>17</td>
<td>60</td>
<td>22.1</td>
<td>28</td>
<td>25</td>
<td>52.8</td>
<td>45</td>
</tr>
</tbody>
</table>

\( \chi^2 \) test = 3.52
\( P = 0.172 \)
\( \chi^2 \) test = 33.79
\( P < 0.0001 \)
\( \chi^2 \) test = 23.15
\( P < 0.0001 \)
\( \chi^2 \) test = 20.116
\( P < 0.0001 \)

* + = above UB2M cut-off level; - = below UB2M cut-off level.
Cut-off levels (UB2M in mg/l creatinine):
- males aged <45 years = 9-355;
- males aged \( > 45 \) years = 2500; and
- females, all ages = 9-500.

and to the body burden of cadmium (17). The relationship between blood cadmium and UB2M can therefore be expected to differ in different populations depending on the length and intensity of exposure to cadmium for the population studied. In a population like the one studied in the present investigation, where the whole group in the polluted area was exposed to similar concentrations via the diet for approximately 25 years, the blood cadmium level can be expected to reflect the body burden of cadmium to a large extent. The dose–response relationships found in the present study were statistically highly significant, but can be expected to be valid only for populations with exposure conditions similar to those prevailing in the present population. A somewhat different relationship can be expected in population groups with other exposure conditions.

Urinary cadmium is considered to be a more constant indicator of body burden and renal accumulation (17) and has been used previously by Buchet et al. (9) and Lauwerys et al. (20) in dose–response analyses. In the present study there was an increase in UB2M that had a similar relation to urinary cadmium as the studies by Buchet et al., although a detailed comparison is not possible because the units used to express urinary cadmium were different in the two studies. Various aspects related to the comparability of previously published studies have been discussed by Andersen et al. (21).

Dose–response relationships for estimated daily and/or cumulative intakes have been reported previously. For example, Nogawa et al. concluded that cumulative exposures by the oral route amounting to \( \geq 2000 \) mg increased the prevalence of renal dysfunction in a Japanese population (7). Since the lowest point in the dose–response curve shown in Fig. 1 represents the control group, the observations in the present study indicate that an increased prevalence of low relative molecular mass proteinuria does occur at a dose index corresponding to absorbed doses of \( \geq 150 \) mg. Also, there is a tendency towards an increase in the dose-index group corresponding to intakes of 100–150 mg, but because of the limited
number of observations in this dose category in the present study, it is difficult to evaluate this tendency. These observations are similar to those reported by Nogawa et al. (7), since an oral intake of 2000mg corresponds to an absorbed dose of 100mg at a fractional gastrointestinal (g.i.) absorption of 5%. The present observations are also in general agreement with the dose–response relationships calculated from knowledge about critical concentrations of cadmium in the human renal cortex (12). The increase in response (UB2M) above the background (10%) observed in the present study is more pronounced than predicted under the assumption of 4.8% g.i. absorption but less than that predicted for the 20% g.i. absorption in the model calculations reported by Nordberg & Strangert (22). In making comparisons of the present data with other reports on dose–response relationships for UB2M in cadmium exposure, it should be noted that we had to choose high values as cut-off levels in the present study because there was a noncadmium-related effect that caused a comparatively high background excretion of UB2M in this area of China, particularly for males aged >45 years. The nature of this effect is not understood at present, but it is possibly related to the occurrence of hepatic diseases and, because of the similarity in all other respects (apart from cadmium exposure) between the control and exposed group, it is reasonable to assume that it occurred to a similar extent in both groups. There is no indication of a correlation between this factor and cadmium exposure and it would therefore not be expected to seriously confound the dose–response relationship between cumulative cadmium exposure and UB2M. However, for statistical reasons, the high cut-off levels make it difficult to detect a low-level response and to analyse its possible relationship to dose.

It may be appropriate to consider whether the findings in the present study are compatible with the evaluations of a provisional tolerable weekly intake (PTWI) of cadmium of 400–500μg proposed by the Joint FAO/WHO Expert Committee on Food Additives (23). A cadmium intake of 500μg per week corresponds to 26mg per year. The uptake of cadmium from food is usually considered to be 5% (g.i. absorption) of the cadmium intake, i.e. 1.3mg per year. In a person aged 70 years the cumulative uptake will amount to approximately 91mg, which is just below the lowest level that gave rise to an increased prevalence of UB2M in the present studies. Although the present observations are not in conflict with the recommended PTWI, there appears to be only a small safety margin between the latter and the intakes that give rise to renal tubular dysfunction.

Acknowledgement
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Résumé
Dysfonctionnement rénal dû à une contamination de l'eau d'irrigation par le cadmium: analyse de la relation dose-réponse dans une population chinoise

Dans le cadre d'études portant sur une éventuelle relation entre l'exposition au cadmium (dose = apport total) et la réponse en termes de dysfonctionnement rénal, 342 personnes ont été sélectionnées dans une zone contaminée par le cadmium en Chine et dans une zone voisine non contaminée. On a utilisé comme indicateur de la réponse une augmentation de l'excrétion urinaire de bêta-2 microglobuline (UB2M), ajustée à l'âge et le sexe. Une relation statistiquement significative a été observée entre la concentration en cadmium dans le sang total (intervalle: <3,5–15µg/l) et le taux d'UB2M, avec une tendance linéaire statistiquement significative. Il existait de même une relation positive statistiquement significative entre le taux urinaire de cadmium (<4–16µg par g de créatinine) et l'UB2M lorsqu'on analysait la série totale de données pour les deux sexes. La relation entre un indice de dose, obtenu en calculant la dose absorbée sur toute la vie, et l'UB2M était statistiquement significative. Les résultats de ce premier rapport portant sur les relations dose-réponse dans une population chinoise sont similaires à ceux trouvés dans d'autres populations.

References
4. Shiroshi K et al. Urine analysis for detection of cadmium-induced renal changes, with special refer-
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