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The Threshold Cadmium Level That Causes a Substantial Increase in β_2-Microglobulin in Urine of General Populations

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IKEDA, M., EZAKI, T., MORIGUCHI, J., SAKURAI, H. *The Threshold Cadmium Level That Causes a Substantial Increase in β_2-Microglobulin in Urine of General Populations.* Tohoku J. Exp. Med., 2005, **205**(3), 247-261 —— Cadmium (Cd) is a toxic element ubiquitous in the environment, and general populations have been exposed to this element primarily via foods. The critical level of non-occupational Cd exposure to cause any health effects among general populations is of public health as well as toxicological concern. The objectives of the present study were to examine the quantitative relationship between cadmium (Cd-U) and β_2-microglobulin in urine (β_2-MG-U) as a marker of exposure to Cd and as a marker of renal tubular dysfunction, respectively, and to identify a threshold Cd-U, if present, in causing a substantial increase in β_2-MG-U. Thus, paired data on geometric mean (GM) Cd-U_{cr} (i.e., Cd-U as corrected for creatinine [cr] concentration) and GM β_2-MG-U_{cr} (β_2-MG-U as corrected for cr) of residents in polluted as well as nonpolluted areas in Japan were retrieved in international and domestic sources. In practice, 245 cases of the data pairs were obtained in 51 articles published since 1975. Statistical analysis on ordinary scales disclosed that β_2-MG-U_{cr} increased markedly when Cd-U_{cr} exceeded a certain level. The relation between the two parameters after double-logarithmic conversion was in a shape of the letter J or a stick for ice hockey. Analysis for Cd-U_{cr} at the flexion point gave Cd-U_{cr} of 4 (on double logarithmic scales) or 7 μg / g cr (on ordinary scales). Cd-U_{cr} levels that correspond to a β_2-MG-U_{cr} of 1,000 μg / g cr were estimated to be 8-9 μg / g cr, by ordinary and logarithmic assumption as well as by the 3rd degree regression analysis. Thus, it is concluded that there is a threshold Cd-U_{cr} level that leads to a substantial increase in β_2-MG-U_{cr}, and that the threshold level is greater than 4 μg / g cr.

——— cadmium; general population; Japan; β_2-microglobulin; urine

It is well known that cadmium (Cd) is a nephrotoxic metal and that exposure to Cd primarily via foods may occur among the general population because this element is ubiquitous in the environment including food materials (International Programme on Chemical Safety

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1992a, b). It is further known that long-term environmental exposure to Cd even at low doses may result in dysfunction of renal tubules, and that Cd and β_2-microglobulin (β_2-MG) levels in urine (Cd-U and β_2-MG-U) are markers of exposure to Cd and resulting health effects (tubular dysfunction), respectively (International Programme on Chemical Safety 1992a, b). Thus, it is of public health importance to know whether or not a threshold Cd-U exists in causing a substantial increase in β_2-MG-U, especially for the general population in Japan where dietary Cd intake has been higher than those in neighboring countries (Ikeda et al. 2000a).

In order to examine the quantitative relation between Cd and β_2-MG in urine, this study group had searched for publications on the two markers, and succeeded to identify 12 articles (Saito et al. 1977; Nogawa et al. 1979; Aoshima 1987; Ishizaki et al. 1989; Iwata 1991; Aoshima et al. 1995a; Ikeda et al. 1995, 2000b; Yamanaka et al. 1998; Oo et al. 2000; Arisawa et al. 2001; Ezaki et al. 2003) by computerized retrieval systems. It was found that the increase in β_2-MG-U was not linearly related to Cd-U and that the increase was markedly accelerated when Cd-U exceeded a certain level, so that the over-all relation was in a shape of the letter "J" or an ice hockey stick (Ikeda et al. 2003a). In a succeeding period of further literature retrieval, it was realized that substantial amounts of data (namely, the pairs of Cd-U and β_2-MG-U) were available in domestic media such as the proceedings of the annual meetings of the Cadmium Research Group (organized by Japan Public Health Association). Compilation of such data sets was more than three times of what were published in international journals.

Thus, analyses were conducted with this newly-built larger database to reconfirm the previous preliminary observation (Ikeda et al. 2003a) that β_2-MG-U increases at a much greater rate when Cd-U is high as compared with the rate at low Cd-U. Further efforts were made to detect the point of flexion in the relation between Cd-U_{cr} and β_2-MG-U_{cr}. The results are described in the present report.

Materials and Methods

Ethical consideration

The protocol of the present analysis was approved by the Ethics Committee of Kyoto Industrial Health Association.

Literature survey

In addition to search for literature since 1975 by conventional computerized retrieval systems, issues of *Kankyo Hoken Report* published since 1975 were sorted manually for paired data on Cd-U and β_2-MG-U of populations in polluted or non-polluted areas in Japan. In addition, the compilation was supplemented by other data available, e.g., in the proceedings of the annual meetings of Japanese Society for Hygiene and Japanese Society of Public Health. Because of the characteristics of these materials such as meeting proceedings (for *Kankyo Hoken Report*, see the Discussion section), the same data appeared both in the proceedings and in a full paper in some cases; priority was given to the full paper in citing as a data source. The sorting thus gave 51 articles with 345 pairs of Cd-U and β_2-MG-U as summarized in Table 1 (Kono et al. 1976, 1980; Uruno et al. 1976; Ogata et al. 1976; Saito et al. 1977, 1997; Honda et al. 1978; Nogawa et al. 1979, 1980, 2002; Shiroishi et al. 1980; Takegawa et al. 1980; Shitomi et al. 1981; Nakano et al. 1985; Tohyama et al. 1986; Aoshima 1987, 2004; Kido et al. 1987, 1988, 1997, 2004; Saito 1988; Ishizaki et al. 1989; Aoshima et al. 1995a, 1995b, 2000a, 2001, 2002; Nishijo et al. 1990, 1991; Nishijo 1999; Iwata et al. 1991; Kasuya et al. 1992; Kodama et al. 1993; Tsuritani et al. 1994; Ikeda et al. 1995, 2000b; Kido 1995, 2000; Fan et al. 1998; Yamanaka et al. 1998; Yamada 1999; Oo et al. 2000; Suwazono et al. 2000; Arisawa et al. 2001; Cai et al. 2001; Ezaki et al. 2003; Kikuchi et al. 2003; Nakadaira and Nishi 2003; Horiguchi et al. 2004; Sugita et al. 2004). It should be noted that many studies reported on both polluted and non-polluted areas (as controls), with men and women separately or in combination. Thus, the 'Total' in Table 1 does not necessarily meet with the simple summation of the numbers on the line or the column.

Treatments for creatinine-corrected values and geometric means

In a majority of articles, Cd-U and β_2-MG-U values were presented after correction for creatinine (CR) concentration (i.e., Cd-U_{cr} and β_2-MG-U_{cr}), and in terms of geometric mean (GM) and geometric standard deviation

(GSD) for a group of individuals. Three papers (Uruno et al. 1976; Kono et al. 1980; Takegawa et al. 1980) however gave uncorrected values only (the values were thus assumed to be as observed), and the values were taken as if they had been corrected for creatinine. When only arithmetic means (AM) and arithmetic standard deviations (ASD) were available, the corresponding GM and GSD values were estimated by use of the moment method (Sugita and Tsuchiya 1995). Medians were given in cases of Tohyama et al. (1986) and Arisawa et al. (2001), and the medians were taken as if they had been GM values. It should be noted that the number of individuals represented by a pair of GM Cd-U_{cr} and β_2-MG-U_{cr} were various depending on the articles.

Statistical analysis

A pair of GM Cd-U_{cr} and GM β_2-MG-U_{cr} for a group of individuals will be called "a case" in the present analyses. PC software STATVIEW Version 5 was employed for statistical analyses including linear and cubic (the 3rd degree) regression as well as Wilcoxon signed rank test. Both Cd-U_{cr} and β_2-MG_{cr} distribute log-normally (e.g., Ikeda et al. 1995; Sugita et al. 2004). Accordingly, logarithmic distributions on double-logarithmic scales were considered in regression analyses, in addition to normal distributions on ordinary scales.

Results

Distribution of GM Cd-U_{cr} and β_2-MG-U_{cr} in polluted and non-polluted areas

A whole data were classified into cases from polluted and nonpolluted areas following the classification by the original author(s) of each article, and also by the gender of the subjects (men and women either separately or in combination); in practice, 6 articles gave the results for a combination of two genders whereas others gave the results for men and women separately (Table 1). The GM values for Cd-U_{cr} of the cases in nonpolluted areas distributed in a wide range of up to 7.8 μg / g cr (Table 2). The GM Cd-U_{cr} reported for cases in polluted areas also distributed widely down to the level of 0.8 μg / g cr, indicating that there is a substantial overlapping in the distribution of Cd-U_{cr} between the polluted and nonpolluted areas (Table 2 and Fig. 1).

In an area that was selected as a control to a known polluted area (Ogata et al. 1976), the GM β_2-MG-U_{cr} for residents was as high as 2,000 μg / g cr (GM Cd-U_{cr} being 3.4 μg / g cr) suggesting that the residents in the control area were also affected by Cd exposure even though less intensively than those in the polluted area. Accordingly, the cases in the control area were classified in the present analyses as those in a polluted area, although separately from those with more intensive Cd exposure. Otherwise, the highest GM β_2-MG-U_{cr} for those in the non-polluted areas was 386 μg / g cr (Table 2).

In contrast, the highest GM Cd-U_{cr} and GM β_2-MG-U_{cr} for those in polluted areas (who were in practice Itai-itai disease patients or patients suspected of the disease) were 31.6 μg / g cr and 200 mg (or 200,000 μg) / g cr, respectively (Nogawa et al. 1979). Thus, the GM β_2-MG-U_{cr}

Table 1. *Number of reports and number of pairs of Cd-U_{cr} and β_2-MG-U_{cr} available in literature*

Gender	Number of reports (number of cases[a] of Cd-U and β_2-MG)[b] in			
	Polluted areas	Non-polluted areas	Total[c]	I-I patients and Suspects[d]
Men	19 (74)	13 (49)	23 (123)	1 (1)
Women	35 (118)	20 (75)	43 (193)	8 (8)
Mixed	5 (25)	2 (4)	6 (29)	1 (1)
Total[c]	42 (217)	23 (128)	51 (345)	9 (10)

[a] Each case has a pair of GM values for Cd-U_{cr} and β_2-GM-U_{cr} of a group of subjects.
[b] Number of reports (number of cases in parenthesis).
[c] Because some reports cover both polluted and non-polluted areas or both men and women, the total numbers for reports do not meet with simple summation of the values on the line or the column.
[d] Itai-itai disease patients and the patients suspected of the disease.

TABLE 2. *Minimum and maximum values for Cd-U_{cr} and β_2-MG-U_{cr} availble in literature*

Item	Cases in			
	Polluted areas	Non-polluted areas	Total[c]	I-I and Suspects[d]
No. of subjects per case				
Minimum[a]	1	5	1	1
Maximum[a]	696	1,323	1,323	64
Age (years)				
Mean[b]	28-83	21-77	21-78	64-83
Minimum[a]	13	13	13	40
Maximum[a]	92	99	99	75
Cd-U_{cr} (μg/g cr)				
Minimum[a]	0.8	0.2	0.2	6.9 (9.4[e])
Maximum[a]	31.6	7.8	31.6	29.8
β_2-MG-U_{cr} (μg/g cr)				
Minimum[a]	26	32	26	4,008 (50,778[e])
Maximum[a]	200,000	386	200,000	200,000

[a] The minimum and the maximum among the individuals.
[b] The range of arithmetic (age) or geometric means (Cd-Ucr and β_2-MG-U_{cr}) for cases.
[c] The sum of cases in polluted and nonpolluted areas.
[d] Itai-itai disease patients and subjects suspected of the disease all in polluted areas.
[e] Excluding Shiroishi et al. (1980), who studied un-hospitalized Itai-itai disease-suspected subjects.

value for some exposed subjects was more than 500 times higher than the levels for residents in nonpolluted areas (Table 2).

Knowing the overlapping in Cd-U_{cr} between the polluted and nonpolluted areas, the cases of paired data on GM Cd-U_{cr} and GMβ_2-MG-U_{cr} from both areas are plotted together in Fig. 2. The scatter diagram on the ordinary scales showed that dots tended to disperse in a wide range when Cd-U_{cr} was high, e.g., in excess of 5 μg / g cr. Further plotting on double-logarithmic scales shows that the over-all distribution is not linear but in a shape of the letter "J" or an ice hockey stick. Analysis with men and women separately showed that the distribution pattern after ordinary and double-logarithmic plotting was essentially the same between the two genders (figures not shown), and the results of analysis with cases of mixed gender was also similar although the number of cases was limited (Table 1). Thus, further analyses were conducted with a combination of men, women and the mixed gender.

Analyses for possible point of flexion in the "J" shape

In order to estimate the point of flexion in Fig. 2, all cases (i.e., the combination of cases in polluted and nonpolluted areas) were divided at the various Cd-U_{cr} levels (from 2 to 10 μg / g cr as the cut-off value), and the correlation with β_2-MG-U_{cr} (in terms of the regression line) for those below the cut-off value was compared with the regression line for the relation above the cut-off value, both on ordinary scales as well as on double-logarithmic scales (Table 3). The analysis on the ordinary scales (the top half in Table 3) showed that the regression lines for the cases below the cut-off value from 2 to 5 μg / g cr did not vary very much, although the correlation coefficients were generally small and insignificant ($p > 0.10$) in some cases. It should be noted that cases with greater β_2-MG-U_{cr} (i.e., log β_2-MG-$U_{cr} > 3$) were observed when log Cd-Ucr exceeded 0.6 (or Cd-Ucr > 4 μg / g cr) (Fig. 2B). In a sharp contrast, the regression lines for the cases above the cut-off values became steeper with smaller (i.e.,

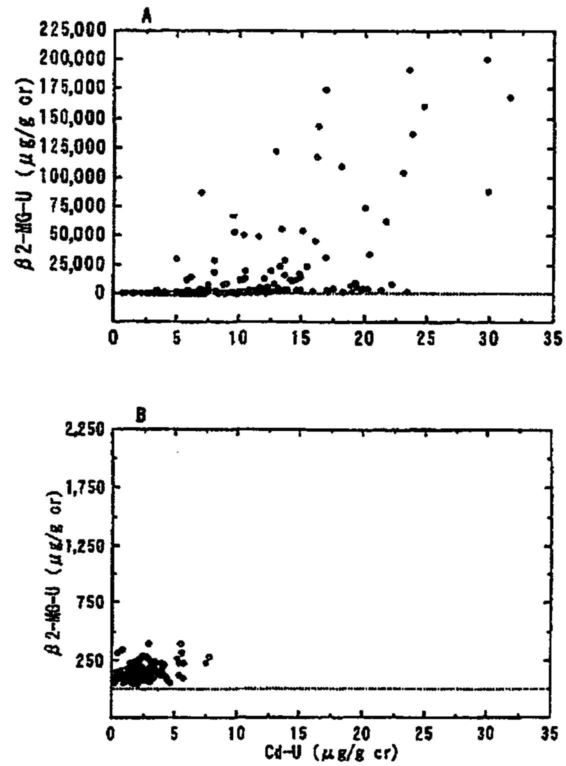

Fig. 1. Relation of β_2-MG-U_{cr} with Cd-U_{cr}. A: Relation in polluted areas (n = 217). B: Relation in nonpolluted areas (n = 128).
Note that the vertical axis in Fig. 1B is magnified by 100 times for better illustration.

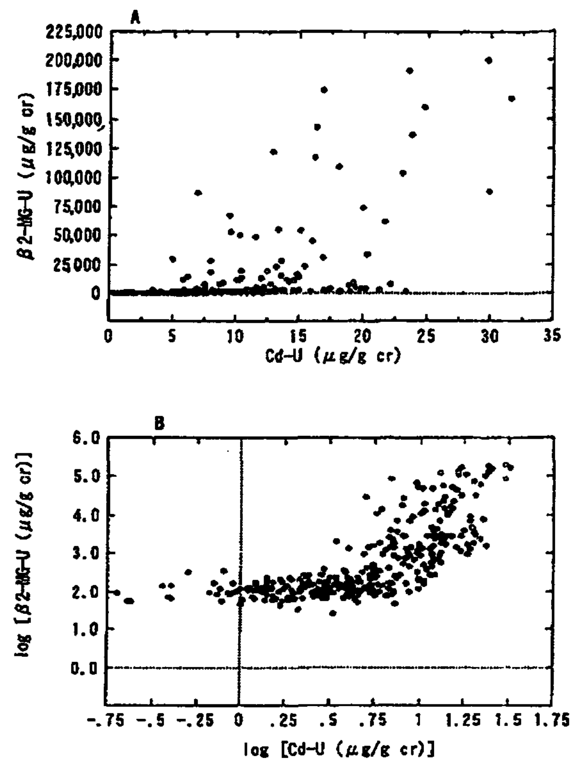

Fig. 2. Relation of β_2-MG-U_{cr} with Cd- U_{cr}, in polluted and non-polluted areas in combination (n = 345). A: Plotting on ordinary scales. B: Plotting on double-logarithmic scales.

greater in the absolute value) intercepts on the vertical axis as a function of an increase in the cut-off value (i.e., from 2 to 10 μg Cd / g cr). For example, the slope for the group of cases with Cd-U > 10 μg / g cr was almost twice as steep as that for those with Cd-U > 2 μg / g cr, and the absolute value of the intercept on the vertical axis was more than 4 times greater. The trends were reproduced when the analyses were made on double-logarithmic scales (the bottom half in Table 3).

Thus, when the point of flexion was estimated as a point of intersection between the two regression lines on ordinary scales (left half in Table 4) (i.e., the first line with lower Cd-U_{cr} of ≦ 2 or ≦ 5 μg / g cr, and the second one with higher Cd-U_{cr} of > 2 to > 10 μg / g cr), the Cd-U_{cr} value at the intersection point did not vary as a function of the cut-off value for the first line (i.e., 5.1 μg Cd / g cr both for the ≦ 2 μg Cd / g cr line [the left-most column] and the ≦ 5 μg Cd / g cr line [the second left-most]), but increased substantially (e.g., from 5.1 to 10.8 μg Cd / g cr in case of the left-most column) as a function of the increase in cut-off values for the second line from 2 to 10 μg Cd / g cr (from the top line to the bottom). Such increase suggest that the relation between Cd-U_{cr} and β_2-MG-U_{cr} at higher Cd-U_{cr} is not linear but slightly concave upward.

The trends were essentially reproduced when similar analyses were conducted on double-logarithmic scales (right half in Table 4). The change in Cd-U_{cr} at the point of intersection was less remarkable and was in a relatively narrow range of 3.1 to 5.1 μg Cd / g cr. Cd-U_{cr} of 2 μg / g cr (or

TABLE 3. *Regression line parameters for cases in various Cd-U_{cr} ranges*

Cd-U_{cr} range	Parameters				
	n	α[a]	β[a]	r	p
On ordinary scales					
Cd-U_{cr} ≦ 2 μg / g cr	67	112	4	0.032	>0.10
Cd-U_{cr} ≦ 3 μg / g cr	108	98	17	0.197	>0.05
Cd-U_{cr} ≦ 4 μg / g cr	145	81	30	0.184	>0.05
Cd-U_{cr} ≦ 5 μg / g cr	174	85	27	0.182	>0.05
Cd-U_{cr} > 2 μg / g cr	278	−16,155	3,200	0.590	<0.01
Cd-U_{cr} > 3 μg / g cr	237	−20,362	3,499	0.592	<0.01
Cd-U_{cr} > 4 μg / g cr	200	−25,373	3,835	0.589	<0.01
Cd-U_{cr} > 5 μg / g cr	171	−30,897	4,189	0.585	<0.01
Cd-U_{cr} > 6 μg / g cr	145	−38,222	4,638	0.582	<0.01
Cd-U_{cr} > 7 μg / g cr	130	−45,594	5,067	0.600	<0.01
Cd-U_{cr} > 8 μg / g cr	116	−51,796	5,419	0.595	<0.01
Cd-U_{cr} > 9 μg / g cr	102	−58,186	5,769	0.587	<0.01
Cd-U_{cr} > 10 μg / g cr	91	−67,125	6,237	0.602	<0.01
On double-logarithmic scales					
Cd-U_{cr} ≦ 2 μg / g cr	67	2.02	0.10	0.114	>0.10
Cd-U_{cr} ≦ 3 μg / g cr	108	2.02	0.18	0.217	<0.05
Cd-U_{cr} ≦ 4 μg / g cr	145	2.02	0.22	0.255	<0.05
Cd-U_{cr} ≦ 5 μg / g cr	174	2.02	0.20	0.226	<0.05
Cd-U_{cr} > 2 μg / g cr	278	0.17	3.10	0.709	<0.01
Cd-U_{cr} > 3 μg / g cr	237	0.85	2.45	0.758	<0.01
Cd-U_{cr} > 4 μg / g cr	200	0.45	2.84	0.746	<0.01
Cd-U_{cr} > 5 μg / g cr	171	0.24	3.03	0.627	<0.01
Cd-U_{cr} > 6 μg / g cr	145	0.18	3.09	0.573	<0.01
Cd-U_{cr} > 7 μg / g cr	130	0.02	3.23	0.567	<0.01
Cd-U_{cr} > 8 μg / g cr	116	−0.04	3.27	0.537	<0.01
Cd-U_{cr} > 9 μg / g cr	102	−0.19	3.40	0.511	<0.01
Cd-U_{cr} > 10 μg / g cr	91	−0.29	3.48	0.516	<0.01

[a] α and β are parameters of a regression equation of $Y = \alpha + \beta X$, where X is Cd-U_{cr} (or log Cd-U_{cr}) and Y is β_2-MG-U_{cr} (or log β_2-MG-U_{cr}) on ordinary (or double-logarithmic scales), respectively. N is the number of cases.

log Cd-U_{cr} of 0.3) is well within the levels for cases without substantial increase in β_2-MG-U_{cr} (Fig. 2A) and that log Cd-U_{cr} of 0.6 (or 4 μg Cd / g cr) appeared to be the upper limit (Fig. 2B). The Cd-U_{cr} at the point of intersection for the first regression line with > 4 μg Cd / g cr and the second line with ≦ 2 or ≦ 5 μg Cd / g cr was 6.7 μg / g cr on the ordinary scales and it was 3.7 μg Cd / g cr on the double-logarithmic scales. Thus, 7 and 4 μg Cd / g after rounding of figures appear to be Cd-U_{cr} for the point of flexion by analyses on ordinary and double-logarithmic scales, respectively. The corresponding β_2-MG-U_{cr} was about 100-300 μg / g cr by the analyses on the two scales. Such β_2-MG-U_{cr} value appeared to be somewhat conservative when compared with the

TABLE 4. *Cd-U_{cr} and β_2-MG-U_{cr} at the cross of the two regression lines*

Regression line with higher Cd-U_{cr} (μg / g cr)	Regression line with lower Cd-U_{cr}: On ordinary scales: Cd-$U_{cr} \leqq 2\,\mu g$ / g cr: Cd-U_{cr} at POI[b] (μg / g cr)	β_2-MG-U_{cr} at POI[b] (μg / g cr)	Cd-$U_{cr} \leqq 5\,\mu g$ / g cr: Cd-U_{cr} at POI[b] (μg / g cr)	β_2-MG-U_{cr} at POI[b] (μg / g cr)	Critical Cd-U_{cr}[a]	On double-logarithmic scales: Cd-$U_{cr} \leqq 2\,\mu g$ / g cr: Cd-U_{cr} at POI[b] (μg / g cr)	β_2-MG-U_{cr} at POI[b] (μg / g cr)	Cd-$U_{cr} \leqq 5\,\mu g$ / g cr: Cd-U_{cr} at POI[b] (μg / g cr)	β_2-MG-U_{cr} at POI[b] (μg / g cr)	Critical Cd-U_{cr}[a]
> 2	5.1	133	5.1	224	6.1	4.1	119	4.1	119	7.6
> 3	5.9	136	5.9	245	6.9	3.1	116	3.1	116	7.9
> 4	6.7	139	6.7	267	7.6	3.7	118	3.7	118	8.1
> 5	7.4	142	7.4	287	8.5	4.0	119	4.2	140	8.2
> 6	8.3	146	8.3	311	9.2	4.1	119	4.3	141	8.4
> 7	9.0	149	9.1	331	9.7	4.3	120	4.6	142	8.5
> 8	9.6	151	9.6	347	10.3	4.4	120	4.7	143	8.7
> 9	10.1	153	10.1	361	10.9	4.7	120	4.9	144	8.8
> 10	10.8	156	10.8	379	11.5	4.8	121	5.1	145	9.3
					8.9[c]					

[a] Cd-U_{cr} at β_2-MG-U_{cr} = 1,000 μg / g cr.
[b] POI, point of intersection.
[c] Calculated by the equation of the 3rd degree, $Y = 1.956 + 0.006X + 0.575X^2 + 0.611X^3$ ($r = 0.804$), where Y is log (β_2-MG_{cr} [μg / g cr]), and X is log (Cd-U_{cr} [μg/g cr]).

observation in non-polluted areas (i.e., $\leqq$ 386 μg / g cr; Table 2).

Cd-U_{cr} levels corresponding to β_2-MG-U_{cr} of 1,000 μg / g cr

From the regression equations summarized in Table 2, Cd-U_{cr} was estimated for the levels at which β_2-MG-U_{cr} was equal to 1,000 μg / g cr. This level of 1,000 μg β_2-MG / g cr was taken as the critical β_2-MG-U_{cr} concentration for tubular dysfunction (for rationale, see the Discussion section) due to Cd exposure. As summarized in Table 4 (shown as "critical Cd-U_{cr}" in the table), the analyses on ordinary scales gave Cd-U_{cr} of 7.6 μg / g cr, and that on double-logarithmic scales resulted in 8.1 μg / g cr.

Separately, analyses with total cases (i.e., cases in polluted and non-polluted areas in combination) and with assumption of higher order regression (up to the 6th order) were conducted for correlation coefficients between Cd-U_{cr} and β_2-MG-U_{cr}. The analyses on ordinary scales gave the regression coefficients of 0.34, 0.47, 0.48, 0.48, 0.49 and 0.49 for the 1st, 2nd, 3rd, 4th, 5th and 6th order equation, while it was 0.51, 0.64, 0.65, 0.65, 0.65 and 0.65 in the order on double-logarithmic scales. The results suggest that the coefficient was greater ($p < 0.05$ by Wilcoxon signed rank test) on double-logarithmic scales than on ordinary scales and that the improvement in the coefficient was small beyond the 3rd degree equation. Thus, the 3rd degree was selected for regression analysis. The calculation gave an equation of

$$Y = 1.956 + 0.006X + 0.575X^2 + 0.611X^3$$

($r = 0.647$), where X is log Cd-U_{cr} and Y is log β_2-MG-U_{cr} (both in μg / g cr). X for Y = 1,000 μg / g cr was calculated as 8.9 μg / g cr (at the bottom in Table 4).

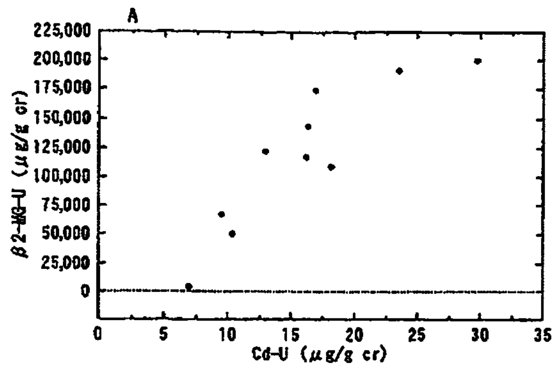

Fig. 3. Relation of β_2-MG-U_{cr} with Cd- U_{cr} in Itai-itai disease patients and suspects (n = 10).

Cd-U_{cr} and β_2-MG-U_{cr} levels in Itai-itai disease patients and the suspects

Through the present literature survey, the data on Cd-U_{cr} and β_2-MG-U_{cr} levels in urine samples from Itai-itai disease patients and the suspects were available in 9 articles (Honda et al. 1978; Nogawa et al. 1979, 1980; Aoshima 1987; Shiroishi et al. 1980; Takegawa et al. 1980; Nishijo et al. 1991; Kasuya et al. 1992; Aoshima et al. 2000a); the mean ages of subjects in each article were all 65 years or older. The cases are plotted in Fig. 3, in which the two genders are shown as separate dots (for man, one case only). Except for the case reported by Shiroishi et al. (1980) (with relatively low Cd-U_{cr} [6.9 μg / g cr as GM] and relatively low β_2-MG_{cr} [4,008 μg / g cr as GM]) which were on non-hospitalized subjects who had been followed up with suspect of Itai-itai disease, Cd-U_{cr} levels were about 10 μg / g cr or higher and β_2-MG-U_{cr} levels were ≧ 50,000 μg (50 mg) / g cr. Whereas β_2-MG-U_{cr} increased as a function of increasing Cd-U_{cr}, there was a tendency that β_2-MG-U_{cr} leveled off when Cd-U_{cr} was in excess of e.g. 20 μg / g cr.

Discussion

A single journal of Kankyo Hoken Report accounted for some 37% of the articles cited as data sources, or 28% of the cases analyzed. Thus introduction might be necessary because this journal is not indexed in conventional publication retrieval systems. The regular issues of this series of publication (usually once a year) contain the proceedings (or expanded abstracts of presentations) for annual meetings organized by the Japan Public Health Association under sponsorship of Ministry of the Environment (formerly the Environment Agency) of the Government of Japan. The materials to be published in the proceedings are prepared after presentation and discussion in the annual meeting, and data were thought valid for statistical evaluation. The articles are written basically in Japanese, but recent articles are usually accompanied by English abstracts.

The critical β_2-MG-U_{cr} concentration as a marker of Cd exposure-associated tubular dysfunction certainly deserves discussion. Kido et al. (1988) and Iwata et al. (1993) reported that the dysfunction of renal tubules after Cd exposure may become irreversible when β_2-MG-U_{cr} levels exceed 1,000 μg / g cr. In a long run, an increase in mortality and reduction in life span was also observed among the residents with ≧ 1,000 μg β_2-MG / g cr in urine (Iwata et al. 1991; Nishijo et al. 1994; Arisawa et al. 2001). Aoshima et al. (1990, 2000b) proposed the same value of 1,000 μg β_2-MG / g cr as a screening level for renal dysfunction among Cd-exposed populations. Similarly, Roels et al. (1997) summarized their experiences in Cd-exposed factory workers that β_2-MG-uria may not be alleviated when the level exceeds 1,500 μg / g cr. Taking such information together, the level of 1,000 μg β_2-MG / g cr was taken in the present analysis as the critical concentration in evaluating tubular dysfunction due to Cd exposure.

The reason for the difference in the estimated point of flexion between the present analysis (Cd-U_{cr} of 4 to 7 μg / g cr) and the previous results (about 10-11 μg / g cr as a combination of results for two genders; Ikeda et al. 2003a), despite the fact that the database for the previous analysis was in fact a substantial part (92 cases in 12 articles out of 345 cases in 52 articles, or about one fourth) of the present database, apparently needs discussion. Whereas the database for the previous analysis was limited to the publications in international journals, that for the present analysis included meeting proceedings as described above, so that four times more cases of Cd-U_{cr} and β_2-MG-U_{cr} pairs were made available (Table 1).

In order to examine possible sources of the difference, comparison was made between the regression lines in terms of regression parameters. The regression line for cases in polluted areas in the present analysis was Y = −20,060 + 3,465X (r = 0.581, n = 217), or log Y = 0.862 + 2.347 log X (r = 0.716, n = 217), where Y a nd X are β_2-MG-U_{cr} and Cd-U_{cr} (both in μg / g cr), respectively. The counterpart regression lines in the previous analysis for polluted areas (Ikeda et al. 2003a) were Y = −58,187 + 5,949X (r = 0.738, n = 44) or log Y = −0.667 + 3.755 log X (r = 0.826, n = 44). For nonpolluted areas, the present analyses gave Y = 100 + 17.13X (r = 0.348, n = 128) or log Y = 2.031 + 0.222 log X (r = 0.311, n = 128), whereas the previous analysis gave Y = 138 + 11.42X (r = 0.232, n = 53) or log Y = 2.161 + 0.087 log X (r = 0.126, n = 53). Comparison of the slopes, the intercepts and the correlation coefficients (Ichihara 1995) of the lines for polluted areas showed that both slopes and intercepts were significantly different ($p < 0.01$) irrespective of logarithmic conversion, whereas the correlation coefficients were not different ($p \geqq 0.10$). The two lines for nonpolluted areas however did not show significant ($p \geqq 0.10$) difference except that the intercepts after logarithmic conversion were different ($p < 0.05$). Thus, the difference came from the lines for polluted areas and not from that for nonpolluted areas.

Further comparison of two data sets of cases in polluted areas (Fig. 4), one from the present analysis (small circles) and the other from previous study (large squares; Ikeda et al. 2003a), disclosed the presence of additional cases in four areas in the diagram for the present analysis. They could be classified into four groups in terms of areas of distribution (Table 5). The group in Area A in the upper-left corner in the figure included many cases of Itai-itai disease patients and suspects who were all at advanced ages (AM age of cases was in a range of 65 to 82 years with the eldest at 91 years; e.g., Kasuya et al. 1992; Aoshima 2004). It is conceivable that while Cd-U_{cr} decreased during hospitalization, tubular dysfunction stayed unimproved or even progressed (Kido et al. 1988; Iwata et al. 1993), so that Cd-U_{cr} levels were relatively low although β_2-MG-U_{cr} levels were high. In Area B which is just below Area A, there was no case of the patients or suspects (e.g., Ogata et al. 1976; Saito et al. 1997). Even below these areas and close to the horizontal axis is Area C (Table 5). The cases in the area can be better identified in Fig. 4B, as a group of dots which forms a horizontal tail to the left. Whereas Cd-U_{cr} was up to 2.9 μg / g cr to suggest moderate pollution, there was no increase in β_2-MG-U_{cr}. The observation that 7 cases out of 15 appeared in domestic sources may suggest the issue of so-called publication-bias in international journals.

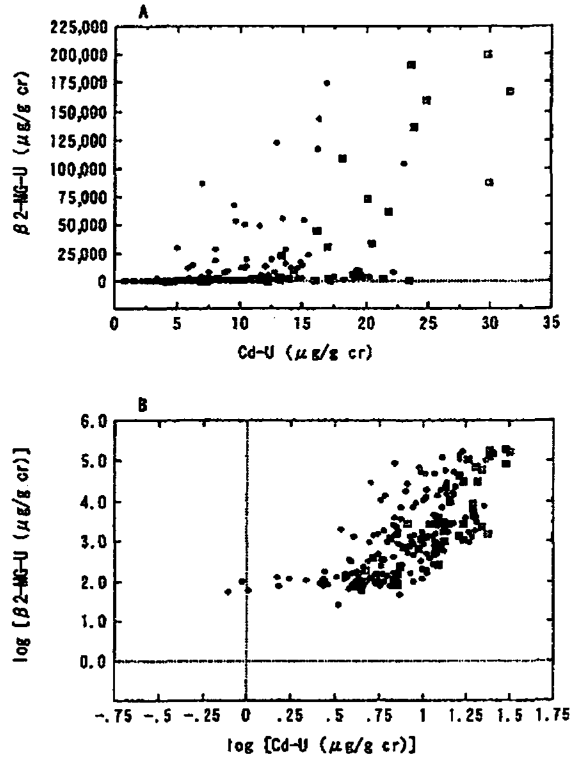

Fig. 4. Comparison of the cases in polluted areas for present analysis (small circles; n = 217) with that for a previous analysis (large squares; n = 44).
The data for previous analysis are cited from Ikeda et al. (2003).

TABLE 5. *Cases, by distribution area in Fig. 4, that affect the parameters of the regression line*

	No. of cases	Cd-U_{cr}[a] (μg / g cr)	β_2-MG-U_{cr}[a] (μg / g cr)	No. of subjects[b]	AM age[c] (years)	Age[d] (years)	GM Cd-U_{cr}[e] (μg / g cr)	GM β_2-MG-U_{cr}[e] (μg / g cr)
Area A	10	>5, <17	>48,000	3	64.83	50	7.0	48,671
				153	83.3	91	16.9	173,630
Area B	14	>5, ≦ 12.5	>5,000, ≦ 30,000	3	74.2	30	5.0	7,116
				134	78.2	88	12.5	29,390
Area C	15	<3	<1,000	5	45.1	15	0.8	53
				80	57.3	69	2.9	169
Area D	51	>10	<5,000	2	50.8	40	10.1	156
				153	75.9	92	23.4	4,590

Values on the first and the second line for each area show the minimum and the maximum in the area.

[a] Cd-U_{cr} and β_2-MG-U_{cr} range to define the area of distribution.

[b] The number of individuals in each case.

[c] Arithmetic means were calculated for ages of the individuals in each case, of which the min. and the max. values are shown.

[d] The max. and min. ages of the individuals.

[e] Geometric means were calculated for Cd-U_{cr} or β_2-MG-U_{cr} of the individuals in each case, of which the min. and the max. values are shown.

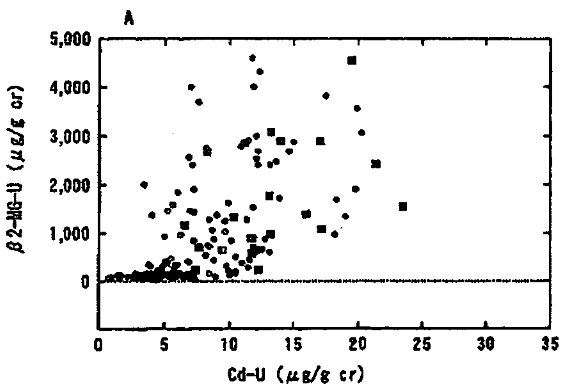

Fig. 5. Comparison of the low β_2-MG-U_{cr} cases for present analysis with that for the previous analysis on a magnified scale.
Note that the vertical axis is magnified by 45 times as compared with that in Fig. 4.

Although not very clearly seen in Fig. 4A, the enlargement of the lower part of the figure (Fig. 5) makes it clear that there is a heavy clustering of 51 cases in Area D, or the area in the right half of the figure and rather close to the horizontal axis (Figs. 4 and 5). The fact that Cd-U_{cr} was >10 μg / g cr indicates heavy exposure to Cd, but the response in terms of elevation in β_2-MG-U_{cr} was rather moderate, e.g., < 1,000 μg / g cr in 12 cases. Cases with discrepancy in intensity between exposure to Cd and response in terms of tubular dysfunction were observed also in the previous analysis (i.e., 17 cases out of 33 [51%] with Cd-U_{cr} > 10 μg / g cr; Ikeda et al. 2003a), but it was even more so in the present analysis (51 cases out of 91 (56%); $p < 0.10$ by chi-squares test). The presence of these cases (e.g., Nakano et al. 1985; Tohyama et al. 1986; Aoshima 1987; Fan et al. 1998; Arisawa et al. 2001; Cai et al. 2001) suggests that some subjects may be more resistant to Cd nephrotoxicity that others. Underlying mechanism certainly deserves further study. After removal of the cases in the four areas from the database of the present analysis, the regression analyses gave equations of Y = −26912.074 + 4111.810X (r = 0.725, n = 127), or log Y = 0.120

+ 3.112 log X (r = 0.825, n = 127). The slopes and the intercepts as well as the correlation coefficients of these equations were no longer different (p > 0.10), as expected, from the results of previous analysis (Ikeda et al. 2003a) except for the intercepts on ordinary scales (p < 0.01).

A major limitation of the present analysis with regard to the database is that no mechanism was available to adjust even if the same individuals were repeatedly introduced after different classification, e.g., grouping in terms of age in one article and by place of residence in another. It was possible to make adjustment only when the same data (e.g., GM Cd-U_{cr}) was presented on separate occasions. It should also be noted that many, if not all, studies were conducted at the time before the practice of external quality assurance (Aitio 1996) was brought into environmental health research. Regarding the method to estimate the point of flexion, the linear regression is apparently the simplest approach, but this approach is hampered by the fact that the relation of β_2-MG-U_{cr} with Cd-U_{cr} is not linear in the high Cd-U_{cr} range. As a result, the point of intersection varied depending on the high Cd-U_{cr} range employed for calculation of the regression line (Table 4).

Only Cd-U and β_2-MG-U as corrected for creatinine concentration were employed in the present analysis, as was in the previous analysis (Ikeda et al. 2003a). Criticism has been raised since early days on the adequacy of dividing urinary analyte level by creatinine concentration as a measure to correct for different urine density (e.g., Alessio et al. 1985; Berlin et al. 1985). This study group also observed that bias may be caused by creatinine correction in the evaluation of β_2-MG-U (Ikeda et al. 2003b), because creatinine concentration will decrease at advanced ages (Moriguchi et al. 2004a) simultaneously with physiological increases in Cd-U and β_2-MG-U (Moriguchi et al. 2004b). It is nevertheless a common practice both in occupational and environmental health to express Cd-U and β_2-MG-U levels as corrected for creatinine concentration (World Health Organization 1996; American Conference of Governmental Industrial Hygienists 2003). Experiences show that a majority of data available in literature is after correction for creatinine. It is apparently desirable that data without correction or corrected for a specific gravity of urine be also made available.

Furthermore, although β_2-MG-U has been most popularly employed in the epidemiology of Cd exposure-associated tubular dysfunction (Lauwerys et al. 1994; Kawada 1995), use of other markers in urine, such as α_1-microglobulin (α_1-MG) (Nogawa et al. 1984; Tohyama et al. 1986; Holmqvist et al. 1993; Pless-Mulloli et al. 1998; Uchida et al. 2004) and N-acetyl-β-D-glucosamindase (NAG) (Kawada 1995; Noonan et al. 2002; Uchida et al. 2004) have also been practiced. It is certainly important to have data on these parameters in parallel with that of Cd-U and β_2-MG-U for more precise evaluation of tubular dysfunction in relation to Cd exposure.

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