腎臓への影響について追加を提案する論文、およびコメント（姫野）

1. Ikeda et al., Biol Trace Elements Res 2006
No meaningful increase in urinary tubular dysfunction markers in a population with 3 μg cadmium/g creatinine in urine

日本の非汚染地域の中でも、尿中Cd濃度が3 μg/g Cre以上の高い地域（Area H）と低い地域（Area L）を比較すると、尿中β_2-MG濃度にほとんど差がなかった。

2. Moriguchi et al., Int Arch Occup Env Health 2010
Cadmium and tubular dysfunction marker levels in urine of residents in non-polluted areas with natural abundance of cadmium in Japan

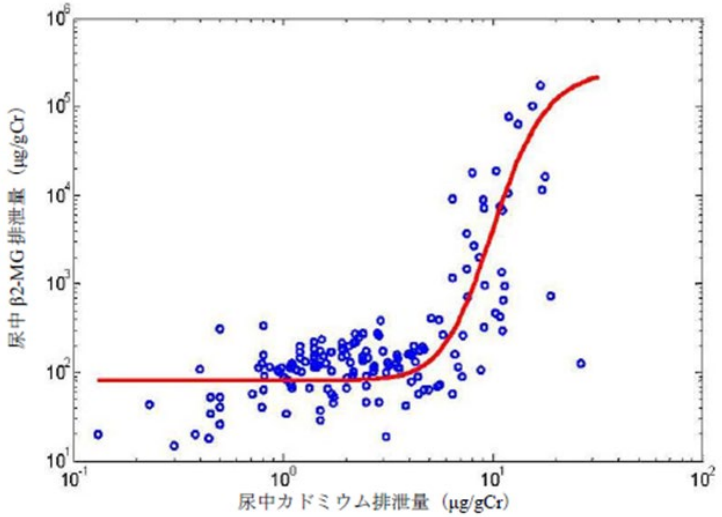
日本海側の5つの県の一般住民の尿中Cd濃度は、日本全体の平均値と比べるとやや高い値を示す。しかし、尿中β_2-MG濃度は日本全国との差がほとんどなかった。

3. Ikeda et al., Int Arch Occup Env Health 2012
Bi-linear dose–response relationship in general populations with low-level cadmium exposures in non-polluted areas in Japan

日本の非汚染地域の尿中Cdと尿中β_2-MGの関係を再評価した。尿中Cd濃度が2.3 μg/Lのあたりに傾きの分岐点がある。尿中β_2-MGが291 μg/L（分布の95%値）を超える人の割合が5%を超えるのは、尿中Cd濃度が2 μg/Lのあたり。BMD、BMDLも計算。

（上記の論文は、いずれも最初の論文リストに含まれていなかった）

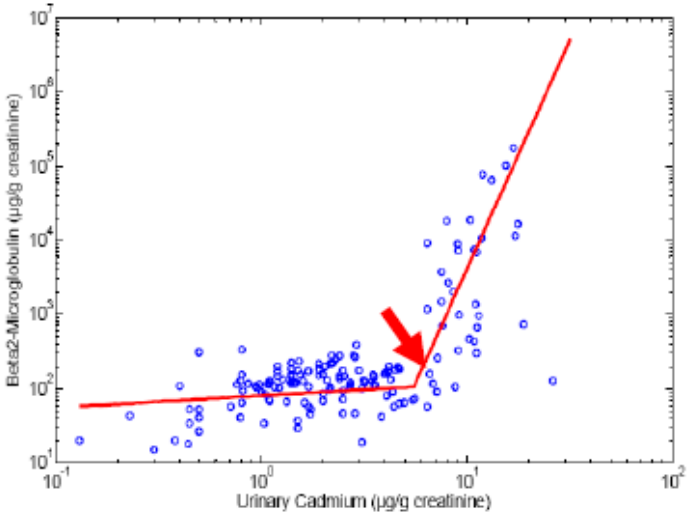
EFSA 2009（第2版評価書）



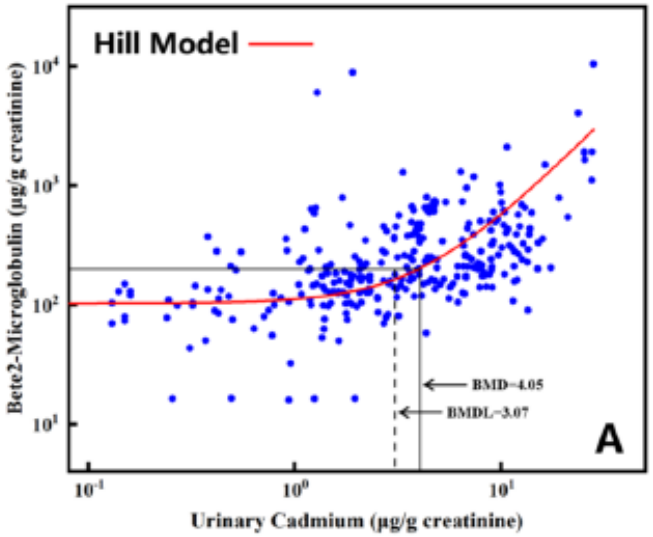
※ EFSA（2009）より引用（第 2 版関係 文献 3）

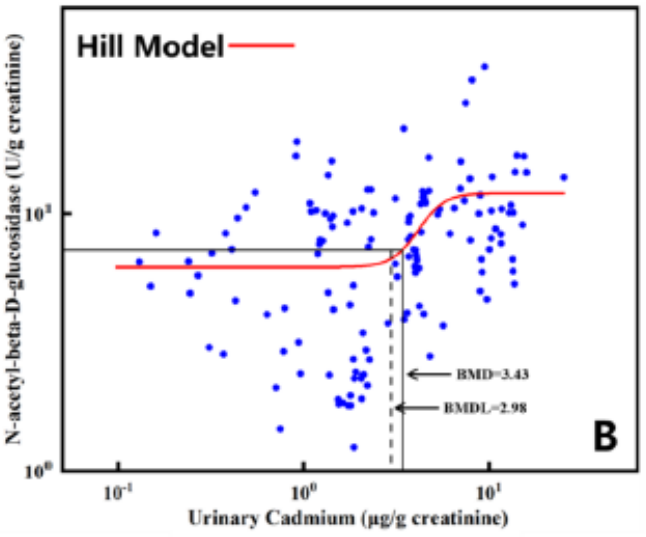
図 8 Hill モデル

JECFA 2010（from ANSES 2017）

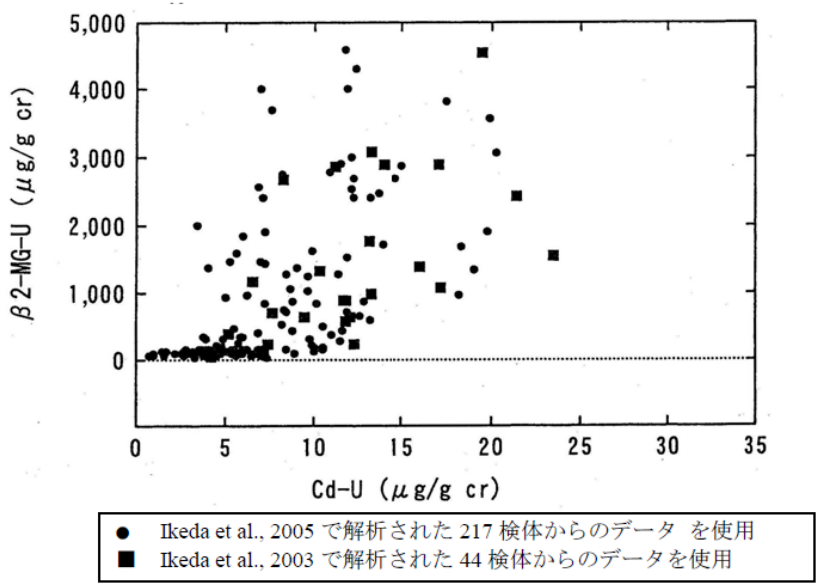


Qing et al., Env Health 2021





第2版評価書でのIkeda論文の紹介



※ Ikeda M. et al（2005）より引用（文献 8 - 2）

図 10 低レベルの尿中 β2-MG 排泄量における尿中カドミウム排泄量

Ikeda et al., Tohoku J Ext Med 2005

（両対数）

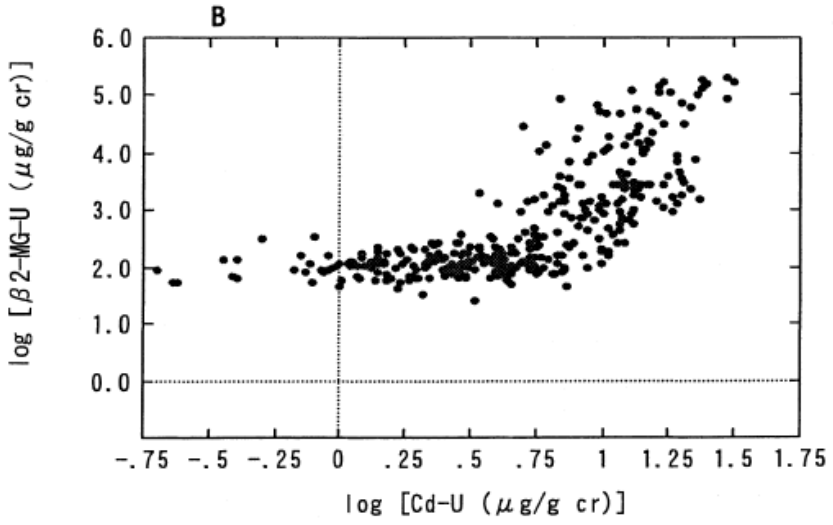


Fig. 2. Relation of β_2-MG-U_{cr} with Cd- U_{cr}, in polluted and non-polluted areas in combination (n = 345). A: Plotting on ordinary scales. B: Plotting on double-logarithmic scales.

海外でのデータには、smokerも職業的にCdに曝露された人も含まれている。日本の非汚染地域のNon-smokerの女性における尿中Cdと尿中β_2-MGのデータのみに基づいて、日本のCdの基準を決めることは可能か？特に、尿中β_2-MGが1000 μg/g Cre以下のレベルで、一般日本人のデータを解析するとどうなるか？

Ikeda et al., Biol Trace Elements Res 2006

Table 1
Possible Difference in Cd, α_1-MG, and β_2-MG Between 742 Age-Matched Pairs from Area H and Area L

Item	Unit	Forward matching[a]					Backward matching[a]				
		Area H	Area L	Δ[b]	*p*[c]	*A/B ratio*[d]	Area H	Area L	Δ[b]	*p*[c]	*A/B ratio*[d]
Creatinine	g/l	0.98	0.93	0.04	ns	1.05	0.99	0.92	0.07	<0.05	1.05
Factor G		17.7	16.3	1.4	<0.01	1.09	17.9	16.0	1.9	<0.01	1.09
Cd_{ob}	μg/l	2.4	0.6	1.8	<0.01	3.99	2.3	0.6	1.8	<0.01	3.99
Cd_{cr}	μg/g cr	2.8	0.8	2.0	<0.01	3.53	2.7	0.8	2.0	<0.01	3.53
Cd_{sg}	μg/l	2.3	0.7	1.6	<0.01	3.42	2.2	0.6	1.6	<0.01	3.42
α_1-MG_{ob}	mg/l	2.3	1.6	0.8	<0.01	1.49	2.3	1.5	0.8	<0.01	1.49
α_1-MG_{cr}	mg/g cr	2.8	2.1	0.7	<0.01	1.31	2.7	2.1	0.6	<0.01	1.31
α_1-MG_{sg}	mg/l	2.2	1.8	0.5	<0.01	1.27	2.2	1.8	0.4	<0.01	1.27
β_2-MG_{ob}	μg/l	105	88	17	<0.01	1.20	104	84	20	<0.01	1.20
β_2-MG_{cr}	μg/g cr	125	118	7	ns	1.06	122	116	6	ns	1.06
β_2-MG_{sg}	μg/l	101	98	2	ns	1.02	99	97	2	ns	1.02

Note: 42 pairs of age-matched cases were analyzed. Values for age, creatinine, and factor G are arithmetic means and values for Cd, α_1-MG and β_2-MG are geometric means (geometric standard deviations <2.5).

[a] Forward and backward matching stand for age-maching with priority for cases of ealier or later registration, respectively.

[b] Δ indicates the mean for Area H minus the mean for Area L.

[c] Probability for the difference between the 742 pairs; ns stands for $p > 0.05$ by the paired *t*-test.

[d] The ratio of the arithmetic (or geometric) mean for Area H over that for Area L.

日本の非汚染地域の中でも、尿中Cd濃度が2 μg/L以上の高い地域（Area H）と1 μg/L未満の低い地域（Area L）を比較すると、尿中β_2-MG濃度にほとんど差がなかった。

Moriguchi et al., Int Arch Occup Env Health 2010

Table 2 Cadmium levels in urine

Prefecture	Cd_{ob} (μg/l)					Cd_{cr} (μg/g cr)					Cd_{sg} (μg/l)				
	GM[a]	P[b]	GSD[a]	MED[a]	P[c]	GM[a]	P[b]	GSD[a]	MED[a]	P[c]	GM[a]	P[b]	GSD[a]	MED[a]	P[c]
Akita pref.	1.89	↑↑	2.18	1.9	↑↑	2.12	↑↑	1.88	2.23	↑↑	1.87	↑↑	1.87	1.87	↑↑
Yamagata pref.	1.10	↑↑	2.23	1.2	↑↑	1.19	NS	2.00	1.23	NS	1.04	NS	1.99	1.10	↑
Ishikawa pref.	1.75	↑↑	2.29	1.8	↑↑	1.78	↑↑	1.95	1.87	↑↑	1.65	↑↑	1.95	1.69	↑↑
Niigata pref.[d]	2.65	↑↑	2.11	2.9	↑↑	3.16	↑↑	1.87	3.25	↑↑	2.53	↑↑	1.85	2.56	↑↑
Toyama pref.[e]	1.86	↑↑	2.66	1.9	↑↑	1.98	↑↑	2.10	2.01	↑↑	1.76	↑↑	2.17	1.78	↑↑
All Japan-A[f]	0.99		2.34	1.1		1.14		1.99	1.17		0.98		2.01	1.01	

[a] *GM* geometric mean, *GSD* geometric standard deviation, *MED* median

[b] Two arrows show statistical significance of the difference from All Japan by unpaired *t*-test: ↑↑ for an increase, and NS for $P \geq 0.05$

[c] Two and one arrows show statistical significance of the difference from All Japan by Mann–Whitney test: ↑↑ with $P < 0.01$, ↑ with $P < 0.05$, and NS for $P \geq 0.05$

[e] Cited from Ezaki et al. (2003a, b)

[f] Cited from Yamagami et al. (2006)

[g] Re-calculated from Ezaki et al. (2003a, b) excluding Niigata prefecture (that is examined separately in this study) from the original 10 prefectures

日本海側の5つの県の一般住民の尿中Cd濃度は、日本全体の平均値（0.99 μg/L、1.14 μg/g Cre ）と比べるとやや高い値を示す。しかし、尿中β_2-MG濃度（Table 3、次頁）についてみると、いずれも100 μg/L、あるいは110 μg/g Cre前後であり、 日本全国との差がほとんどなかった。

Table 3 Levels of α_1-microglobulin, β_2-microglobulin and *N*-acetyl-β-D-glucosaminidase in urine

Marker	Observed value				CR-corrected value				SG-corrected value			
Prefecture	GM[a]	P[b]	MED[a]	P[c]	GM[a]	P[b]	MED[a]	P[c]	GM[a]	P[b]	MED[a]	P[c]
α_1-Microglobulin (mg/l or mg/g cr)												
Akita pref.	2.80	↑↑	2.80	↑↑	3.15	↑↑	3.15	↑↑	2.77	↑↑	2.69	↑↑
Yamagata pref.	2.15	NS	2.20	NS	2.33	↓	2.24	↓↓	2.03	↓	1.96	↓↓
Ishikawa pref.	2.52	↑↑	2.60	↑↑	2.56	NS	2.55	NS	2.38	↑↑	2.32	↑↑
Niigata pref.[d]	2.53	↑↑	2.70	↑↑	3.02	↑↑	3.11	↑↑	2.42	↑↑	2.47	↑↑
Toyama pref.[e]	2.26	NS	2.40	NS	2.41	NS	2.40	NS	2.14	NS	2.14	NS
All Japan-A[f]	2.17		2.41		2.49		2.51		2.14		2.20	
β_2-Microglobulin (μg/l or μg/g cr)												
Akita pref.	105	↑	107	NS	118	NS	110	NS	104	↑↑	100	NS
Yamagata pref.	100	NS	101	NS	108	↓	106	↓↓	94	NS	91	↓↓
Ishikawa pref.	95	NS	99	↓↓	96	↓↓	95	↓↓	90	↓↓	91	↓↓
Niigata pref.[d]	109	↑↑	110	↑↑	129	↑↑	126	↑↑	104	↑↑	99	↑
Toyama pref.[e]	97	NS	102	NS	103	↓↓	103	↓↓	92	↓↓	93	↓↓
All Japan-A[f]	99		103		113		113		97		98	
N-acetyl-β-D-glucosaminidase (unit/l or unit/g cr)												
Akita pref.	3.53		3.60		3.96		3.97		3.49		3.50	
Yamagata pref.	3.19		3.40		3.46		3.46		3.01		3.07	
Ishikawa pref.	3.47		3.80		3.54		3.53		3.29		3.33	
Niigata pref.[d]	NA[g]		NA[g]		NA[g]		NA[g]		NA[g]		NA[g]	
Toyama pref.[e]	2.66		2.90		2.84		2.82		2.52		2.57	
All Japan-A[f]	NA[g]		NA[g]		NA[g]		NA[g]		NA[g]		NA[g]	

[a] *GM* geometric mean, *MED* median

[b] One and two arrows show statistical significance of the difference from All Japan by unpaired *t*-test: ↑↑ and ↓↓ for an increase or decrease, respectively, with $P < 0.01$, ↑ and ↓ with $P < 0.05$, and NS for $P \geq 0.05$

[c] One and two arrows show statistical significance of the difference from All Japan by Mann–Whitney test: ↑↑ and ↓↓ for an increase or decrease, respectively, with $P < 0.01$, ↑ and ↓ with $P < 0.05$, and NS for $P \geq 0.05$

[d] Cited from Ezaki et al. (2003a, b)

[e] Cited from Yamagami et al. (2006)

[f] Re-calculated from Ezaki et al. (2003a, b) excluding Niigata prefecture (that showed high Cd values) from the original 10 prefectures

[g] *NA* means that data are not available

Ikeda et al., Int Arch Occup Env Health 2012

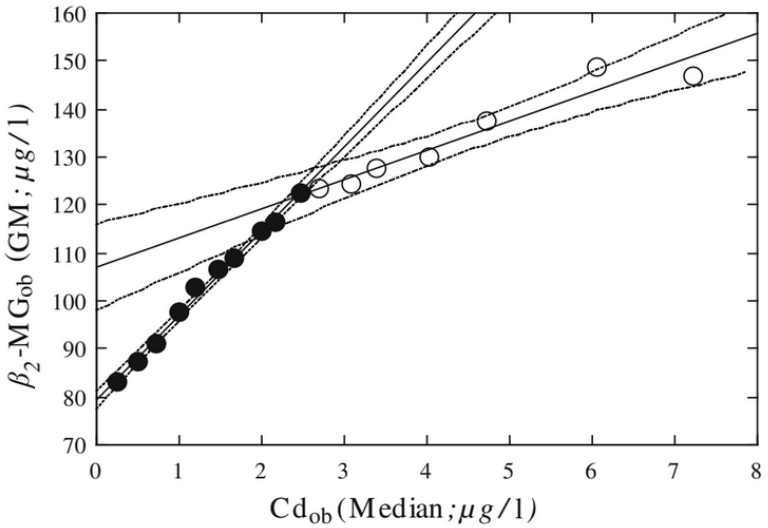


Fig. 2 The relation of cadmium (Cd) with β_2-microglobulin (β_2-MG) in urine. Two *solid lines* are regressions calculated for the regions ≤2.5 (10 *solid circles*) and > 2.5 μg Cd/l (7 *open circles*), respectively. *Curves* on both sides of the two regression *lines* show the 95% ranges for the means. Note the bending in the region of Cd$_{ob}$ ≒ 2–3 μg/l. See Table 3 for equation parameters of the two regression *lines* and the point of flexion

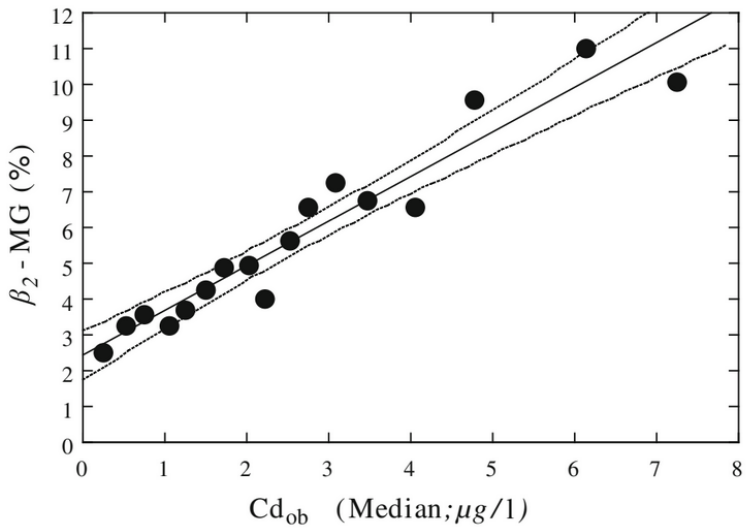


Fig. 3 The percentage of β_2-microglobulin (β_2-MG) cases that exceed the 95% tile (291 μg/l) for β_2-MG. The 95% tile was calculated for 5,306 cases in the AD-selected group. Note that Cd$_{ob}$ is about 2 μg/l when β_2-MG is at 5%. The *line* in the *middle* is a calculated regression *line*, and two *curves* on both sides show the 95% range for the mean. Each *dot* represents one case in Table 2

日本の非汚染地域のNon-smokerの女性のみを対象に、尿中Cdと尿中β_2-MGの関係を再評価した。尿中クレアチニン濃度が高齢化で低下する影響を避けるため、クレアチニン補正はしていない。 尿中β_2-MGが1000 μg/g Creを超える人はほとんどいない。尿中Cd濃度が2.3 μg/Lのあたりに傾きの分岐点（Fig. 2）がある。尿中β_2-MGが291 μg/L（分布の95%値）を超える人の割合をresponseとすると、直線的な関係があり、その割合が5%を超えるのは、尿中Cd濃度が2 μg/Lのあたり（Fig. 3）。