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FACTORS MODIFYING CRITICAL CONCENTRATION AND BIOLOGICAL HALF-TIME OF CADMIUM

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ABSTRACT

Each heavy metal has been believed to have proper critical concentration and biological half-time. However, we found that the critical concentration varied according to the environmental temperatures at which animals were kept. The biological half-time varied as well. The experiment on mice indicated that the 0.3 mg/kg/day group showed a longer biological half-time of tissue cadmium than the 1.0 mg/kg/day group. The experiment on rabbits also indicated a longer biological half-time for the 0.5 mg/kg/day group than for the 1.5 mg/kg/day group. Another experiment on rabbits, in which various doses of cadmium were given and the rabbits were left untreated over a period of 2 years, indicated that the biological half-time of tissue cadmium was longer for the rabbits given a small dose of cadmium than that of the rabbits which received a large dose. Furthermore, monkeys fed with 0, 0.3, 3.0, or 30 mg/day cadmium over a period of one year showed a longer biological half-time of tissue cadmium in the lower dose group. These data suggest that the biological half-time of cadmium for an unknown exposure group is not applicable to an excess exposure group.

Our recommendation is that we should not be in haste to estimate the maximum allowable concentration and the maximum allowable intake of cadmium but to collect sufficient data to establish the critical concentration and biological half-time for cadmium workers or the residents in cadmium polluted areas.

Cadmium taken into the body accumulates in the liver and then transfers to the kidneys. The total amount of cadmium in the liver and the kidneys occupies two thirds of the body burden[8] mostly in the chemical form of metallothionein. The kidney is a critical organ for cadmium and the renal dysfunctions are characterized by proteinuria, low-molecular-weight proteinuria, glycosuria, aminoaciduria, and renal tubular dysfunction. The critical concentration of cadmium in the renal cortex was estimated by the WHO Working Group as 200 μg/g[41]. The WHO Working Group[41] tried to estimate the maximum allowable concentration of cadmium in the working environment and the allowable daily intake of cadmium for the general environment based on the above critical concentration of 200 μg/g of cadmium and the long biological half-time of cadmium such as 19 or 38 years.[6,9,40]

The WHO Working Group[41] thought that the critical concentration and the biological half-time were proper for cadmium and calculated the maximum

allowable concentration in the working environment and the allowable daily intake of cadmium for the general population. However, our experimental data suggest that the biological half-time is a function of dose, and that the critical concentration varies according to environmental temperature as well.

MATERIAL, METHODS AND RESULTS

Factors modifying the critical concentration of cadmium in the renal cortex[23]

One hundred and sixty-two male four-week-old mice of the ICR-JCL strain were divided into three groups, each of which was adjusted to environmental temperature of 8, 22 or 37 °C for two weeks. Each group of mice was then again divided into three subgroups; the first subgroup was given daily a subcutaneous injection of 1.0 mg/kg/day cadmium on the back as cadmium chloride over a period of 8 months, the second subgroup 0.3 mg/kg/day and the third subgroup served as a control. The earlier appearance of proteinuria and the higher incidence of proteinuria were observed in the 37 °C subgroup of mice given 1.0 mg/kg/day cadmium, while cadmium accumulation did not differ with environmental temperature. The critical concentration of cadmium in the renal cortex in terms of proteinuria was found to be dependent on environmental temperature; 270 μg/g for the 8 °C group, 225 μg/g for the 22 °C group and 150 μg/g for the 37 °C group, respectively.

Factors modifying the biological half-time of cadmium

The above experiment on mice[23] suggested, as shown in Table 1, that the biological half-time of cadmium in the higher dose group was shorter than that of the lower dose group. However, environmental temperature had no effect on the biological half-time of cadmium.

Thirteen male rabbits of the Japanese white strain were given daily a subcutaneous injection of 0.5 mg/kg/day cadmium over a period of 42 weeks[24], while 12 male rabbits were given 1.5 mg/kg/day cadmium for 5 weeks[16]. As shown in Table 1, the biological half-time of cadmium in the liver and the kidneys of the 1.5 mg/kg/day group was shorter than that of the 0.5 mg/kg/day group.

TABLE 1
Dose as a factor modifying biological half-time.

Animal species	Dose (mg/kg/day)	Number of animals	Biological half-time (day)			Reference
			Whole body	Liver	Kidney	
Mouse	0.3	18	60	81	60	23
	1.0	18	21	24	24	23
Rabbit	0.5	13	35	42	21	24
	1.5	12		12	11	16

Another group of 17 rabbits were divided into three groups; four rabbits of the first group were given 0.5 mg/kg/day cadmium for 5 weeks amounting to 17.5 mg/kg, eight rabbits of the second group 1.5 mg/kg/day for 3 weeks totally 31.5 mg/kg, and five rabbits of the third group 1.5 mg/kg/day for 5 weeks totally 52.5 mg/kg cadmium[21].

Proteinuria was detected at the end of the last injection, but the rabbits recovered in a couple of weeks. They were left untreated over a period of 30 weeks. Cadmium concentration in the renal cortex and the liver decreased with time, and as shown in Figure 1 rabbits with a larger body burden were found to have a shorter biological half-time.

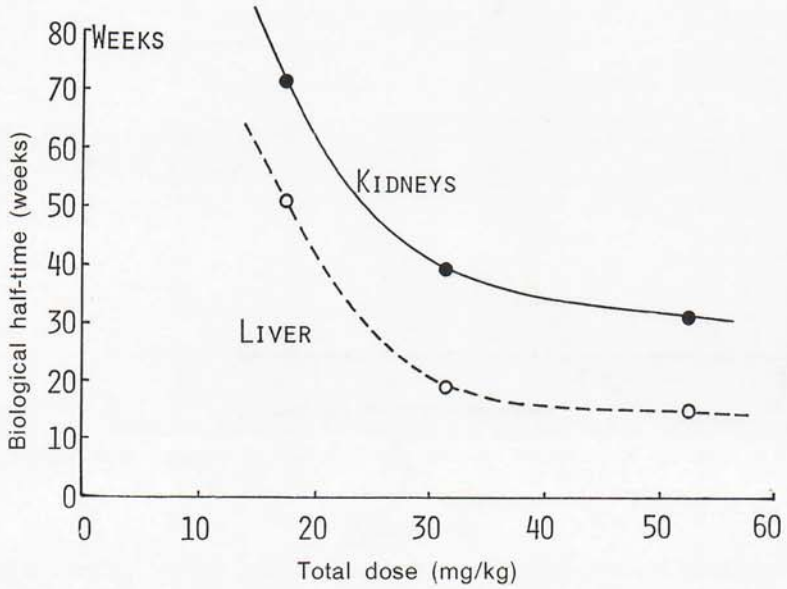

FIG. 1 – Relationship between dose and biological half-time of cadmium in rabbits.

Ten young male Rhesus monkeys were divided into four groups; three monkeys of the first group were given 30 mg/day cadmium orally as cadmium chloride over a period of 55 weeks, three monkeys of the second group 3 mg/day, two monkeys of the third group 0.3 mg/day and two monkeys of the fourth group served as controls (commercial pelleted food contained 0.14 μg/g cadmium[25]. The biological half-time at the time of killing was calculated in the following formula:

$$\mathrm{BHT} = \frac{\ln 2}{k}, \quad \text{where} \quad k = \frac{\text{Urinary excretion of cadmium}}{(\text{Liver} + \text{Kidney cadmium}) \times 3/2}$$

The biliary excretion of cadmium was not included in the present calculation. This might have resulted in the inaccuracy in the estimates of the biological half--time. The results shown in Figure 2 indicate a shorter biological half-time for the larger dose level group.

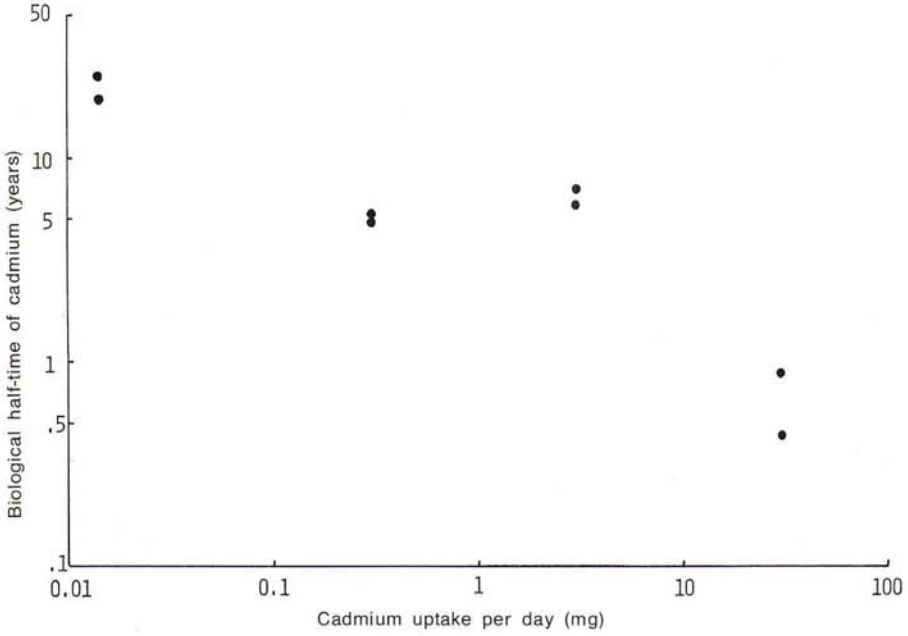

FIG. 2 – Relationship between dose and biological half-time of cadmium in monkeys.

DISCUSSION

The critical concentration of cadmium in the renal cortex, which has been reported so far, is listed in Table 2. The most critical concentrations in terms of proteinuria ranged from 200 to 300 μg/g cadmium in mice, rats and rabbits, while in monkeys the critical concentration was higher. However, as already mentioned in this paper, the critical concentration of cadmium in the renal cortex was not a fixed value, but varied according to environmental temperature. Although no difference was observed in cadmium accumulation, the mice in a hot environment showed an earlier appearance of proteinuria. This might have been due to a decreased formation of metallothionein to result in the enhancement of cadmium toxicity. Japan is a country which has four seasons, and this might alter the toxicity of cadmium. Therefore, the changes in environmental temperature should be taken into consideration when the maximum allowable concentration in the working environment is discussed. Attention should be paid also to the extreme daily fluctuations in environmental temperature in some countries.

TABLE 2
Critical concentration of cadmium in animals.

Animal species	Index media	Cadmium level μg/g	References
Mouse	Proteinuria	250	27
		225	23
	Glycosuria	225	23
Rat	Proteinuria	225	37
		234	14
		255	13
	Enzymuria	135	28
		300	13
	Pathological change	400	2
		300	13
		56	11
Rabbit	Proteinuria	300–900	7
		142	10
		300	26
		230	22
		300	24
	Low-molecular-weight proteinuria	300	24
	Glycosuria	117	10
		300	26
		300	24
	Aminoaciduria	200	26
		230	22
		300	24
	Enzymuria	117	10
		200	26
	Decreased tubular function	250	18
		238	15
	Pathological change	250	1
		250	34
		200	11
Monkey	Proteinuria	450	25
		550	19
	Low-molecular-weight proteinuria	380	25
	Glycosuria	450	25
	Aminoaciduria	450	25
		550	19
	Pathological change	300–465	25

The WHO Working Group estimated the critical concentration of cadmium in the human renal cortex as 200 μg/g on the basis of all the data on cadmium levels in the renal cortex of cadmium workers and residents in cadmium-polluted areas available until 1975 (Fig. 3). However, there remained some discussions as to the estimate of the WHO Working Group on the critical concentration of cadmium as we already mentioned in detail elsewhere[18]. The critical organ concentration was primarily defined as the mean concentration in the organ at the time when any of its cells reaches the critical concentration[35]. Therefore, the critical concentration can be estimated when the mean cadmium level in the renal cortex of the proteinuria-positive group is significantly higher than that of the

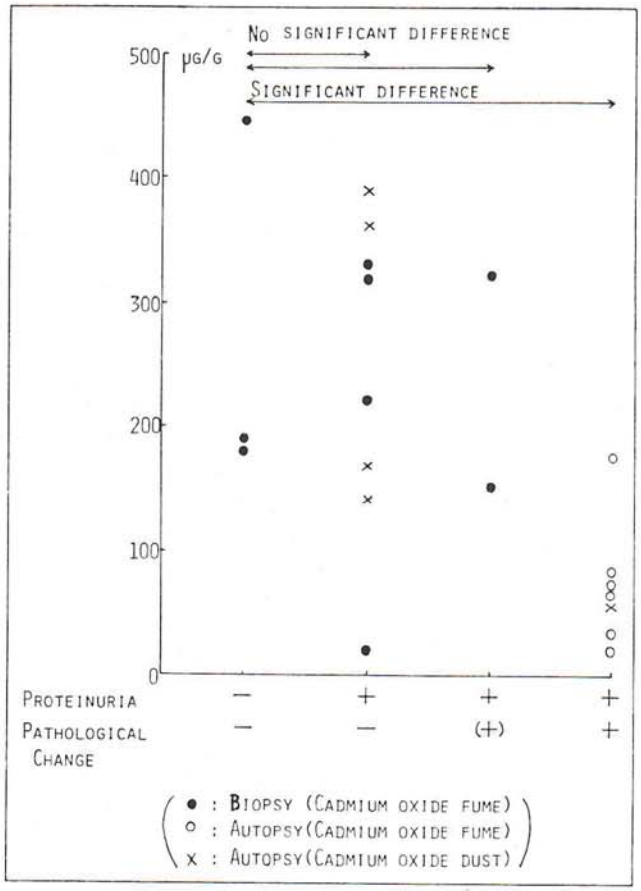

FIG. 3 – Data available at present to estimate critical level of cadmium in the human renal cortex[18].

TABLE 3
Biological half-time of cadmium in animals.

Species	Route	Compound	Dose	Animals		Biological half-time (day)			Reference
				Sex, age	No	Whole body	Liver	Kidney	
Mouse	sc	$^{109}CdCl_2$	1 μCi	M		21.5			39
				F		32.0			
	sc	$^{109}CdCl_2$		M & F	80		76		36
	sc	$^{109}CdCl_2$	1 μCi	M, 8 W		280			38
	ip	$^{109}CdCl_2$	17 μCi			100 <			4
	ip	$^{109}CdCl_2$	1 μCi	M, 7 W		280			38
				M, 16 W		260			
				M, 50 W		660			
	ip	$Cd(NO_3)_2$	50 μg		16	60	55		12
	iv	^{109}Cd				40			30
	iv	$^{109}CdCl_2$	10 μCi				90		32
Rat	po	$^{109}CdCl_2$		Young		30–35			33
	po	$^{115m}CdCl_2$	1 mg			15			31
	iv	$^{115m}CdCl_2$	1 mg			333			31
	im	^{109}Cd	2 μCi			300			5
Dog	ip	$^{115}Cd(NO_3)_2$				260–500			3
Monkey	po	$^{115}CdCl_2$	1.7 mg/kg		2	2 Y <			27
			0.17 mg/kg		2				
Human	po	$^{115m}CdCl_2$		M, 53 Y	1	20 Y			42
Mouse	sc	$CdCl_2$	0.3 mg/kg x 8M	M	18	60*	81*	60*	23
			1.0 x 8M	M	18	21*	24*	24*	
Rat	ip	$CdCl_2$	0.75 mg/kg x 6M				60*	60*	2
	ip	$Cd(NO_3)_2$	100 μg x 30		24		450-500*	100-200*	12
Rabbit	sc	$CdCl_2$	1.5 mg/kg x 35	M	12		12*	11*	15
	sc	$CdCl_2$	1.5 mg/kg x 21	M	9		160*		16
	sc	$CdCl_2$	0.5 x 35	M	4		357	497	21
			1.5 x 21	M	8		133	273	
			1.5 x 35	M	5		105	217	
	sc	$^{115m}CdCl_2$	Carrier Free	M	3		Blood	98 H	17
			50–150 mg	M	13		Blood	1.8H	
	sc	$CdCl_2$	0.5 mg/kg x 42W	M	13		42*	21*	24
Monkey	po	$CdCl_2$	30 mg/day x 54 W	M	2	0.66 Y			25
			3 x 54W	M	2	6.4 Y			
			0.3 x 54W	M	2	5.2 Y			
			0.01 x 54W	M	2	22.4 Y			

M and F represent male and female animals, and H, W, M and Y indicate hours, weeks, months and years.

*Value calculated from the cadmium accumulation curve.

proteinuria-negative group. Nevertheless, as indicated in Figure 3, three cadmium workers who had about 200 μg/g cadmium in the renal cortex did not suffer from proteinuria, and no significant difference in the cadmium levels was observed between the proteinuria-positive group and the proteinuria-negative group. Therefore, it is not the right time to estimate the critical concentration of cadmium in the human renal cortex based on such uncertain data. Instead, we should concentrate all our efforts to collect data on the cadmium level in the renal cortex of cadmium workers and of residents in cadmium-polluted areas. If anyone still insists on estimating the critical concentration of cadmium for administrative purposes, it might be better to use the monkey data (380 μg/g in terms of low-molecular-weight proteinuria or 450 μg/g in terms of proteinuria, glycosuria and aminoaciduria) in Table 2, because the monkey is the animal which most closely resembles human beings.

As shown in Table 3, the biological half-time of cadmium in animals varied widely. This might be caused by several factors: 1) the difference in the data obtained – the accumulation data or the decrease data, 2) the different phase – a rapid decrease phase or a slow decrease phase, and 3) the difference in animal species and dose of cadmium. However, Table 3 shows that the animals given a larger dose of cadmium had a shorter biological half-time.

The biological half-time of cadmium in the human renal cortex, the critical organ for cadmium, has been reported to be as long as 19–38 years[6], 17.6 years[40] or 9–18 years[9] based upon the data obtained in people with unknown exposure to cadmium. The WHO Working Group[41] discussed the theoretical maximum allowable concentration of cadmium in the working environment and the allowable daily intake of cadmium for residents in cadmium-polluted areas applying the very long biological half-time of cadmium of the people with unknown exposure to cadmium to the formula of a single compartment model. However, as discussed above, our mouse, rabbit and monkey data suggest that the biological half-time is shortened if cadmium dose is increased, while other heavy metals have proper biological half-time independent of the dose. Therefore, the long biological half-time of cadmium of the people with unknown exposure to cadmium can not be applicable in estimating the maximum allowable concentration in the working environment or the allowable daily intake of cadmium for people exposed to excess cadmium such as cadmium workers and residents in cadmium-polluted areas.

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