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Estimation of cumulative cadmium intake causing Itai–itai disease

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Abstract

This study was undertaken to estimate the amount of cadmium (Cd) exposure needed for the development of Itai–itai disease. The investigated subjects comprised 82 Itai–itai disease patients and 11 persons requiring observation who were admitted in 1977 and 1978 for medical testing. With the period when the Itai–itai disease patients started to perceive leg/back pain defined as the 'mild disease onset', and the period when they experienced the most severe manifestations such as ambulatory disturbance and bone fractures defined as 'severe disease onset'. Relative cumulative person number distribution according to life time cadmium intake (LCD) at mild disease onset, severe disease onset, and time of death was depicted as an sigmoid curve and the establishment of probit regression lines was demonstrated between them. LCD at the time when mild disease onset and severe disease onset were recognized in half of the Itai–itai disease patients was 3.1 and 3.8 g, respectively. Furthermore, LCD at the time when mild disease onset and severe disease onset were recognized in 5% of the Itai–itai disease patients was calculated to be 2.6 and 3.3 g, respectively. The present results clarify that Itai–itai disease, the most severe stage of chronic Cd poisoning, occurs at levels of Cd consumption amounting to approximately three-fold of those currently seen in Japan.

Keywords: Itai–itai disease; Amount of cadmium exposure; Life time cadmium intake; Probit regression line

1. Introduction

Itai–itai disease, which developed in numerous inhabitants of the Jinzu River basin in Toyama Prefecture, is the most severe form of chronic cadmium (Cd) poisoning caused by prolonged oral Cd ingestion. The characteristic clinical picture of Itai–itai disease shows renal injury manifested by tubular and glomerular dysfunction and bone injury consisting of a combination of osteomalacia and osteoporosis. Femoral pain and lumbago are frequently seen as the initial manifestation, after which painful sites gradually spread all over the body. Pressure on bones such as femur, backbone, and ribs produces further pain. This state continues for several years until a sprain or other minor trauma causes a disturbance in walking. Clinical conditions progress rapidly once the patient is bed-ridden. Bone fractures

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can be caused by the slightest external pressure, such as coughing, and skeletal deformities develop. Serum and hematological findings include elevated serum alkaline phosphatase, decreased serum Ca and inorganic P and moderate/severe anemia while the urinary findings characteristically include increased excretion of low molecular weight proteins, glucose and amino acids (Nogawa, 1981). The clinical course of all Itai–itai disease patients and persons requiring observation was examined as the research project conducted by the Research Committee for Itai–itai Disease organized by the Japan Environment Agency from 1989. The clinical course of 13 cases showed that renal tubular dysfunction had deteriorated culminating in end-stage renal failure. After the serum creatinine exceeded 2.5 mg/dl death ensued in 3–4 years (Kasuya, 1999).

Its cause has been clarified to be environmental Cd pollution originating from effluent from a zinc mine located in the upper reaches of the river, with the inhabitants thereby exposed developing severe chronic Cd poisoning. In Japanese Cd-polluted areas, 50%–70% of the amount of Cd ingested orally derives from rice, and in practice a close association has been reported between the prevalence of Itai–itai disease and the Cd concentration in rice (Fukushima et al., 1974; Ogawa et al., 2004). The long-term Cd intake is an important factor determining the development of Itai–itai disease, but until now no study has estimated the amount of Cd exposure needed for the development of Itai–itai disease. As basic information regarding Cd toxicity from the viewpoint of its influence on the human body and the devising of prophylactic countermeasures, knowledge of the amount of Cd exposure needed for the development of Itai–itai disease is of extreme importance. With this in mind, this study was undertaken to estimate the amount of Cd exposure needed for the development of Itai–itai disease based on a detailed determination of the residence history of individual Itai–itai disease patients and estimates of the amount of their environmental Cd exposure.

2. Materials and methods

2.1. Study subjects and their residence history

Itai–itai disease patients and persons requiring observation were diagnosed by the Differential Diagnosis Committee on Itai–itai Disease and Cadmium Poisoning established by the Toyama Prefecture Health Authority. The diagnostic criteria for Itai–itai disease were based on the notification by the Japan Environment Agency in 1972. There were four diagnostic criteria: (1) subjects have to have a residence history in a heavy Cd-polluted area for a certain period and have a history of exposure to Cd, (2) conditions (3) and (4) are not congenital, (3) existence of renal tubular dysfunction, (4) existence of osteomalacia and osteoporosis which were demonstrated by bone X-ray or bone biopsy. Subjects who satisfied all of these four conditions were diagnosed as Itai–itai disease patients. Subjects who did not show clear bone changes (osteomalacia) were classified as persons requiring observation. All of the study subjects in the present study were diagnosed and recognized by the Committee. The sampling method for the population under study was shown in Fig. 1. Up to 2004 the number of recognized patients amounted 188 (3 men and 185 women) and the number of subjects requiring observation 256 (46 men and 210 women). Of 60 Itai–itai disease patients and 9 persons requiring observation who were admitted in 1977 and 1978 for medical testing to Kanazawa Medical University Hospital or Toyama Prefectural Central Hospital, 60 of the former and 7 of the latter whose residence history was clear and for whom the Cd concentrations in rice in the present and previous hamlets of residence were known were selected as subjects for analysis at the mild disease onset and severe disease onset. Similarly, 82 Itai–itai disease patients and 11 persons requiring observation whose residence history was clear and for whom the Cd concentrations in rice in the present and previous hamlets of residence were known were selected as subjects for analysis at the time of death. These subjects analyzed at death included some whose clinical symptomatic course had been unclear. All of the Itai–itai disease patients and persons requiring observation were women. The Itai–itai disease patients focused on here were all recognized by 1977, up to which time no particular changes had been made in their living environment that would affect the status of Cd pollution such as removal of Cd-polluted rice paddy soil.

In the case of the Itai–itai disease patients the residence history was determined from materials available at public offices from resident lists which were examined by the Itai–itai Disease Countermeasures Council.

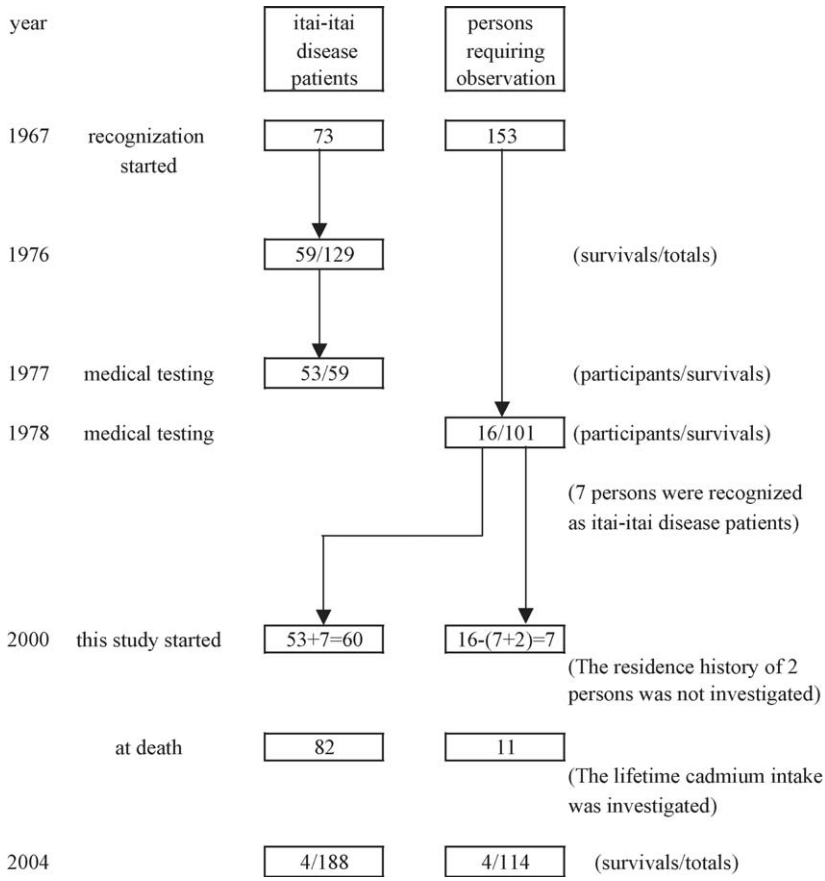

Fig. 1. Flowchart of numbers of itai–itai disease patients and persons requiring observation under the study.

In the case of the persons requiring observation it was determined from questionnaires conducted in the Jinzu River basin in 1967 and 1968 at the time of mass health screening examinations (age ≥30 years, men 6155, women 7028, total 13,183 persons, participation rate 90.3%). The dates of birth and death of both the Itai–itai disease patients and persons requiring observation were determined from materials of the Itai–itai Disease Countermeasures Council.

Ages at mild disease onset and severe disease onset were determined by direct questioning of the Itai–itai disease patients and persons requiring observation who were admitted in 1977 and 1978 at Kanazawa Medical University Hospital or Toyama Prefectural Central Hospital. Age at mild disease onset corresponded most frequently to the age at which the patient started to perceive leg/back pain, and age at severe disease onset to that at which the patient experienced the hitherto severest pain, associated especially in the Itai–itai disease patients with disturbed ambulation and/or bone fractures. These records were verified in the medical charts in the hospital. For each individual, time of mild disease onset, severe disease onset, time of death and lifetime Cd intake (LCD) in each time were shown in Table 1.

2.2. Method of calculation of lifetime Cd intake (LCD)

The method used to calculate LCD was based essentially on the formula devised by Nogawa et al. (1989). LCD (g) of the Itai–itai disease patients and persons requiring observation was calculated by the following three methods according to residence history. In

Table 1
Year at mild disease onset, severe disease onset, and death, and lifetime cadmium intake in each itai–itai disease patient and person requiring observation (all women)

Subjects		At mild disease onset		At severe disease onset		At death	
Type	No	Year	LCD (g)	Year	LCD (g)	Year	LCD (g)
1	1	1926	1.250	1955	2.351	1982	3.377
1	2	1932	1.004	1958	1.675	1989	2.475
1	3	1935	1.184	1968	3.200	1985	4.178
1	4	1937	2.946	1942	3.409	1987	7.583
1	5	1939	2.025	1942	2.274	1981	5.512
1	6	1940	3.760	1967	6.725	1977	7.822
1	7	1940	2.374	1967	5.043	1986	6.921
1	8	1943	2.315	1947	2.584	1984	5.003
1	9	1944	2.117	1967	3.943	1988	5.609
1	10	1945	3.901	1968	7.154	1983	9.276
1	11	1945	2.565	1969	4.003	1984	4.901
1	12	1945	2.314	1968	3.523	1985	4.364
1	13	1945	2.582	1968	4.408	1990	6.154
1	14	1947	2.575	1947	2.575	1983	4.731
1	15	1949	2.304	1965	3.145	1979	3.829
1	16	1949	2.279	1968	3.510	1982	4.416
1	17	1950	3.603	1961	4.395	1984	5.981
1	18	1950	1.154	1967	2.048	1985	2.941
1	19	1950	3.255	1965	5.176	1985	7.609
1	20	1951	3.827	1956	4.468	1994	9.205
1	21	1952	4.843	1967	6.764	1977	8.044
1	22	1952	2.958	1962	3.800	1984	5.653
1	23	1952	3.519	1954	3.655	1985	5.708
1	24	1953	2.800	1955	2.956	1987	5.457
1	25	1954	4.249	1963	4.941	1979	6.095
1	26	1954	2.697	1968	3.330	1989	4.236
1	27	1954	2.824	1956	2.980	1989	5.559
1	28	1954	0.780	1967	1.242	1991	2.095
1	29	1955	3.626	1965	4.274	1982	5.310
1	30	1955	4.722	1956	4.811	1984	7.306
1	31	1955	2.157	1959	2.431	1985	4.209
1	32	1955	2.650	1962	3.078	1994	5.033
1	33	1956	1.145	1967	1.389	1983	1.721
1	34	1957	3.327	1957	3.327	1983	5.037
1	35	1958	1.527	1968	1.785	1979	2.068
1	36	1958	3.192	1967	4.016	1981	5.297
1	37	1959	3.520	1977	4.598	1987	5.137
1	38	1959	2.976	1959	2.976	1991	5.587
1	39	1960	3.808	1963	3.998	1979	4.951
1	40	1960	2.587	1973	3.476	1980	3.887
1	41	1960	1.439	1964	1.562	1983	2.145
1	42	1960	3.251	1970	3.886	1985	4.840
1	43	1960	2.126	1960	2.126	1993	3.342
1	44	1961	1.910	1962	1.946	1984	2.728
1	45	1961	1.763	1967	2.144	1989	3.478
1	46	1962	3.438	1968	3.907	1990	5.548
1	47	1963	5.097	1963	5.097	1977	6.327
1	48	1963	5.139	1963	5.139	1977	6.932
1	49	1963	3.923	1971	4.538	1982	5.384
1	50	1963	3.354	1967	3.623	1986	4.832
1	51	1964	4.636	1965	4.703	1981	5.711
1	52	1965	5.702	1965	5.702	1977	6.771
1	53	1965	3.789	1965	3.789	1980	4.627
1	54	1965	1.651	1966	1.677	1981	2.038
1	55	1965	3.472	1968	3.706	1992	5.582
1	56	1966	3.713	1966	3.713	1977	4.312
1	57	1973	2.502	1974	2.537	1984	2.893
1	58	1974	3.668	1978	4.063	1994	5.546
1	59	1955	3.603	1965	4.323		
1	60	1973	2.346	1975	2.466		
1	61					1980	4.033
1	62					1980	9.806
1	63					1980	10.855
1	64					1982	5.299
1	65					1982	5.708
1	66					1983	4.649
1	67					1983	5.449
1	68					1984	3.697
1	69					1985	2.922
1	70					1986	2.217
1	71					1986	4.444
1	72					1986	4.645
1	73					1986	4.728
1	74					1986	4.788
1	75					1987	6.462
1	76					1987	7.559
1	77					1989	9.171
1	78					1990	1.880
1	79					1992	4.691
1	80					1992	6.077
1	81					1995	7.659
1	82					1996	2.974
1	83					1996	7.794
1	84					1997	6.227
2	1	1945	2.342	1940	1.951	1982	5.155
2	2	1949	2.150	1963	2.647	1979	3.181
2	3	1953	1.329	1972	2.467	1984	3.185
2	4	1953	2.507	1969	3.310	1985	4.112
2	5	1963	3.027	1972	3.730	1988	4.981
2	6	1967	5.479	1973	5.977	1985	6.973
2	7	1967	5.584	1967	5.584	1987	7.414
2	8					1981	5.541
2	9					1983	6.396
2	10					1983	9.459
2	11					1985	1.917

Type 1: itai–itai disease patient; type 2: person requiring observation.

addition, subsequent to the release of the opinion of the Japanese Ministry of Health and Welfare in 1970, LCD(1) and LCD(2) were calculated based on the respective assumption that either after 1970 Cd-contaminated rice continued to be consumed or that after 1970 Cd-non-contaminated rice was consumed.

1. In the case of persons living in the present hamlet of residence since birth
   (1) (mean rice Cd concentration in present hamlet of residence × 333.5 + 34) × 365 × number of years of residence in hamlet (=age)/10^6
   (2) {(mean rice Cd concentration in present hamlet of residence × 333.5 + 34) × age in 1970 + 50 × (age − age in 1970)} × 365/10^6
2. In the case of persons moving from a non-polluted area
   (1) {(50 × age at move) + (mean rice Cd concentration in present hamlet of residence × 333.5 + 34) × (age − age at move)} × 365/10^6
   (2) {(50 × age at move) + (mean rice Cd concentration in present hamlet of residence × 333.5 + 34) × (age in 1970 − age at move) + 50 × (age − age in 1970)} × 365/10^6
3. In the case of persons moving from a polluted area
   (1) {(mean rice Cd concentration in hamlet of birth) × 333.5 + 34} × age at move + (mean rice Cd concentration in present hamlet of residence × 333.5 + 34) × (age − age at move)} × 365/10^6
   (2) {(mean rice Cd concentration in hamlet of birth) × 333.5 + 34} × age at move + (mean rice Cd concentration in present hamlet of residence × 333.5 + 34) × (age in 1970 − age at move) + 50 × (age − age in 1970)} × 365/10^6

   333.5 g is the mean daily rice intake of inhabitants of Ishikawa Prefecture. Thirty-four micrograms is the mean daily intake of Cd from sources other than rice in the Kakehashi River basin, and 50 μg is the mean daily total intake of Cd in Japanese non-Cd-polluted areas.

   Cd concentrations in rice were based on investigations carried out by Toyama Prefecture from 1971 to 1976 in which rice paddies in the entire Jinzu River basin were divided into about 2500 lots measuring 2.5 ha each, from the center of which standing rice was collected. Cd concentrations in a total of 2446 samples were then classified according to hamlet and the calculated mean values adopted. Mean Cd concentrations in rice in the hamlets were 0.02–1.06 ppm, with the number of samples per hamlet ranging from 5 to 145.
4. LCD of control subjects was calculated as 50 μg × age × 365 days/10^6.

3. Results

Table 2 lists age at the mild disease onset, severe disease onset, and death as well as geometric mean, geometric standard deviation, and minimum and maximum values of LCD(1) and LCD(2) based on the results of interviews of the Itai–itai disease patients and persons requiring observation who were admitted for medical testing in 1977 and 1978, data of the Itai–itai Disease Countermeasures Council, and screening questionnaire of the entire Jinzu River basin. As compared to the mild disease onset, at severe disease onset the Itai–itai disease patients and persons requiring observation were respectively a mean of 9.5 and 8.4 years older, with the respective LCD(1) value in the Itai–itai disease patients and persons requiring observation increased by 0.7 and 0.5 g, and the respective LCD(2) value by 0.6 and 0.4g. In both the Itai–itai disease patients and persons requiring observation geometric mean, and minimum and maximum values of LCD(1) and LCD(2) at the mild disease onset and severe disease onset were virtually the same. Accordingly, the subsequent analysis of the mild disease onset and severe disease onset was limited to LCD(1). At the time of death LCD(1)(2) in the Itai–itai disease patients were 4.8 and 4.1 g, respectively, and in the persons requiring observation 4.9 and 4.2 g, respectively, with the two groups showing similar levels. Since LCD(1) at the time of death exceeded LCD(2) by 0.7 g in both the Itai–itai disease patients and persons requiring observation, subsequent analysis at the time of death was performed using both LCD(1)(2).

Fig. 2 shows the distribution of the number of Itai–itai disease patients according to LCD at the time of mild disease onset, severe disease onset, and death(1)(2).

Fig. 3 shows the respective relative cumulative person number distribution according to LCD. Relative cumulative person number distribution according to

Table 2
Lifetime cadmium intake of Itai–itai disease patients and persons requiring observation (all women) admitted in 1977, 1978 at mild disease onset, severe disease onset, and death

	No. of persons	Mean value[a]	S.D.[a]	Minimum value	Maximum value
Itai–itai disease patients					
At mild disease onset					
Age	60	48.9	10.2	28	70
LCD(1) (g)	60	2.7	1.5	0.8	5.7
LCD(2) (g)	60	2.7	1.5	0.8	5.7
At severe disease onset					
Age	60	58.4	9.2	36	80
LCD(1) (g)	60	3.4	1.5	1.2	7.2
LCD(2) (g)	60	3.3	1.5	1.2	7.2
At death					
Age	82	78.9	7.2	61	97
LCD(1) (g)	82	4.8	1.5	1.7	10.9
LCD(2) (g)	82	4.1	1.5	1.7	9.6
Persons requiring observation					
At mild disease onset					
Age	7	51.9	8.2	42	66
LCD(1) (g)	7	2.9	1.6	1.3	5.6
LCD(2) (g)	7	2.9	1.6	1.3	5.6
At severe disease onset					
Age	7	60.3	10.4	38	72
LCD(1) (g)	7	3.4	1.5	1.9	5.8
LCD(2) (g)	7	3.3	1.5	1.9	5.8
At death					
Age	11	77.6	5.0	70	84
LCD(1) (g)	11	4.9	1.5	1.9	9.5
LCD(2) (g)	11	4.2	1.5	1.7	7.9

[a] Age is expressed as calculated mean and standard deviation values. Other values are expressed as geometric mean and standard deviation values. LCD(1): calculated assuming that after 1970 as well Cd-polluted rice was consumed (according to Ministry of Health). LCD(2): calculated assuming that after 1970 as well Cd intake was the same as that of non-Cd-polluted areas (exchanged rice) (according to Ministry of Health). In-patient testing: Performed in 1977, 1978 at Kanazawa Medical University or Toyama Prefectural Central Hospital. Mild disease onset: year in which patient first perceived leg/back pain. Severe disease onset: year in which patient perceived hitherto severest pain.

Table 3
Probit regression analysis of distribution of the relative cumulative number of itai–itai disease patients (all women) admitted in 1977 according to lifetime cadmium intake at mild disease onset, severe disease onset, and at death

	Regression equation[a]
At mild disease onset	$Y = 0.9229X - 2.3577$
At severe disease onset	$Y = 0.8153X - 2.6228$
At death(1)	$Y = 0.6031X - 2.7618$
At death(2)	$Y = 0.5546X - 2.7008$

Y = PROBIT(p), X = LCD.

LCD at mild disease onset, severe disease onset, and time of death(1)(2) formed in each case an S-curve, with probit regression analysis demonstrating linearity.

The probit regression equations are shown in Table 3. Table 4 shows values of LCD, Cd concentration in rice and daily Cd intake at the time of mild disease onset, the severe disease onset and death were recognized in 50% or 5% of Itai–itai disease patients. LCD of relative cumulative person number 0.5 (50% value) was 3.1 g at the mild disease onset, 3.8 g at severe disease onset, and 5.4 g at the time of death (LCD(1)). Moreover, LCD of relative cumulative person number 0.05 (5% value) was 2.6 g at the mild disease onset, 3.3 g at severe disease onset, and 4.7 g at the time of death.

4. Discussion

We calculated LCD using the present formulae with regard to inhabitants of the Cd-polluted Jinzu River

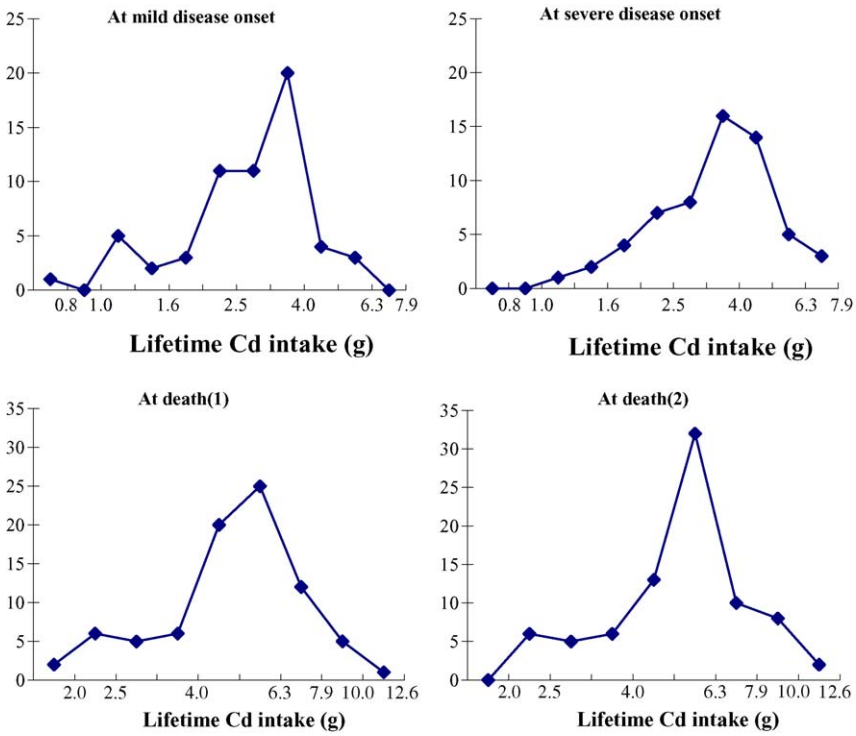

Fig. 2. Number of itai–itai disease patients (all women) admitted in 1977, according to lifetime cadmium intake at mild disease onset, severe disease onset, and death. At death(1): calculated assuming that after 1970 as well Cd-polluted rice was consumed (according to Ministry of Health). At death(2): calculated assuming that after 1970 as well Cd intake was the same as that of non-Cd-polluted areas (exchanged rice) (according to Ministry of Health).

basin in Toyama Prefecture and Kakehashi River basin in Ishikawa Prefecture, confirmed the presence of a dose–response relationship between it and the development of renal injury, and estimated the allowable value of LCD to be approximately 2 g (1.5–2.1 g) (Nogawa et al., 1989; Kido et al., 1991, 1993; Kido and Nogawa, 1993; Hochi et al., 1995; Chiyoda et al., 2003; Watanabe et al., 2004). In addition, LCD calculated in inhabitants of the Kakehashi River basin, whether observed on a hamlet or individual basis, was found to be highly correlated with urinary Cd, a marker of Cd accumulation within the body (Kido et al., 2004; Kobayashi et al., 2005). Also, in the present study, the amount of rice intake and intake of Cd from sources other than rice were determined using actually measured values. Accordingly, we consider the method to calculate LCD used here as making possible estimation of LCD.

Determination of each individual's residence history necessary for the calculation of LCD was based on the materials of the Itai–itai Disease Countermeasures Council in the case of the Itai–itai disease patients and on questionnaires obtained at the time of the health examinations conducted in 1967 and 1968 in the case of the persons requiring observation. A comparison of LCD calculated in 58 subjects for whom the residence history was known from both the Itai–itai Disease Countermeasures Council materials and questionnaire data revealed good agreement, with a correlation coefficient of 0.93 obtained. Accordingly, we considered that the fact that the source materials of the LCD calculation differed between the Itai–itai disease patients and persons requiring observation did not present any particular problem.

Since the opinion of the Japanese Ministry of Health and Welfare was released in 1970, a system has been

Table 4
Values of cadmium concentration in rice and daily cadmium intake at mild disease onset, severe disease onset, or death was recognized in 50% or 5% of the itai–itai disease patients

	Type of residence history	50% of patients			5% of patients		
		LCD (g)	RCD (ppm)	DCD (μg)	LCD (g)	RCD (ppm)	DCD (μg)
At mild disease onset (mean age was 48.9 y.o.)	a	3.1	0.42	174	2.6	0.33	146
	b	3.1	0.68	259	2.6	0.53	212
At severe disease onset (mean age was 58.4 y.o.)	a	3.8	0.43	178	3.3	0.36	155
	b	3.8	0.63	245	3.3	0.53	209
At death (mean age was 78.9 y.o.)	a	5.4	0.46	188	4.7	0.39	163
	b	5.4	0.60	234	4.7	0.50	202

Type of residence history a: assuming the case of patients residing in the same hamlet since birth. b: assuming the case of a move to the current hamlet of residence from a non-polluted area at the age of 20 years. LCD: life time Cd intake, RCD: Cd concentration in rice in the current hamlet, DCD: daily Cd intake in the current hamlet.

implemented whereby on demand rice with a Cd concentration of 0.4–1.0 ppm can be exchanged, with rice with a Cd concentration ≥1.0 ppm being considered inedible. The Itai–itai Disease Countermeasures Council considers that approximately one half of the farming families participate in this exchange of contaminated rice, but does not know the names of individual households. In this study, LCD was calculated assuming both that from 1970 Cd-polluted rice continued to be consumed (LCD(1)) and that from 1970 Cd-non-polluted rice was consumed (LCD(2)). In practice, virtually no difference was found between LCD(1) and LCD(2) at either the mild disease onset or severe disease onset. This result was thought to be due to the fact that the year recognized as the mild disease onset or severe disease onset was prior to 1970 when the rice exchange system was introduced or because not many years had elapsed. In contrast, because the year of death of most of the Itai–itai disease patients and persons requiring observation was later than 1970, in both groups a difference of 0.7 g was noted between the geometric mean values of LCD(1) and (2).

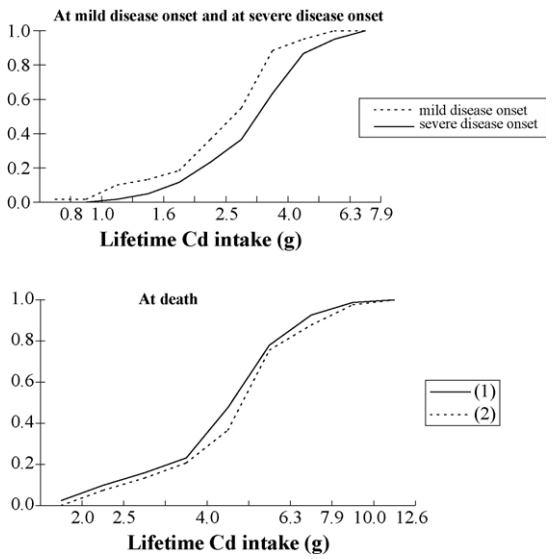

Fig. 3. Distribution of the relative cumulative number of itai–itai disease patients (all women) admitted in 1977 according to lifetime cadmium intake at the mild disease onset, severe disease onset, and death. At death(1): calculated assuming that after 1970 as well Cd-polluted rice was consumed (according to Ministry of Health). At death(2): calculated assuming that after 1970 as well Cd intake was the same as that of non-Cd-polluted areas (exchanged rice) (according to Ministry of Health).

As part of a research project of the Japanese Ministry of the Environment, in 1977 and 1978 Itai–itai disease patients and persons requiring observation were admitted for medical testing at Kanazawa Medical University Hospital or Toyama Prefectural Central Hospital. LCD at the age identified by the patient herself at this time as that at which symptoms were most severe was calculated. In the Itai–itai disease patients severe disease onset was perceived most frequently as the time when the patient experienced ambulation impairment and/or bone fractures. The mean age of the Itai–itai disease patients at severe disease onset was 58.4 years, with the respective geometric mean values of LCD(1) and

(2) at this time 3.4 and 3.3 g and the minimum value 1.2 g. Seven of the patients had an LCD of ≤2.0 g. The Cd concentration in contaminated rice regarded as collected in each Cd-polluted hamlet represents the mean Cd concentration of the hamlet and not the Cd concentration in rice collected by each individual. This fact may explain why the calculated LCD of these seven persons was found to be low.

As shown in Fig. 3, the relative cumulative person number distribution according to LCD of the Itai–itai disease patients at the mild disease onset and severe disease onset formed a sigmoid curve, with probit regression analysis demonstrating linearity. Accordingly, the existence of a dose–response relationship between LCD at the time of mild disease onset, severe disease onset and death and the number of Itai–itai disease patients was clarified. LCD at the point at which the time of mild disease onset or severe disease onset was recognized in half of the Itai–itai disease patients (50% value) was calculated to be 3.1 and 3.8 g, respectively (Table 4), showing greater values than the respective geometric mean values of 2.7 and 3.4 g. Assuming the case of Itai–itai disease patients residing in the same hamlet since birth with the number of years of residence amounting to 48.9, the Cd concentration in rice resulting in an LCD of 3.1 g is calculated as 0.42 ppm, and the daily Cd intake as 174 μg. In the case of a move to the current hamlet of residence from a non-polluted area at a mean age of 20 years, the Cd concentration in rice is calculated as 0.68 ppm and the daily Cd intake as 259 μg. In the case of a patient residing in the same hamlet since birth with the number of years of residence amounting to 58.4 at severe disease onset, the Cd concentration in rice resulting in an LCD of 3.8 g is calculated as 0.43 ppm, and the daily Cd intake as 178 μg. In the case of a move to the current hamlet of residence from a non-polluted area at a mean age of 20 years, the Cd concentration in rice is calculated as 0.63 ppm and the daily Cd intake as 245 μg. Moreover, LCD at the time when onset or severe disease was recognized in 5% of the Itai–itai disease patients was calculated to be 2.6 and 3.3 g, respectively, with it estimated that at the mild disease onset rice with a Cd concentration of 0.33 ppm (daily Cd intake 146 μg) had been consumed for 48.9 years, while at the time of severe disease onset rice with a Cd concentration of 0.36 ppm (daily Cd intake 155 μg) had been consumed for 58.4 years (Table 4).

As mentioned above, we already reported that significant associations were identified between urinary finding positive rates (protein, glucose) in 13,183 persons in 1967/68 and Cd concentrations in 2446 rice samples investigated from 1971 to 1976 or LCD in the Jinzu River basin. Permissible values determined from the regression lines of the dose–response relationship were estimated to be 0.11 ppm for rice Cd concentrations and 1.5–1.6 g for LCD (Chiyoda et al., 2003; Watanabe et al., 2002, 2004; Osawa et al., 2001). In the Kakehashi River basin as well, similar dose–response relationships were identified between each of urinary finding positive rates (β_2-microglobulin, metallothionein, protein, glucose) and mean Cd concentrations in rice in each hamlet, with permissible values reported to be <0.05 ppm for rice Cd concentrations and 1.7–2.1 g for LCD (Nogawa et al., 1989; Kido et al., 1993; Nakashima et al., 1997). The present study indicated that LCD at the time when onset of mild disease was recognized in 5% of Itai–itai disease patients was 2.6 g. It was thought that our assumption of continuing rice consumption may have led to overestimation of intake since there was a substantial decrease in food consumption due to aging or sickness. The Joint FAO/WHO Expert Committee on Food Additives (JECFA) allocated a provisional tolerable weekly intake (PTWI) of 400–500 μg of Cd per person in 1972 (WHO, 1972). They were based on a critical concentration of Cd of 200 μg/g kidney cortex, attainable after Cd intake of 140–260 μg/day for over 50 years or 2000 mg of Cd over a life time. The initial guideline was retained, but it was later expressed more rationally in terms of intake per kg body weight, corresponding to 7 μg per kg body weight per week. A daily intake of 50 μg (body weight used for calculation of Japanese people is 50 kg) for 50 years corresponds to 913 mg. Therefore it is reasonable to say that the permissible values of LCD calculated from our studies including the present study were close to those considered in derivation of the PTWI for Cd.

Watanabe et al. (2000) collected food-duplicate samples from 588 non-smoking women during the period 1991–1997 from six districts located throughout Japan and determined their daily Cd intake. They reported that the maximum mean daily Cd intake value from among the individual districts was 51.3 μg and the national mean value 25.5 μg. Also, in a similar survey conducted in 1977–1981 the corresponding values were 65.1 and 37.5 μg (Watanabe et al., 2000).

The Japanese Ministry of Agriculture and Forestry (2002) measured Cd concentrations in 37250 rice samples obtained from throughout Japan in 1997–1998 and announced the mean Cd concentration to be 0.06 ppm, with values $\geq$0.2 ppm found in 3.2% of the samples and $\geq$0.4 ppm in 0.2%.

The present results clarify that Itai–itai disease, the most severe stage of chronic Cd poisoning, occurs at levels of Cd consumption amounting to approximately three-fold of those currently seen in Japan and suggest that the implementation of countermeasures to prevent the adverse health effects of Cd is an pressing issue.

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