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A new index for evaluation of cadmium pollution in birds and mammals

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Abstract The degree of cadmium (Cd) contamination in wildlife is often used as an indicator in the environmental monitoring of Cd poisoning. However, previous studies have not clarified the correlation between levels in wildlife and levels in the environment by comparing levels among different species of animals; therefore, assessing the level of pollution in this manner is not considered a reliably accurate indicator of levels in the environment. The aim of this study was to establish a new indicator for the non-polluted warm-blooded animals, one that is not species-dependent, which will facilitate using different species for Cd monitoring. First, the previous publications regarding Cd contents in wildlife, 27 reports in which Cd contents were represented as arithmetic means and described for both kidney and liver were selected. A regression line (CSRL) between Cd contents of kidney and that of liver was obtained in a high correlation coefficient (R^2=0.943, P<0.01). The mean values from land and waterfowl, terrestrial mammals, seabirds, marine mammals, and non-polluted humans were located on the line and aligned in order. CSRL might allow an accurate determination of whether an animal is polluted by Cd. CSRL was confirmed using well-established and widely recognized pollution models such as Itai-itai patients and Cd-exposed experimental animals. The Cd contents from these models were located in different positions relative to CSRL depending on the level of contamination. Thus, this new indicator determining the Cd-pollution status of animals would be useful for environmental monitoring.

Keywords Cadmium · Biological monitoring · Wildlife

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Introduction

Cadmium (Cd) poisoning has been widely recognized as one of the serious pollution-triggered diseases, and leaking of Cd into the environment is severely restricted in many countries including Japan (Asami

Table 1 Cd contents (μg/g dry wt.) in the kidney and the liver of wildlife as reported by other authors

Species	Cd contents				References
	n	Kidney	*n*	Liver	
a. Seabirds					
Penguin					
(1) Emperor penguin	8	23.8	8	5.7	Steinhagen-Schneider 1986
(2) Ade'lie penguin	9	175	9	15.2	Steinhagen-Schneider 1986
	–	173[a]	–	19.8[a]	Schneppenheim 1981
(3) Chinstrap penguin	13	76[b]	13	7.6[b]	Norheim 1987
(4) Macaroni penguin	9	196[b]	9	35.2[b]	Norheim 1987
Procellariidae					
(5) Southern flumar	6	152[b]	6	20.4[b]	Norheim 1987
(6) Sooty shearwater	35	116.5	–	16.06	Hamanaka 1984
(7) Short-tailed shearwater	27	32.07	24	6.22	Hamanaka 1984
(8) Cory's shearwater	35	9.31	34	2.03	Stewart et al. 1996
	16	111.37	17	23.43	Stewart and Furness 1998
Laridae					
(9) Herring gull	16	13.0	23	2.01	Hutton 1981
	8	3.95	8	0.85	Leonzio et al. 1986
	7	3.75	7	0.73	Leonzio et al. 1986
	5	8.26	5	3.54	Leonzio et al. 1986
	3	4.50	3	1.91	Leonzio et al. 1986
(10) Black-headed gull	6	12.88	6	3.62	Leonzio et al. 1986
	10	17.28	10	4.20	Leonzio et al. 1986
(11) Glaucous gull	11	92[b]	11	14.4[b]	Norheim 1987
(12) Black-tailed gull	7	98.4[b]	7	13.04[b]	Lee et al. 1989
(13) Lesser black-backed gull	21	28.86	28	2.83	Stewart et al. 1996
	58	24.48	58	5.60	Stewart and Furness 1998
	18	18.92	18	4.47	Stewart and Furness 1998
Stercoriidae					
(14) South polar skua	3	179	3	26.2	Steinhagen-Schneider 1986
	3	132	3	17.3	Steinhagen-Schneider 1986
	8	100[b]	8	18.8[b]	Norheim 1987
(15) Great skua	12	81.4	12	7.52	Hutton 1981
	24	40.90	24	5.30	Stewart and Furness 1998
(16) Brown skua	8	132[b]	8	21.2[b]	Norheim 1987
Jacanidae					
(17) Oystercatcher	35	27.0	21	10.5	Hutton 1981

Alicidae					
(18) Guillmot	24	9.00	24	1.56	Stewart et al. 1994
	21	11.72	21	2.49	Stewart et al. 1994
	20	6.14	20	1.66	Stewart et al. 1994
(19) Brűnnich's guillemot	9	64[b]	9	15.6[b]	Norheim 1987
	25	59.16	25	12.99	Hamanaka 1984
(20) Tufted puffin	20	61.27	20	16.42	Hamanaka 1984
	10	62.76	10	13.49	Hamanaka 1984
(21) Horned puffin	9	34.83	7	7.15	Hamanaka 1984
(22) Crested auklet	7	18.59	6	4.42	Hamanaka 1984
(23) Least auklet	4	41.00	2	5.11	Hamanaka 1984
(24) Rhinoceros auklet	1	10.66	1	1.06	Hamanaka 1984
(25) Ancient murrelet	3	14.90	2	4.09	Hamanaka 1984
(26) Little auk	9	84[b]	9	17.2[b]	Norheim 1987
Anatidae					
(27) Eider	9	56[b]	9	17.2[b]	Norheim 1987
b. Land birds and waterfowls					
Strigidae					
(1) Tawny owl	1	1.76[b]	1	0.56[b]	Frank 1986
(2) Ural owl	1	0.6[b]	1	0.32[b]	Frank 1986
Accipitridae					
(3) Kestrel	1	4.88[b]	1	0.48[b]	Frank 1986
(4) Osprey	1	0.52[b]	1	0.12[b]	Frank 1986
(5) Honny buzzrad	1	16.4[b]	1	1.68[b]	Frank 1986
(6) Rough-legged buzzrad	1	2.48[b]	1	0.68[b]	Frank 1986
(7) Carnivore	5	0.76[b]	5	0.24[b]	Lee et al. 1989
Others					
(8) Passerine	5	9.8[b]	5	3.24[b]	Lee et al. 1989
(9) Waterfowl	21	3.28[b]	21	0.76[b]	Lee et al. 1989
(10) Cattle egret	11	0.664[b]	11	0.224[b]	Hulse et al. 1980
	6	0.196[b]	6	0.116[b]	Hulse et al. 1980
	9	4.3[b]	9	0.46[b]	Hulse et al. 1980
c. Terrestrial and marine mammals					
Strigidae					
(1) Wild mink	8	0.73	8	0.26	Harding et al. 1998
(2) Moose	796	11.6[b]	775	2.4[b]	Frøslie et al. 1986
	38	19.12[b]	57	4.72[b]	Medvedev 1999
	9	86.4[b]	9	12.52[b]	O'Hara et al. 2001
(3)Reindeer	204	22.8[b]	248	4.4[b]	Frøslie et al. 1986

Table 1 (continued)

Species	Cd contents				References
	n	Kidney	*n*	Liver	
(4)Roe deer	77	11.2[b]	77	1.6[b]	Frøslie et al. 1986
(5) Red deer	18	3.2[b]	17	0.4[b]	Frøslie et al. 1986
(6) Antelope	21	1.27	20	0.30	Munshower and Neuman 1979
(7) Deer	24	2.70	30	0.51	Munshower and Neuman 1979
(8) Horse	12	98.8[b]	12	9.6[b]	Kowalczyk et al. 1986
(9) Pig	75	0.34[b]	126	0.076[b]	Jorhem et al. 1991
	128	0.44[b]	128	0.068[b]	Jorhem et al. 1991
	136	0.44[b]	136	0.088[b]	Jorhem et al. 1991
	145	0.44[b]	36	0.080[b]	Jorhem et al. 1991
	37	0.3848[b]	38	0.0632[b]	Linden et al. 2001
	40	0.336[b]	40	0.0604[b]	Linden et al. 2001
	39	0.346[b]	39	0.06[b]	Linden et al. 2001
	38	0.3732[b]	39	0.0636[b]	Linden et al. 2001
(10) Cattle	6	1.88[b]	7	0.372[b]	Jorhem et al. 1991
	12	1.24[b]	12	0.24[b]	Jorhem et al. 1991
	11	1.52[b]	11	0.292[b]	Jorhem et al. 1991
	16	1.68[b]	3	0.192[b]	Jorhem et al. 1991
(11) Dog	7	1.32[b]	7	0.36[b]	Morita et al. 1979
	5	4[b]	5	1.16[b]	Morita et al. 1979
	7	7.96[b]	7	1.48[b]	Morita et al. 1979
(12) Mouse	8	0.36[b]	8	0.4[b]	Schroeder et al. 1967
(13) Rat	8	0.4[b]	10	0.16[b]	Schroeder et al. 1967
	8	0.4[b]	10	0.4[b]	Schroeder et al. 1967
(14) Squirrel	18	2.72[b]	18	1.88[b]	Medvedev 1999
(15) Brown bear	12	24.2[b]	15	4.48[b]	Medvedev 1999
(16) Wild boar	8	2.72[b]	9	0.64[b]	Medvedev 1999
(17) Polar bear	24	34.76[b]	24	1.88[b]	Woshner et al. 2001a
Marine mammals					
(1) Dolphin	27	194.76[b]	27	34.88[b]	André et al. 1990
(2) Striped dolphin	6	48.8[b]	6	12.12[b]	Honda and Tatsukawa 1983
	5	138.8[b]	5	29.52[b]	Honda and Tatsukawa 1983
	8	116.4[b]	8	24.68[b]	Honda and Tatsukawa 1983
	9	102[b]	9	25[b]	Honda and Tatsukawa 1983
(3) Crabeater seal	4	139.4	4	34.7	Steinhagen-Schneider 1986
	2	98.7	2	13.7	Steinhagen-Schneider 1986
(4) Weddell seal	7	174.3	7	22.7	Steinhagen-Schneider 1986

	2	114.6	2	14.9	Steinhagen-Schneider 1986
(5) Ringed seal	17	104.04[b]	17	21.08[b]	Woshner et al. 2001a
(6) Steller sea lion	21	20.92	20	2.59	Hamanaka et al. 1982
(7) Bowhead whale	48	80.08[b]	55	38.52[b]	Woshner et al. 2001b
(8) Beluga whale	45	48.6[b]	50	15.24[b]	Woshner et al. 2001b

Data was not shown in the original reports.

Waterfowl: Mallard (15), Whooper swan (2), and Whistling swan (4)

Carnivore: Japanese lesser sparrow hawk (1), Buzzard (2), and Kestrel (2)

Passerine: Pale thrush (2), Grey-backed thrush (2), and White's ground thrush (1)

[a] The original data was corrected by Steinhagen-Schneider (1986).

[b] All data was recalculated by dry wt. base when wet wt. base was adopted in the original report. The contents are represented as the mean with sample number (*n*).

2001; Friberg et al. 1974). Recently, the International Agency for Research on Cancer, World Health Organization, categorized the Cd compounds as agents probably carcinogenic to humans (WHO 1992). However, areas where Cd pollutants might cause a health hazard to the population have been spreading throughout the world (Hata 1997; Zakrzewski 1991). To verify availability for environmental monitoring, Cd content has been measured in various wildlife including plants, insects, mussels, fish, birds, mammals. Much effort has been focused on the elucidation of the causal relationship between the pollutants and the disorder (Cd poisoning). Researchers have attempted to establish the epidemiology based on various factors such as age (Honda et al. 1985, 1986; Maedgen et al.1982), sex (Burger and Gochfeld 1992; Gochfeld 1987; Hui 1998), season (Osborn 1979; Rattner and Jehl 1997), location (Dmowski 1997; Vermeer and Castilla 1991) and food habit (Ma et al. 1991; Gochfeld and Burger 1982). However, available epidemiological data have not yet clarified the interaction of these factors for the diverse range of wildlife. Furthermore, it is difficult to make a detailed comparison among different species, because the data of the non-polluted wildlife (control) are obscurity. Therefore, the assessment of contamination has usually been based on a comparison of the data obtained within a species. However, this approach might have some limitation, given that it is difficult to obtain data on the same species in different areas in the world. Extrapolations of the contamination of wildlife to humans, thus, might not provide accurate information with which to assess the effects.

The aim of this study was to establish an integrated new index available for a broad range of species, which will facilitate Cd-monitoring for the environment. This new index will be much more time- and cost-effective. Once we establish the index, the number of animals that needed for epidemiological study might be substantially reduced as a result of the ease of comparison of the degree of contamination among different areas, animals, and time periods.

For this purpose, we first reviewed previous reports regarding the Cd contamination in birds and mammals. After a selection of the data for non-polluted animals, the integrated new index was established and was verified by the well-recognized pollution models of Itai-itai disease patients and Cd-exposed experimental animals.

Materials and methods

Selection of previous references

After reviewing previous publications regarding Cd contents in mammals and birds, 27 reports in which Cd contents were represented as arithmetic means and described for both kidney and liver without any noted contamination were selected (Table 1). In addition, some references on Cd-contaminated human subjects such as Itai-itai disease patients (Friberg et al. 1974; Kuzuhara et al. 1992; Yamada et al. 1992) and Cd-contaminated rhesus monkeys (Otaki and Kimura 1992) were selected for use as established Cd-contaminated models.

Conversion of the data in wet tissue weight into values for dry tissue weight

In the previous reports, the Cd contents were reported based on wet tissue weight and/or dry tissue weight (wt.). Thus, the Cd contents based on the wet tissue wt. were converted into dry wt. values to facilitate a comparison of values among all reports. The ratios were measured using samples from 29 wild birds of six species. A portion of the kidney and the liver were removed, weighed as wet tissue weight and then dried at 70°C until the dry tissue weight reached a constant value. The obtained mean ratios (dry wt./ wet wt, n= 29) of kidney and liver were 24.8±2.2 and 28.9± 4.1%, respectively, (Table 2). There was no significant

Table 2 The comparison between the wet wt. and the dry wt

Species	Kidney			Liver		
	wet wt. (mg)	dry wt. (mg)	dry/wet (%)	wet wt. (mg)	dry wt. (mg)	dry/wet (%)
Mallard	121.1	26.1	21.6	63.2	17.9	28.3
Mallard	309.6	80.9	26.1	223.4	77.2	34.6
Mallard	425.6	100.8	23.7	384.3	133.8	34.8
Mallard	236.8	56.7	23.9	147.3	36.8	25.0
Mallard	174.6	40.7	23.3	200.5	59.4	29.6
Spotbill duck	148.2	35.3	23.8	108.3	30.7	28.3
Spotbill duck	258.1	62.8	24.3	104.0	35.0	33.7
Spotbill duck	298.3	72.1	24.2	220.4	61.0	27.8
Spotbill duck	94.4	24.6	26.1	56.8	47.4	30.2
Spotbill duck	105.0	25.9	24.7	99.6	24.7	24.8
Wigeon	210.2	52.2	24.8	189.6	51.3	27.1
Wigeon	130.0	31.5	24.2	148.3	45.3	30.5
Wigeon	224.2	60.1	26.8	112.1	36.1	32.2
Wigeon	157.0	39.8	25.4	155.0	45.7	29.5
Wigeon	137.0	36.6	26.7	183.0	56.5	30.9
Wigeon	99.3	23.2	23.4	133.5	36.4	27.3
Wigeon	59.3	15.3	25.8	112.0	30.6	27.3
Wigeon	137.3	46.5	33.9	81.7	22.1	27.1
Wigeon	183.9	48.5	26.4	138.6	32.8	23.7
Wigeon	210.6	52.6	25.0	169.6	47.2	27.8
Gadwall	203.4	50.8	25.0	107.8	33.3	30.9
Gadwall	300.5	66.3	22.1	271.9	76.8	28.2
Teal	128.5	28.4	22.1	259.1	84.4	32.6
Teal	142.0	34.9	24.6	205.2	77.7	37.9
Teal	180.7	43.2	23.9	227.5	63.7	28.0
Teal	164.7	44.3	26.9	140.8	40.8	29.0
Pintail	92.1	22.2	24.1	200.7	31.1	15.5
Pintail	105.5	24.4	23.1	108.0	30.6	28.3
Pintail	81.0	19.3	23.8	129.9	35.2	27.1
			24.8±2.2			28.9±4.1

difference between the ratio of kidney and that of liver when differences were tested for significance using Student's *t*-test. Thus, approximately 25% was employed as the conversion factor, and all Cd contents based on wet tissue wt. were multiplied by 4.

Experimental animals

Wistar male rats (n=11) of about 250 g body weight were anaesthetized with i.p. injection of sodium pentobarbital (3.0 mg/100 g body weight) and infused intravenously with $CdCl_2$ after tracheostomy. The rats were infused with 0.1, 1, or 2 mM $CdCl_2$ in a total volume of 4.0 ml saline over a 2 h period at a diminishing rate with a Harvard syringe pump to maintain serum Cd concentration at a constant level during the experiment. Details of this method have been described in other reports (Bradbury and Deane 1986; Ueda et al. 1993).

Statistics

All statistical analyses were carried out with the computer software Lotus 2001 for the regression line, the confidence intervals, and the logarithm transformation. The error was set at 0.01 or 0.05 for all statistical testes. Analysis of the statistical difference in the regression line was also carried out using Excel add-in software (Esumi, Japan).

Results

Regression of Cd contents in kidney and liver

In the present study, we selected 27 references in which Cd contents in the kidney and the liver were measured in birds and mammals of areas non-contaminated with Cd. Table 1, in which animals are

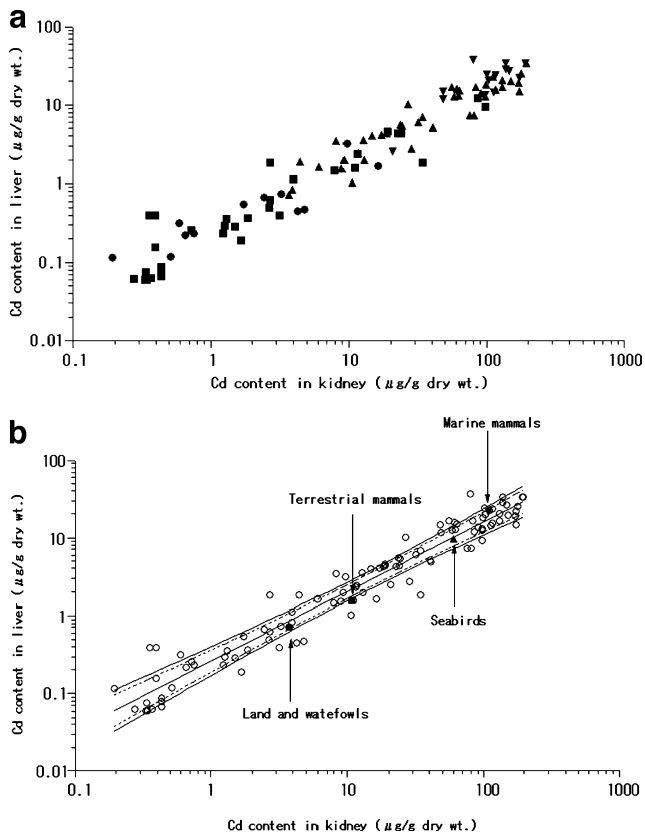

Fig. 1 **a**. The relation between the Cd content in the kidney and that in the liver from 101 data cited in Table 1. The contents were recalculated in terms of common logarithmic values. *Filled triangle*: seabirds, *filled circle*: land birds and waterfowls, *filled square*: terrestrial mammals, *inverted filled triangle*: marine-mammals. **b**. The regression line and the confidence interval from the 101 samples (*empty circle*). The *four solid symbols* represent the mean value of the corresponding categories. – : 99% ⋯: 95% Confidence interval for the population regression line

classified by species, shows the sample numbers and the mean Cd contents in the respective organs: 27 species of seabirds (Table 1a), 10 species of land and waterfowls (Table 1b), 17 species of terrestrial mammals, and eight species of marine mammals (Table 1c). The Cd contents in wet tissue wt. were converted into dry tissue wt. as described in "Materials and methods." When the Cd contents in the cortex and medulla were separately described, the values in the renal cortex were adopted.

When the 101 data cited in Table 1 were plotted on a graph as Cd contents in the liver for the abscissa and Cd content in the kidney for the ordinate, a straight line was obtained. After log transformation, a higher correlation coefficient was obtained (Y=0.902X–1.334, Y=log(y), X=log(x), R^2=0.943, p<0.01). As shown in Fig. 1a, the data of a similar group appeared in a similar area on the line. Thus, the mean values in the land birds, waterfowls, terrestrial mammals, seabirds, and marine mammals were aligned on the line (Fig. 1b). The position of the values on the line might be related to differences among species and their respective feeding habits. The 99% confidence intervals and the predicated values are also shown in

Table 3 Cd contents in the kidney and the liver of human (μg/g dry wt.)

Area	*N*	Cd content		Reference	Note
		Kidney	Liver		
The data from the human lived in non-polluted area					
England	3	54[a]	9.2[a]	Friberg et al. 1974	
Sweden	4	90[a]	5.6[a]	Friberg et al. 1974	
West Germany	11	40[a]	8.8[a]	Friberg et al. 1974	
	302 (kidney) 107 (liver)	74.2	11.3	Takács and Tatár 1987	The data referred to Iynger et al.
Hungary (male)	584	77.88	6.6	Takács and Tatár 1987	
Hungary (female)	448	50.55	6.61	Takács and Tatár 1987	
Poland (male)	45	191.6[a]	13.6[a]	Bem et al. 1993	
Poland (female)	25	158[a]	14.8[a]	Bem et al. 1993	
Poland (male)	42	212[a]	14[a]	Piotrowski et al. 1996	
Poland (female)	18	180[a]	13.6[a]	Piotrowski et al. 1996	
Japan	50	337.6[a]	46.8[a]	Kuzuhara et al. 1992	
Japan	12 (kidney) 20 (liver)	414.32[a]	75.8[a]	Teranishi et al. 1999	The mean values were calculated by authors.
The data from Itai-itai disease patients and human lived in polluted area					
Japan (female, 79 years)	1	164.4[a]	376.4[a]	Friberg et al. 1974	Gastric cancer
Japan (female, 71 years)	1	127.2[a]	472.4[a]	Friberg et al. 1974	Bronchitis
Japan (female, 60 years)	1	79.2[a]	253.2[a]	Friberg et al. 1974	Endocarditis
Japan (female, 67 years)	1	48[a]	528[a]	Friberg et al. 1974	Uremia
Japan (female, 82 years)	1	132.8[a]	90.4[a]	Kuzuhara et al. 1992	Gastric cancer in early stage
Japan (female, 87 years)	1	94[a]	132[a]	Kuzuhara et al. 1992	
Japan (female, 61–91 years)	42	108[a]	260[a]	Yamada et al. 1992	Itai-itai disease patients; 17, man under observation; 22, resident in polluted area; 3
Japan	72	162.8[a]	313.2[a]	Kuzuhara et al. 1992	

[a] The data was recalculated by dry weight base when wet weight base was adopted in the original reports.

Fig. 1b. Next, outliers in 101 data were checked. Consequently, the data from Ural owl (*Strix uralensis*) and cattle egret (*Bubulcus ibis*) in Table 1b, mouse and rat in Table 1c were decided as outliers ($P<0.05$). However, a straight regression line also obtained ($Y=0.943X–1.368$, $R^2=0.943$, $P<0.01$), when 97 data except these four data were plotted. Further, there was no significant differences between the regression lines obtained 101 data and that of 97 data except four outliers. Thus, we used all data containing outlier in this study.

Anomaly of Cd contents in Itai-itai disease patients based on CSRL

Table 3 presents a summary of Cd contents in human kidney and liver reported in England, West Germany, Hungary, Poland and Japan. In some of those cases, the Cd contents in the kidney are conversions of those reported in the renal cortex and the renal medulla. Although, in one report, a factor of 1.5 was employed to convert the contents in the whole kidney to values in the renal cortex(Geldmacher-v Mallinckrodt and Opitz 1968), the Cd contents in the renal cortex in wildlife (i.e., without conversion) did not deviate from the CSRL in the present report. The Cd contents in the renal cortex were, therefore, adopted as that in the kidney, and they were superimposed on the CSRL (Fig. 2). Line a show the regression based on the results derived from the humans living in a polluted area.

Relationship between CSRL and the regression line from experimental animals

The Cd contents in the kidney were markedly higher than those in the liver (Otaki and Kimura 1992) of 14-year-old parous female rhesus monkey fed with a diet containing 30 ppm $CdCl_2$ for a period of 5–26 months (Tanioka et al. 1992). The Cd contents in the kidney and liver reported in that reference are plotted in Fig. 3. The values from the non-contaminated monkey remained relatively low and located at a position similar to that of the non-contaminated human, although they lay outside the confidence interval on CSRL. The values after the 5-month treatment with the Cd-supplemented diet, however, were higher than the highest value in seabirds, and the slope became significantly steeper ($P<0.01$) than that of CSRL.

Discussion

The Cd contents in the kidney and liver obtained from the wildlife were in the range of 0.196–196 and 0.06–38.52 μg/g dry tissue wt., respectively. The Cd contents in seabirds and marine mammals appeared to be generally higher than those in the land birds, waterfowls, and terrestrial mammals. Among these animals, the highest contents were observed in kidney of macaroni penguin and liver of bowhead whale, in which the Cd contents in the kidney and liver were

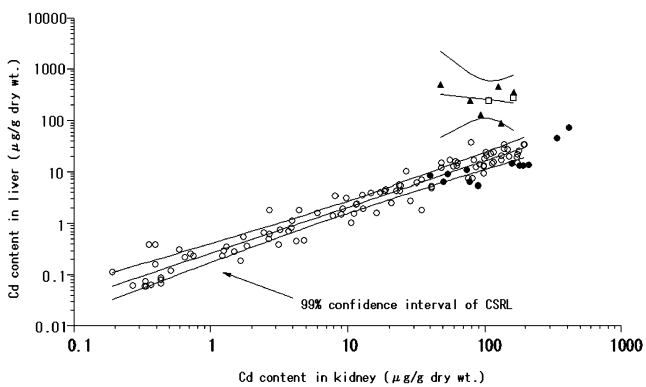

Fig. 2 The relation between CSRL and the values obtained from contaminated humans. The regression line a and the 99% confidence interval was obtained from Itai-itai disease patients and humans who lived in a polluted area. *Empty circle*; 101 data for CSRL, *filled circle*; humans who lived in a non-polluted area, *filled triangle*; Itai-itai disease patients, *empty square*; humans who lived in a polluted area

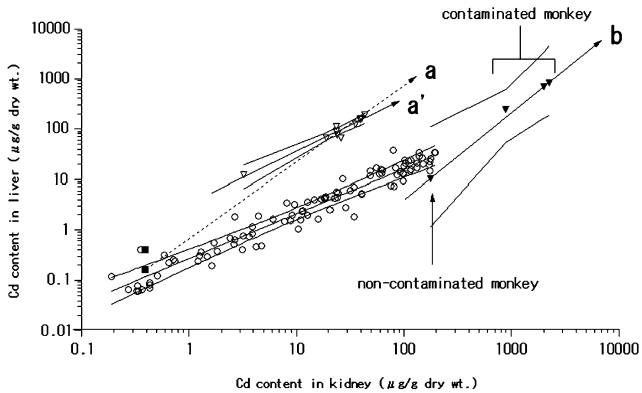

Fig. 3 The relation between CSRL and the values obtained in contaminated experimental animals. The lines a and b with each 99% confidence interval show the regression lines from rat and monkey, respectively. *Filled circle*; 101 data for CSRL, *inverted filled triangle*; rhesus monkey, *inverted empty triangle*; rat, *filled square*; rat (Control)

196 and 38.52 μg/g dry tissue wt., respectively. Several reports have pointed out the much higher Cd level in the organs of seabirds and marine mammals (Bunyan and Stanley 1982; Hamanaka 1984; Elinder 1992).

On the other hand, the Cd contents in animals reared under a diet in which Cd was well controlled are generally low, and have been reported to be less than 1 μg/g wet tissue wt. (4 μg/g dry tissue wt.) in both the kidney and liver (Richardson et al. 1974; White and Finley 1978). In neonatal animals, the contents in both organs were less than 20 ng/g wet tissue wt.; this is due to the presence of the placenta as an effective barrier in the maternal environment and the short period of exposure to Cd after birth (Henke et al. 1970). The biological half-life of toxicity of Cd is relatively long, and has been estimated as 100 days after abdominal injection of ^{109}Cd in mice (Cotzias et al. 1961) and 260–500 days after intravenous injection of ^{115}Cd in dogs (Burch and Walsh 1959), although the durations were different depending on the loaded burden, length of the observation, and the method of administration (Friberg et al. 1974). The Cd contents in kidney and liver have been reported to increase with age in wild birds (Frank 1986; Hutton 1981; Maedgen et al. 1982), in marine mammals (Hamanaka et al. 1982; Honda and Tatsukawa 1983) and in terrestrial mammals (Elinder et al. 1981; Kowalczyk et al. 1986) However, it is usually difficult to estimate the age of wild animals, especially for avian species, and scarcely any descriptions of age appear in most of the reports cited in Table 1. This fact, together with the long biological half-life of Cd, suggests the possibility that the estimation of Cd contamination is not always accurate, when comparison was made with the standard values without the information on the duration of exposure.

Metallothionein, Cd-binding protein, is known to be involved in Cd metabolism in the liver and kidney (Groten and van Bladeren 1994). Therefore, the relationship between Cd contents in the kidney and liver were investigated, and then we obtained significant correlation between Cd contents of kidney and that of liver.

There are several papers in which the ratio or the regression line of the Cd contents in kidney and liver was calculated (Groten et al. 1991; White and Finley 1978). The Cd contents in renal cortex and liver reached a maximum of approximately 400 and 450 μg/g wet tissue wt., respectively, after the subcutaneous administration of Cd chloride (0.25 mg/kg) to rabbit. The continuous exposure resulted in a plateau and a subsequent decline (Axelsson and Piscator 1966). In rat, a linear increase was observed until the equilibrium states of 200–300 and 350 μg/g wet tissue weight in kidney and liver, respectively, after a 0.75 mg/kg intraperitoneal injection of Cd silver nitrate (Bonnell et al. 1960). Similar correlations and regressions between Cd contents in liver and kidney were observed in wildlife such as fulmar (*Flumarus glacialis*) and southern fulmar (*Flumarus glacialoides*) (Norheim 1987) oystercatcher (*Haematopus ostralegus*) and great skua (*Chatharacta skua*) (Hutton 1981), and ducks (Mochizuki et al. 2002). The linearity of the regression line was lost when the Cd contents in

kidney and liver exceeded the toxic level in the white-tailed ptarmigan (*Lagopus leucurus*) living in the ore belt of the Colorado mountains (Larison et al. 2000). Further, a significant correlation (R^2=0.831, P<0.001) has been observed between Cd contents in the renal cortex and those in the liver of humans who lived in non-polluted areas, though no correlation and regression were found for patients of Itai-itai disease and humans who had lived in a polluted area (Yamada et al. 1992). Neither Larison et al. 2000 nor Yamada et al. 1992 found any correlation between Cd contents in the liver and those in the kidney at the Cd-poisoning level. The single order of regression line obtained in the present study appears to be reasonably accurate. When metallothionein involvement in the Cd metabolism is considered; it is in good agreement with findings in previous studies (Groten and van Bladeren 1994; Friberg et al. 1974; Scheuhammer 1988). Thus, this regression line, hereafter called the Cd standard regression line (CSRL), might be a useful control to determine non-pollutedness in animals.

Next, we examined the data of non-polluted and polluted humans and experimental animals for fitting to the CSRL to confirm its usefulness. The levels obtained in humans who lived in a non-polluted area were considerably higher than the mean value of the terrestrial mammals, and closer to those of seabirds and marine mammals. A biological half-life of Cd is long, thus, higher Cd contents have been obtained from the animals with long life spans such as seabirds and marine mammals. As shown in Table, the use of data obtained from aged human is reason for high Cd contents in organs. However, those values (i.e., of humans) located within the 99% confidence interval of CSRL. In contrast, the values in humans from a polluted area and those in the Itai-itai disease patients largely deviated from the 99% confidence interval of CSRL. The regression line a showed a rather negative correlation between the Cd contents in liver and those in the kidney, while the correlation coefficient was not significant, and obviously differed from the CSRL. The Cd contents in the tissues from patients and workers exposed to Cd have been reported to be lower in the kidney and higher in the liver than those of non-polluted humans (Friberg et al. 1974; Kuzuhara et al. 1992), supporting these relationships in the regression lines.

The calculated Cd ratios between the human kidney and liver have been estimated as 6.9 and 12.6 in persons 40–59 years old Japanese living in Kanazawa area and Kobe areas, respectively, and as 5.5 for persons in this age group in Sweden in previous reports (Friberg et al. 1974). These ratios could be recalculated as 0.145 (Kanazawa), 0.079 (Kobe), and 0.182 (Sweden) in terms of the slope for the regression line. The value derived from the Kobe area in Japan was almost the same, and those from the Kanazawa area in Japan and Sweden, respectively, were slightly higher (0.088) than the CSRL though considerably lower than that of the Itai-itai disease patients.

These observations suggested that the Cd contents of Japanese and Swedish subjects had ratios that fell within the confidence interval of CSRL. However, further experimental verifications would be required to propose the hypothesis that the deviation from the CRSL and the confidence interval are actually related to exposure to Cd and Cd poisoning. Subsequent attempts at such verifications used the results of experimental animals in previous reports and our experimental results in rat. The Cd content values reported for the monkey receiving the 26-month treatment were remarkably high in the organs; histopathologic changes in the kidney were observe as ischemia in glomerulus, cloudy swelling of the major tubular epithelium in the renal cortex, degeneration and exfoliation in the tubular epithelium in the renal cortex and medulla, and hemorrhage in the renal tubules (Suzuki and Kaharada 1992). Similar results have been reported in response to an intracardiac injection of ^{115}Cd in rats (Gunn and Gould 1957) and an intravenous injection of ^{115}Cd chloride in dogs (Burch and Walsh 1959). Although the Cd contents in the respective livers of the rats and dogs in these studies were higher than those in the kidneys during the early period of the exposure, the levels in rats were equivalent in the two organs at 1 month after the administration, and the level in dog kidney became 50–100% of the level in the liver 20–30 days after the administration. These results were obtained from a prolonged experiment. In both investigations, the slopes expected from the Cd contents in the kidney and liver were obviously changed, although the histological observations were not described (Burch and Walsh 1959; Gunn and Gould 1957). In the former rhesus monkey (26 months treatment), the histological change and the change in the slope together might allow us to assert that Cd poisoning was established by 5 months after the Cd-administration, though the level

of poisoning was milder than that in Itai-itai disease patients.

On the other hand, even at 14 days after an intravenous injection of ^{109}Cd (0.04 mg/head), the Cd content in goat liver was about three-times higher than that in the kidney (Miller et al. 1968). The Cd distribution considerably varies depending on the dosage and the time course in the experiments of Cd administration.

We designed the experiment to confirm the usefulness of CSRL after a short period of infusion of high concentration Cd to Wistar rats. The Cd content in liver was higher than that in kidney. The values obtained are also superimposed in Fig. 3. Because the values obtained from the non-contaminated rats were not detectable, the data by Schoreder et al. (1967) was employed as the non-contaminated value. The value of the non-contaminated rats was located within the 99% confidence interval for the population regression line of the CRSL at the low level near the origin. The values and the slope of the regression line derived from rats treated with Cd were obviously far outside ($P<0.01$) the interval of CSRL, although the incline of the slope was almost the same as that of CSRL (line a). The slope became significantly steeper when the data integrated the contaminated and non-contaminated values (line a'). These results might be a model for exposure to a high concentration of Cd over a short period of time. A previous report on goat (Miller et al. 1968) appears to support the present results in rats.

In the present study, we attempted to establish an indicator of non-polluted animals in order to facilitate environmental monitoring, and successfully determined the CSRL. Because the conditions of these experimental administrations can be standardized the contamination situation can be clearly understood. However, using wildlife for environmental monitoring, as remarked earlier herein, presents difficulties. The CSRL in the present study represents the integration of 101 points from 27 references. The mean values for the non-contaminated humans are also located on the CSRL. Further, the usefulness of CSRL was confirmed by epidemiological reports on human Itai-itai disease patients and on experimental animal models. These results suggest that the pollution conditions of species of wildlife can be recognized by comparison with CSRL. Further, use of this indicator would contribute to decrease the number of animals needed for biological monitoring using wildlife, because the degrees of contamination would be comparable among different areas, animals, and time periods. Thus, we believe that this new indicator, CSRL, will be useful for distinguishing between polluted and non-polluted animals, and therefore for environmental monitoring.

To further establish the usefulness of CSRL in environmental monitoring, we are continuing to investigate the presence/absence of contamination in wild birds.

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