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Application of hybrid approach for estimating the benchmark dose of urinary cadmium for adverse renal effects in the general population of Japan

Yasushi Suwazono^{a,*}, Kazuhiro Nogawa^a, Mirei Uetani^a, Katsuyuki Miura^b, Kiyomi Sakata^c, Akira Okayama^d, Hirotsugu Ueshima^b, Jeremiah Stamler^e, and Hideaki Nakagawa^f

^a Department of Occupational and Environmental Medicine, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuoku, Chiba, 260-8670 Japan

^b Department of Health Science, Shiga University of Medical Science, Seta-Tsukinowa-cho, Otsu, Shiga, 520-2192, Japan

^c Department of Hygiene and Preventive Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan

^d The First Institute for Health Promotion and Health Care, Japan Anti-Tuberculosis Association, 1-3-12 Misakicho, Chiyodaku, Tokyo, 101-0061 Japan

^e Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, 680 N. Lake Shore Drive, Suite 1400, Chicago, IL, 60611, U.S.A

^f ††Department of Epidemiology and Public Health, Kanazawa Medical University, 1-1 Daigaku, Uchinada, Ishikawa, 920-0293 Japan

Abstract

We used an updated hybrid approach to estimate the benchmark doses and their 95% lower confidence limits (BMDL) for cadmium-induced renal effects in humans. Participants were 828 inhabitants (410 men, 418 women), ages 40–59 years who lived in three areas without any known environmental cadmium pollution. We measured urinary cadmium (U-Cd) as a marker of exposure, and urinary protein, β 2-microglobulin (β 2-MG) and N-acetyl- β -D-glucosaminidase (NAG) as markers of renal effects. For urinary protein, the BMDL ranged from 0.9 to 1.1 μ g/g cre and approximately 1.6 μ g/24h in men, and 1.9 to 3.4 μ g/g cre and 2.0 μ g/24h in women. For the renal tubular markers β 2-MG and NAG, the BMDL for U-Cd ranged from 0.6 to 1.2 μ g/g cre and 0.8 to 1.7 μ g/24h in men, and 0.6–2.3 μ g/g cre and 0.6–2.1 μ g/24h in women. The lowest BMDL for urinary cadmium (0.6 μ g/g creatinine) was somewhat lower than average urinary cadmium in Japanese older population. These results suggest the importance of measures to decrease cadmium exposure in the general population of Japan.

Keywords

Benchmark dose; Human; Renal effect; Risk assessment; Urinary cadmium

*Correspondence to: Yasushi Suwazono, Department of Occupational and Environmental Medicine, Graduate School of Medicine, Chiba University, 1-8-1, Inohana, Chuoku, Chiba, 260-8670 Japan, Tel: +81 43 226 2065 Fax: +81 43 226 2066 suwa@faculty.chiba-u.jp.

INTRODUCTION

Itai-itai disease, which developed in inhabitants of the Jinzu River basin in Toyama Prefecture, Japan is the serious illness caused by long term exposure to cadmium (Cd) (Nordberg *et al.* 2007a). In the general environment, long-term exposure to Cd causes renal dysfunction, which presents initially as tubular damage, followed by glomerular damage (Järup and Åkesson 2009). For the prevention of Cd-induced renal effects, it is essential to establish the reference exposure below which the risk of adverse effects is low (Nordberg *et al.* 2007b).

The benchmark dose (BMD) method has been developed for the health risk assessment of environmental contaminants (Crump 1984; U.S. EPA 1995). The BMD is defined as the exposure level which corresponds to a specific increase in the probability of an adverse response (benchmark response, BMR), compared with zero background exposure. The lower 95% confidence limit of the BMD (BMDL) can be used in risk assessment as a replacement for the no observed adverse effect level (NOAEL) (Crump 1984; U.S. EPA 1995). Several studies in the Japanese population have applied the BMD method to assess the health risks of urinary cadmium (U-Cd) (Kobayashi *et al.* 2006; Kobayashi *et al.* 2008; Shimizu *et al.* 2006; Uno *et al.* 2005).

We previously estimated the BMDL of U-Cd for markers of renal effects in more than 800 inhabitants who were not exposed to any known environmental Cd pollution (Uno *et al.* 2005). Estimation of BMD and BMDL was performed using Benchmark Dose Software (BMDS, version 1.3.1) developed by the United States Environmental Protection Agency. When the BMR was set at 5%, BMDL for the markers of tubular damage, β_2 -microglobulin (β_2 -MG) and N-acetyl- β -D-glucosaminidase (NAG)), ranged from 0.3 to 0.4 $\mu\text{g/g}$ creatinine (cre) in men and 0.6 to 0.7 $\mu\text{g/g}$ cre in women. These BMDL tended to be somewhat lower than values reported in three other studies (Kobayashi *et al.* 2006; Kobayashi *et al.* 2008; Shimizu *et al.* 2006), which ranged from 1.5 (Shimizu *et al.* 2006) to 3.2 $\mu\text{g/g}$ cre (Kobayashi *et al.* 2008). In order to use the BMDS to analyze human data, it is necessary to categorize the participants into several groups according to their original continuous exposure level.

Recently, estimations of BMD/BMDL for continuous outcomes using the hybrid approach have been developed (Crump 1995; Sand *et al.* 2008; Suwazono *et al.* 2006). Using this method, the BMD and BMDL were estimated based on a continuous exposure and a continuous effect marker, thereby avoiding categorization of the participants (Crump 2002; Filipsson *et al.* 2003; Sand *et al.* 2008). This approach allows the establishment of a hybrid concept on the risk and exposure-continuous effect relationship. Hybridization may be of interest for comparing the BMD of dichotomous and continuous endpoints (Filipsson *et al.* 2003). The statistical validity and efficiency of the BMD and BMDL were improved using the hybrid approach compared to methods involving categorization of continuous exposure and effect markers.

The aim of the present study was to apply an updated hybrid approach to estimate BMD and BMDL for Cd-induced renal effects, based on a dataset from our previous investigation (Uno *et al.* 2005).

MATERIALS AND METHODS

Study population and measurements

Participants were 828 inhabitants (410 men, 418 women), ages 40–59 years who lived in three areas without any known environmental cadmium pollution and were a sub-cohort of the INTERMAP (International study of macro- and micro-nutrients and blood pressure)

(Stamler *et al.* 2003; Uno *et al.* 2005). The INTERMAP Study is an international population-based investigation providing resources for elucidation of nutritional/dietary influences on blood pressure (Stamler *et al.* 2003). The participants were selected randomly from four age-gender strata. Participation rate was 93% (Stamler *et al.* 2003; Uno *et al.* 2005). Smokers and nonsmokers were examined simultaneously, as we previously showed that smoking habit did not affect the relationship between U-Cd and renal findings in Japan (Suwazono *et al.* 2000). The ethical committees of the Shiga University of Medical Science, the Kanazawa Medical University, and the Wakayama Medical University approved the study protocol. Written informed consent was obtained from all participants.

In 1997–1998 INTERMAP participants collected two sets of timed 24-hour urine specimens in Cd-free bottles, later aliquoted into Cd-free tubes. We used mean values as measurements for the individuals. Standardization between the two 24-hour urine specimens was obtained by instructing the participants on correct collection methods, as described previously (Uno *et al.* 2005). Total protein was analyzed using a kit (Tonein-TP, Otsuka Pharmacy, Japan), β_2 -MG by radioimmunoassay (Pharmacia β_2 -micro RIA, Pharmacia Diagnostics AB, Sweden), and NAG by a kit (NAG test Shionogi, Shionogi Pharmaceuticals, Japan). U-Cd was determined directly by graphite-furnace atomic absorption spectrometry using a Hitachi Model Z-8100 (Kido *et al.* 1984). Urinary creatinine was determined by the Jaffe reaction method (Bonness and Taussky 1945). The detection limit for Cd was 0.05 $\mu\text{g/L}$. The accuracy of each analysis was evaluated using duplicate measurements. The correlation coefficients for the duplicate measurements were 0.98–1.00, with the slopes of all the correlation equations being approximately 1.0 (Uno *et al.* 2005).

Statistical analysis

The concentrations of the urinary analytes were expressed in the following two ways: corrected creatinine unit ($\mu\text{g/g cre}$) and 24-hour excretion ($\mu\text{g/day}$). We used the maximum likelihood approach to fit the dose-effect model to the data (Crump 1995; Sand *et al.* 2008). To obtain a symmetrical distribution, data on urinary protein, β_2 -MG and NAG were natural log-transformed. We used linear model for the mean response, $\mu(d_i)$:

$$\mu(d_i) = \beta_0 + \beta_1 \times d_i \quad [1]$$

Where d_i = dose for the i -th individual. To control for the possible confounding effects of gender and age, we stratified the participants according to gender and age (40–49 and 50–59 yrs old).

The BMDs and BMDLs were calculated using the hybrid approach, which allows for calculation of risk of continuous data without dichotomizing the outcome (Crump 2002; Sand *et al.* 2008). The BMR was defined as a 5% additional risk. For positive associations between exposure (U-Cd) and renal effects, the effect level associated with a certain BMR equals:

$$\mu(\text{BMD}) = \mu(0) + \sigma(\Phi^{-1}[1 - P(0)] - \Phi^{-1}[1 - P(0) - \text{BMR}])$$

Where σ = the standard deviation of residuals, Φ^{-1} = the inverse of the standard normal cumulative distribution function, and $P(0)$ = the background probability of a response defined in terms of a specified tail proportion of a “hypothetical” control distribution (at U-Cd = 0), which in this study was set at 5%. The corresponding continuous cut-off values, c , for specified values of renal effect markers in terms of $P(0)$ are given by:

$$c = \mu(0) + \sigma \times \Phi^{-1}[1 - P(0)]$$

The BMD was obtained by combining the equation for $\mu(\text{BMD})$ with that of the dose-response model [1]:

$$\text{BMD} = \frac{\sigma}{\beta_1} \times (\Phi^{-1}[1 - P(0)] - \Phi^{-1}[1 - P(0) - \text{BMR}]) \quad [2]$$

The BMDL was calculated as representative reference levels using the profile likelihood method (Crump 1995; Sand *et al.* 2008). SPSS, version 12.0.2J (SPSS Inc., Chicago, IL, USA) and Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA, USA) were used for the statistical analyses.

RESULTS

Age-gender-specific 24-hour urinary Cd data and findings for the three measures of renal dysfunction are presented in Table 1. The geometric mean U-Cd ranged from 0.6 to 1.1 $\mu\text{g/g}$ cre or 1.0 to 1.6 $\mu\text{g}/24\text{h}$ in men and 1.5 to 2.2 $\mu\text{g/g}$ cre or 1.4 to 2.0 $\mu\text{g}/24\text{h}$ in women. Table 2 gives results of the linear regression between U-Cd and markers of renal effects by gender and age. U-Cd related significantly to all natural log-transformed renal effect markers except urinary protein (mg/24h) in women ages 50–59 years. Table 3 shows the BMD and BMDL for U-Cd for the renal markers. For urinary protein, the BMDL ranged from 0.9 to 1.1 $\mu\text{g/g}$ cre and approximately 1.6 $\mu\text{g}/24\text{h}$ in men, and 1.9 to 3.4 $\mu\text{g/g}$ cre and 2.0 $\mu\text{g}/24\text{h}$ in women. For the renal tubular markers $\beta_2\text{-MG}$ and NAG, the BMDL for U-Cd ranged from 0.6 to 1.2 $\mu\text{g/g}$ cre and 0.8 to 1.7 $\mu\text{g}/24\text{h}$ in men, and 0.6–2.3 $\mu\text{g/g}$ cre and 0.6–2.1 $\mu\text{g}/24\text{h}$ in women.

DISCUSSION

To our knowledge, this is the first estimation of BMDL for Cd-induced renal effects in the Japanese population using the recently developed hybrid approach.

A notable feature of this study was that the potential confounding effect of age was controlled by stratification, a method which was not used in our earlier study (Uno *et al.* 2005). Furthermore, the hybrid approach provided several methodological advantages compared to our earlier study (Uno *et al.* 2005). Firstly, the hybrid approach allowed us to avoid inadequacies in the information due to dichotomization of the renal markers. Secondly, we were able to avoid categorization of the Cd exposure. The number and interval in the Cd exposure groups may have affected the results due to a loss of detection power caused by such categorization (Royston *et al.* 2000). Thirdly, we consistently defined the $P(0)$ as 5% in this study, which corresponded to the cut-off values for renal markers, defined as the 95th percentile at no Cd exposure. As the cut-off in our previous study (Uno *et al.* 2005) was defined as the 84th percentile in the whole target population, such dichotomization may have been affected by the distribution of the renal markers in the target population, which may also have reflected the collective Cd exposure. Therefore, the results of our previous study may have been less comparable with different renal markers in the same study or in other studies.

As a result, the lowest BMDL measured in the present study was 0.6 $\mu\text{g/g}$ cre and was the same in both men and women. Therefore, the BMDL of U-Cd obtained by the hybrid approach is generally higher than the range of 0.3 to 0.7 $\mu\text{g/g}$ cre we reported in our earlier study (Uno *et al.* 2005). This lower BMDL may have been obtained as a result of

uncertainties caused by either loss of information due to categorization of exposure, conversion of the continuous effect markers to a binary form or selection of the cut-off values. It is considered reasonable when evaluating reference points in health risk assessment to adopt estimates based on actual information. On the basis of these features, we consider the BMDL calculated in the present study to be a better estimate than reported previously (Uno *et al.* 2005).

In the present study, BMR was set at 5%, a value with probability of an adverse response at the reference U-Cd corresponding to 10% for a $P(0)$ of 5%. Actually, different level of BMR, i.e. 1% or 10% may be adopted, depending on severity of effects (Jacobson *et al.* 2002). Recently, a BMDL with a 5% BMR was adopted for health risk assessment by the European Food Safety Authority (EFSA 2009). We therefore used this value in our study.

Kobayashi et al. (2006) investigated 1270 people ages 50 years or older from a non-polluted area. The cut-off values used in their study were the 84th percentile of urinary total protein, β 2-MG, or NAG of non-smoking control inhabitants living in non-polluted areas. When the BMR was set at 5%, the BMDL for the tubular markers β 2-MG and NAG ranged from 2.0 to 2.5 μ g/g cre in men, and 1.6 to 2.2 μ g/g cre in women. Shimizu et al. (2006) also estimated BMDL in 3178 and 294 participants ages 50 years or older who inhabited Cd-polluted and non-polluted areas, respectively. Cut-off values applied were the 84th or 97.5th percentile of urinary β 2-MG in non-smoking control persons living in non-polluted areas or 1000 μ g/g cre. When the BMR was set at 5%, the BMDL for β 2-MG-uria ranged from 2.9 to 4.0 μ g/g cre in men and 1.5 to 3.6 μ g/g cre in women. Use of the BMDS software in these studies did not take into account confounding effects of age, and the participants were categorized into several groups according to their U-Cd level. Thereafter, Kobayashi et al. (2008) estimated the BMDL of U-Cd in 3103 persons ages $\geq$ 50 years living in Cd-polluted areas and 2929 inhabitants living in non-polluted areas. The cut-off values were the 84th or 97.5th percentile of urinary β 2-MG in controls from non-polluted areas or 1000 μ g/g cre. When the BMR was set at 5%, BMDL for persons ages mean 64 years ranged from 2.7 to 4.6 μ g/g cre in men, and 3.2 to 6.3 μ g/g cre in women. Although the age-adjusted BMDL was estimated using a multiple logistic regression model, without categorization of the participants according to U-Cd, the possibility of reduced information by dichotomization of the renal markers could not be excluded in that study.

Suwazono et al. (2006) also estimated BMDL using a hybrid approach in 790 Swedish women ages 53 to 64 years living in a non-polluted area. When the BMR was set at 5%, the BMDL for the tubular markers NAG and protein HC ranged around 0.5 μ g/g cre. For the glomerular filtration rate as a marker of glomerular ultrafiltration, the BMDL was 0.7 μ g/g cre. Thus, the BMDLs in the present study are consistent with those reported in Swedish women (Suwazono *et al.* 2006). We believe the hybrid approach should be applied further, e.g., to data on BMDL in non-polluted (Kobayashi *et al.* 2006) and polluted areas in Japan (Shimizu *et al.* 2006).

Recently, the Scientific Panel on Contaminants in the Food Chain (CONTAM) of the EFSA carried out a meta-analysis on data from 35 studies based on 30,000 individuals using the BMD method with the hybrid approach (EFSA 2009). When the BMR was set at 5%, the estimated BMDL was 4 μ g/g cre for B2-MG. The CONTAM panel indicated that uncertainty exists in this analysis due to the fact that group means with associated ranges of U-Cd levels were used rather than data points from individuals (EFSA 2009). The estimated BMDL was therefore likely to have been greater than when calculated using individual data (EFSA 2009). Therefore, the BMDL obtained by this meta-analysis is not directly comparable to the BMDL calculated in the present study. Applying a chemical-specific adjustment factor of 3.9 to the BMDL, the CONTAM panel set the reference point of U-Cd as 1.0 μ g/g cre for

renal tubular effects (EFSA 2009). That level was somewhat higher than the BMDL in the present study. Based on a one-compartment model and translating U-Cd into dietary exposure (Amzal *et al.* 2009), the EFSA set the tolerable weekly intake (TWI) at 2.5 µg Cd/kg body weight, a value that was considerably lower than the provisional TWI of 7 µg Cd/kg body weight established by the Joint FAO/WHO Expert Committee on Food Additives (FAO/WHO (Food and Agriculture Organization/World Health Organization) 1988). In previous study, the biological half life of U-Cd has been reported to be 12 to 20 years (Amzal *et al.* 2009; Suwazono *et al.* 2009). Therefore, it takes a considerable time to reduce the health burdens associated with Cd in the population. As the representative level of U-Cd in older Japanese, the geometric mean of U-Cd was reported to be 1.8 in men and 2.4 µg/g cre in non-polluted areas (Suwazono *et al.* 2000). The present results scientifically support the low TWI value, and suggest the importance of measures to decrease cadmium exposure in the general population of Japan.

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Table 1

Exposure to cadmium and markers of renal effects by gender and age.

Variable	Men		Women	
	40–49 yrs	50–59 yrs	40–49 yrs	50–59 yrs
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Age (yrs)	44.8 (2.8)	54.2 (2.7)	44.7 (2.8)	53.7 (2.9)
	GM (GSD)	GM (GSD)	GM (GSD)	GM (GSD)
Urinary cadmium ($\mu\text{g/g cre}$)	0.6 (2.8)	1.1 (2.4)	1.5 (2.4)	2.2 (2.4)
Urinary protein (mg/g cre)	38.5 (1.5)	43.0 (1.9)	44.8 (1.7)	52.5 (1.5)
β_2 -MG ($\mu\text{g/g cre}$)	98.7 (2.0)	130.4 (2.0)	146.5 (1.8)	159.1 (1.8)
NAG (IU/g cre)	0.9 (2.4)	1.1 (2.4)	1.0 (2.2)	1.3 (2.1)
Urinary cadmium ($\mu\text{g}/24\text{-hours}$)	1.0 (2.7)	1.6 (2.4)	1.4 (2.3)	2.0 (2.3)
Urinary protein (mg/24-hours)	59.8 (1.6)	59.1 (1.9)	43.9 (1.7)	47.1 (1.5)
β_2 -MG ($\mu\text{g}/24\text{-hours}$)	152.9 (2.0)	179.5 (2.1)	143.3 (1.8)	143.0 (1.8)
NAG (IU/24-hours)	1.3 (2.4)	1.5 (2.4)	1.0 (2.2)	1.2 (2.2)
Number of people	209	201	215	203

Table 2
Results of linear regression analysis between urinary cadmium (U-Cd) and markers of renal effects by gender and age.

Renal effect markers ^a	Men		Women	
	B ^b (95% CI) ^c	P	B ^b (95% CI) ^c	P
U-Cd (µg/g cre), 40–49 yrs				
Urinary protein (mg/g cre)	0.11 (0.06–0.17)	<0.001	0.06 (0.02–0.10)	0.002
β2-MG (µg/g cr)	0.27 (0.18–0.36)	<0.001	0.09 (0.05–0.13)	<0.001
NAG (IU/g cr)	0.40 (0.29–0.51)	<0.001	0.20 (0.15–0.24)	<0.001
U-Cd (µg/g cre), 50–59 yrs				
Urinary protein (mg/g cre)	0.14 (0.08–0.21)	<0.001	0.03 (0.01–0.04)	0.004
β2-MG (µg/g cr)	0.14 (0.07–0.21)	<0.001	0.08 (0.06–0.10)	<0.001
NAG (IU/g cr)	0.29 (0.21–0.38)	<0.001	0.08 (0.05–0.11)	<0.001
U-Cd (µg/24h), 40–49 yrs				
Urinary protein (mg/24h)	0.05 (0.004–0.10)	0.035	0.06 (0.02–0.10)	0.004
β2-MG (µg/24h)	0.17 (0.09–0.24)	<0.001	0.09 (0.05–0.13)	<0.001
NAG (IU/24h)	0.27 (0.18–0.35)	<0.001	0.20 (0.15–0.25)	<0.001
U-Cd (µg/24h), 50–59 yrs				
Urinary protein (mg/24h)	0.09 (0.05–0.14)	<0.001	0.02 (–0.002–0.04)	0.071
β2-MG (µg/24h)	0.10 (0.05–0.15)	<0.001	0.08 (0.06–0.11)	<0.001
NAG (IU/24h)	0.20 (0.14–0.26)	<0.001	0.09 (0.05–0.13)	<0.001

^a All renal markers were natural log-transformed.

^b Regression coefficients.

^c 95% confidence interval.

Benchmark doses (BMD) of urinary cadmium (U-Cd) with their lower limits (BMDL) for markers of renal effects, calculated using the hybrid approach.

Table 3

Renal effect markers ^a	Men		Women	
	Estimated cut-off value	BMDL (BMD)	Estimated cut-off value	BMDL (BMD)
U-Cd (µg/g cr), 40–49 yrs				
Urinary protein (mg/g cre)	67.7	0.9 (1.3)	94.6	1.9 (3.2)
β2-MG (µg/g cre)	224.5	0.7 (0.9)	298.9	1.5 (2.2)
NAG (IU/g cre)	2.2	0.6 (0.7)	2.1	0.6 (1.3)
U-Cd (µg/g cre), 50–59 yrs				
Urinary protein (mg/g cre)	94.5	1.1 (1.6)	92.7	3.4 (5.7)
β2-MG (µg/g cre)	322.1	1.2 (1.8)	296.7	1.8 (2.4)
NAG (IU/g cre)	2.5	0.8 (1.0)	3.3	2.3 (3.2)
U-Cd (µg/24h), 40–49 yrs				
Urinary protein (mg/24h)	116.8	1.6 (3.2)	95.8	2.0 (3.4)
β2MG (µg/24h)	368.9	1.0 (1.5)	306.8	1.6 (2.3)
NAG (IU/24h)	3.4	0.8 (1.1)	2.1	0.6 (1.3)
U-Cd (µg/24h), 50–59 yrs				
Urinary protein (mg/24h)	134.9	1.6 (2.4)	NA	NA
β2MG (µg/24h)	452.5	1.7 (2.5)	287.0	1.8 (2.4)
NAG (IU/24h)	3.5	1.1 (1.4)	3.2	2.1 (3.1)

^a All renal markers were natural log-transformed.

NA: Not applicable because of an insignificant relationship between U-Cd and renal marker.