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Tolerable Lifetime Cadmium Intake Calculated from the Inhabitants Living in the Jinzu River Basin, Japan

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Recently, in Joint FAO/WHO Codex Alimentarius Commission tolerable values for cadmium (Cd) in food are being reassessed. Tolerable values for Cd concentrations in various foodstuffs, particularly in rice, has major implications in Japan. Thus, for example, when the tolerable Cd concentration in rice is set at 0.2 ppm, 3% of rice becomes unfit for consumption. Toward the reassessment of tolerable values an emergency investigation has been undertaken in Japan, the results of which are to be presented to the Commission.

Given these circumstances, we are at present attempting to determine the tolerable values for Cd concentrations in rice and life-time Cd intake values derived from the large-scale epidemiological survey and survey on Cd concentrations in rice previously undertaken by us in the Jinzu River basin. This is because in Japan until recently no investigations designed to determine the tolerable values for Cd concentrations in rice other than those conducted in 1965-75 in the Jinzu River basin in Toyama Prefecture and 1975-85 in the Kakehashi River basin in Ishikawa prefecture have been undertaken._We are confidant that in this way extremely valuable data will be made available, which at the present time as well will be useful in establishing Cd concentrations in rice and tolerable values for life-time Cd intake.

According to the study of Tsuchiya and Iwao (1978), the inhabitants of Cd-polluted areas in Japan derive one half to two thirds of their life-time Cd intake from rice. Therefore, the Cd concentration in rice is useful as an index of environmental Cd exposure in Japan. However, since the health effects of environmental Cd-exposure are thought to be caused by life-time Cd intake, tolerable limits of Cd should be determined as life-time Cd intake. The tolerable level of life-time Cd intake must be determined to protect the inhabitants from the adverse health effects of Cd-exposure.

Previously, we performed an epidemiological study on 1850 Cd-exposed and 294 non-exposed inhabitants in the Kakehashi River basin (Nogawa et al. 1989). β_2-microglobulinuria (β_2-MG-uria) was used as an index of the health effect, and the Cd concentration in rice was used as an indicator of Cd exposure. We found that Cd exposure affected health in a dose-related manner when the subjects were classified according to the mean Cd concentration in their hamlet rice and their length of residence in the polluted area. Based on the available data, the tolerable level of life-time Cd intake was calculated as approximately 2.0 g for both men and women. Moreover, we reported that when different health effect indices and statistical methods were used to calculate the tolerable level of life-time Cd intake,

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the value also turned out to be about 2.0 g (Kido et al. 1991, 1993; Kido and Nogawa 1993; Hochi et al. 1995).

Because irrigation water and rice were contaminated widely with Cd from a zinc mine located upstream, inhabitants with renal tubular dysfunction are observed in a high proportion along the Jinzu River basin (Fukushima et al. 1974; Nogawa et al. 1980).
In the Jinzu River basin, we investigated the association between life-time Cd intake and health effects using the same manner of study performed in the Cd-polluted Kakehashi River basin. Namely the target population was classified according to the average Cd concentration in their hamlet rice and their length of residence in the Cd-polluted area, and the tolerable level of life-time Cd intake was calculated.

MATERIALS AND METHODS

In 1967 and 1968 large-scale health examinations were conducted among the entire population aged ≥ 30 years of the Jinzu River basin, non-Jinzu River basin, and a region receiving a mixed water supply. The first screening was done by a questionnaire and by semi-quantitative determination of protein (Kingsbury-Clark method) and glucose (Benedict's reaction method) (Fukushima and Sakamoto 1974). In both years the number of subjects receiving urinary examinations was 13183 (men 6155, women 7028), amounting to a participation rate of 90.3%. Of the inhabitants living in hamlets where the Cd concentration in rice was known, subjects who had either resided in the present hamlet since birth or who had moved there from a non-polluted area were selected as the target population of the present study. The target population numbered 7044 (3758 men and 3286 women). The cutoff values defining proteinuria and glucosuria were set at 10mg/dl and 1/32%, respectively.

From 1971 to 1976 the Toyama Prefecture Department of Health (1976) analyzed Cd concentrations in unpolished rice in the entire endemic district in the Jinzu River basin. The mean Cd concentration in rice of each hamlet was calculated from concentrations measured in 2446 samples. The mean Cd concentrations in these rice samples were distributed in the range of 0.02~1.06 ppm, and the number of samples from one hamlet was 5-145. The mean Cd concentration in rice in a given hamlet was used as the index of external Cd exposure of the entire population of that hamlet.

The calculation of life-time Cd intake was based on the formula of Nogawa: (mean Cd concentration in rice per rural community × 333.5 g + 34 μg) × 365 days × number of years of residence in present rural community + 50 μg × 365 days × number of years living in non-Jinzu River basin. 333.5 g represents the daily mean rice intake, 34 μg the mean daily Cd intake from foods other than rice in the Cd-polluted region, and 50 μg the mean daily Cd intake in non-Cd-polluted regions (Nogawa et al. 1989).

The Cd concentration in rice was divided into 4 groups, with 0.00-0.09 ppm, 0.10-0.39 ppm, 0.40-0.59 ppm, and ≥ 0.60 ppm. The length of residence in the present hamlet was divided into 4 groups for men, with 0-29.9 years, 30.0-49.9 years, 50.0-69.9 years, and ≥ 70.0 years, and was divided into 3 groups for women, with 0-29.9 years, 30.0-49.9 years, and ≥ 50.0 years. The mean values of the Cd concentration in rice, the length of residence in the present hamlet, age, life-time Cd intake, and prevalence of proteinuria, glucosuria and proteinuria + glucosuria

Table 1-1. Life-time cadmium intake and prevalences of proteinuria, glucosuria and proteinuria with glucosuria among the inhabitants living in the Jinzu River basin in relation to average rice cadmium concentration and length of residence in Cd-polluted areas [Male].

Cd in rice (Mean) (ppm)	Residence (Mean) (ys)	Mean of age (y.o.)	Life-time Cd intake (mg)	N	Proteinuria (%)	Glucosuria (%)	Proteinuria with glucosuria (%)
0.00-0.09 (0.06)	0-29.9 (16.4)	45.6	850	166	7.8	27.7	1.8
0.00-0.09 (0.06)	30-49.9 (39.3)	42.4	836	272	7.7	19.5	1.8
0.00-0.09 (0.07)	50-69.9 (57.8)	58.9	1194	136	9.6	24.3	2.9
0.00-0.09 (0.07)	70- (75.2)	75.4	1542	26	38.5	30.8	15.4
0.10-0.39 (0.21)	0-29.9 (17.1)	46.3	1183	345	8.4	24.6	3.2
0.10-0.39 (0.24)	30-49.9 (38.7)	41.5	1658	822	7.9	22.3	2.2
0.10-0.39 (0.24)	50-69.9 (58.4)	59.1	2464	481	15.8	24.1	4.4
0.10-0.39 (0.24)	70- (75.7)	75.4	3144	110	51.8	24.6	19.1
0.40-0.59 (0.51)	0-29.9 (15.1)	46.7	1699	162	11.7	22.8	5.6
0.40-0.59 (0.50)	30-49.9 (39.1)	41.1	2904	435	12.6	21.4	3.0
0.40-0.59 (0.50)	50-69.9 (58.9)	59.3	4323	285	40.0	29.5	20.0
0.40-0.59 (0.50)	70- (75.9)	75.9	5533	94	74.5	40.4	39.4
0.60- (0.70)	0-29.9 (15.6)	47.2	2107	63	14.3	22.2	4.8
0.60- (0.76)	30-49.9 (38.8)	40.8	4096	205	12.7	21.5	5.4
0.60- (0.74)	50-69.9 (59.0)	59.2	6034	119	47.9	37.8	26.9
0.60- (0.76)	70- (75.8)	75.8	7908	37	83.8	54.1	51.4

Table 1-2. Life-time cadmium intake and prevalences of proteinuria, glucosuria and proteinuria with glucosuria among the inhabitants living in the Jinzu River basin in relation to average rice cadmium concentration and length of residence in Cd-polluted areas [Female].

Cd in rice (Mean) (ppm)	Residence (Mean) (ys)	Mean of age (y.o.)	Life-time Cd intake (mg)	N	Proteinuria (%)	Glucosuria (%)	Proteinuria with glucosuria (%)
0.00-0.09 (0.06)	0-29.9 (17.2)	43.7	823	274	9.1	13.9	2.6
0.00-0.09 (0.06)	30-49.9 (39.1)	47.6	941	172	12.8	15.7	2.3
0.00-0.09 (0.07)	50- (58.8)	62.3	1266	122	26.2	18.0	6.6
0.10-0.39 (0.23)	0-29.9 (16.7)	42.9	1151	764	10.1	13.0	2.6
0.10-0.39 (0.23)	30-49.9 (38.8)	50.7	1766	577	13.4	12.3	3.7
0.10-0.39 (0.23)	50-69.9 (60.7)	64.3	2531	337	31.8	23.2	13.7
0.40-0.59 (0.50)	0-29.9 (16.4)	42.3	1679	387	16.8	10.3	3.4
0.40-0.59 (0.50)	30-49.9 (38.8)	51.4	3073	244	32.0	26.2	16.4
0.40-0.59 (0.50)	50-69.9 (59.5)	64.2	4414	125	56.8	38.4	32.0
0.60- (0.74)	0-29.9 (15.5)	40.6	2040	132	19.7	12.1	1.5
0.60- (0.75)	30-49.9 (38.1)	49.6	4167	99	34.3	20.2	13.1
0.60- (0.74)	50-69.9 (59.3)	65.9	6201	53	69.8	64.2	56.6

were calculated for every group by sex (16 groups for men and 12 groups for women) (Table 1-1 and 1-2).
The correlation coefficients and regression formulas between the prevalence of proteinuria, glucosuria and proteinuria + glucosuria and life-time Cd intake were calculated. The tolerable value of life-time Cd intake was calculated by substituting the abnormality rate of urinary finding of the control group into every regression formula.

RESULTS AND DISCUSSION

The correlation coefficients and regression formulas between the prevalence of proteinuria, glucosuria and proteinuria + glucosuria and life-time Cd intake are shown in Table 2. Tolerable values of life-time Cd intake were calculated by substituting the abnormality rate of urinary finding of the control group into every regression formula, and are also shown in Table 2.

Table 2. Allowable amounts of life-time cadmium intake according to proteinuria, glucosuria and proteinuria with glucosuria

		Cd-exposed subjects			
	Sex	Mean of age (y.o.)	Correlation coefficient	Regression line	Allowable total Cd intake (mg)
Proteinuria	Male	49.5	0.843 ***	Y=0.0102X-2.362	1324
	Female	50.5	0.944 ***	Y=0.0108X+0.756	1527
Glucosuria	Male	49.5	0.820 ***	Y=0.0036X+17.34	2697
	Female	50.5	0.884 ***	Y=0.0082X+1.862	2175
Proteinuria with glucosuria	Male	49.5	0.889 ***	Y=0.0064X-6.008	1473
	Female	50.5	0.920 ***	Y=0.0091X-9.822	1570

		Non-exposed subjects		
	Sex	Mean of age (y.o.)	Life-time Cd intake	Prevalence of abnormality (%)
Proteinuria	Male	49.6	905	11.1
	Female	48.9	892	17.2
Glucosuria	Male	49.6	905	27.0
	Female	48.9	892	19.6
Proteinuria with glucosuria	Male	49.6	905	3.4
	Female	48.9	892	4.4

***: $P < 0.001$

The correlation coefficient between life-time Cd intake and prevalence of proteinuria was 0.84 for men and 0.94 for women, respectively. The value between life-time Cd intake and prevalence of glucosuria was 0.82 for men and

0.88 for women, respectively. The value between life-time Cd intake and prevalence of proteinuria + glucosuria was 0.89 for men and 0.92 for women, respectively. All values were statistically significant.
Tolerable values of life-time Cd intake were 1.3-2.7 g for men and 1.5-2.2 g for women.

The association between life-time Cd intake and renal dysfunction caused by Cd-exposure was investigated in greatest detail in the Kakehashi River basin among the Cd-polluted regions in Japan. The tolerable level of life-time Cd intake was calculated as about 2.0 g based on the available data. When using different health effect indices and statistical methods, the tolerable level of life-time Cd intake was similarly calculated to be about 2.0 g (Kido et al. 1991, 1993; Kido and Nogawa 1993; Hochi et al. 1995).

In this study, the prevalences of proteinuria, glucosuria and proteinuria + glucosuria were used as the health effect indices. The abnormality rate of urinary finding in the controls was substituted into every regression formula calculated with the life-time Cd intake and abnormality rate of urinary finding in the Cd-exposed subjects, because the difference in the mean and distribution of age in the Cd-exposed subjects and that in non-exposed ones was small. Glucosuria seems to be less sensitive than the other indices as an index of renal dysfunction caused by Cd-exposure as mentioned in previous studies. Therefore, it should be said that the tolerable level of life-time Cd intake was 1.3-1.5 g for men and 1.5-1.6 g for women, respectively, when using proteinuria and proteinuria + glucosuria. Since the calculated daily Cd intake in non-polluted regions is 50 μ g, the life-time Cd intake during a 50-year span works out to 913 mg. The tolerable level of life-time Cd intake is higher by 1.4-1.6 fold for men and 1.4-1.8 fold for women than the life-time Cd intake of the subjects living in non-polluted regions during the 50-year period. The difference is extremely small, amounting to no more than 2-fold.

It should be mentioned that age effects were not considered in this calculation of life-time Cd intake. Also, the indices of the renal effect focused on here were protein and glucose concentrations in urine, which are not routinely used at present. Therefore a more detailed estimation method which includes age factor is necessary to more accurately calculate the tolerable value of life-time Cd intake. Even admitting this, the present results demonstrated that the life-time Cd intake is clearly related to urinary abnormality rates and supported the results obtained from our study in the Cd-polluted Kakehashi River basin, Ishikawa Prefecture, Japan.

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