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Review

Perspectives on Cadmium Toxicity Research

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Satoh, M., Koyama, H., Kaji, T., Kito, H. and Tohyama, C. *Perspectives on Cadmium Toxicity Research.* Tohoku J. Exp. Med., 2002, **196**(1), 23–32 —— Since there are a plethora of studies on cadmium toxicity and poisoning in laboratory animals and humans, we have limited this review to studies that are relevant to human health issues by focusing on carcinogenicity, genotoxicity, circulatory disease, nephrotoxicity and life expectancy. Cadmium exposure has been established to induce cancer in various tissues of laboratory animals. Contrary to early findings of the lack of genotoxicity by cadmium, recent findings of mammalian cell culture studies have revealed genotoxic effects. Furthermore, cadmium exposure at relatively low doses induces circulatory diseases in laboratory animals. Despite such results of various cadmium toxicities in animal studies, data from human studies are lacking and insufficient to support the cause-effect relationship. Although cadmium is currently considered to be a human carcinogen by the International Agency for Research and Cancer, it is inappropriate to conclude that sufficient evidence on the carcinogenicity of cadmium in humans exists. It is also thought that epidemiological studies so far reported do not support the occurrence of cadmium-induced circulatory disease in humans. Since there are inconsistent reports on the relationship of cadmium exposure with the life expectancy of people living in cadmium-polluted areas, further studies are needed for clarification. It is also necessary to examine apparent discrepancies in result between humans and experimental animals. It has been established that long-term exposure to cadmium causes renal dysfunction in both humans and experimental animals, and whether there are any differences in the inducibility of metallothionein in the kidney warrants further study. ———— cadmium; chronic toxicity; metallothionein; low dose effects

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A considerable number of studies on cadmium poisoning have been carried out (Friberg 1948; Nordberg et al. 1992a; WHO 1992; Jarup 1998). Particularly, research interest has been directed to renal and bone toxicities, which are the main symptoms of chronic cadmium poisoning, since cadmium is the main cause of "Itai-Itai" disease (Nogawa et al. 1999). Based upon the major findings of early works, we review the effects of relatively low dose cadmium exposure by focusing on carcinogenicity, reproductive toxicity, cardiovascular diseases, renal toxicity and life expectancy.

Carcinogenicity

Epidemiological studies have revealed that exposure to cadmium causes prostate and lung cancers (Stayner et al. 1992; IARC 1993, 1994; Waalkes and Rehm 1994; Waalkes 2000). In 1993, the International Agency for Research and Cancer (IARC) classified cadmium under Group 1, the classification code of which indicates that the chemical of concern is a human carcinogen, since there is a clear-cut dose-response relationship between the level of cadmium exposure and the incidence of lung cancer in the human population (Stayner et al. 1992). However, it is known that there are some problems in terms of confounding factors in epidemiological studies, such as the estimation of the exposure level of cadmium, the contribution by smoking, and the involvement of nickel and arsenic compounds (Doll 1992; Sorahan and Lancashire 1997). Since some reports did not support the carcinogenic effects of cadmium (Lamm et al. 1992; Sorahan et al. 1995; Jarup 1998), one should bear in mind that the reported epidemiological studies are not yet sufficient for justifying that cadmium is indeed a human carcinogen. In the case of prostate cancer, an early study suggested that the incidence of prostate cancer may be increased by exposure to cadmium (Kipling and Waterhouse 1967), whereas other studies did not show such clear association (Kolonel and Winkelstein 1977; Armstrong and Kazantzis 1983). In addition, no association of cadmium exposure with the incidence of all cancers was reported in people living in a cadmium-contaminated area, in which oral ingestion rather than inhalation was the main route of exposure (Nakagawa et al. 1993).

In experimental studies using rats, it has been reported that exposure to cadmium induced tumors in the testis (Gunn et al. 1964; Roe et al. 1964; Waalkes et al. 1988), lung (Takenaka et al. 1983; Glaser et al. 1990), prostate (Waalkes et al. 1988; Waalkes and Rehm 1994), erythropoietic system (Waalkes et al. 1992; Waalkes and Rehm 1994) as well as in the injection sites of skin and muscle (Heath et al. 1962; Kazantzis 1963; Gunn et al. 1964; Waalkes et al. 1988). Furthermore, various routes of exposure, including inhalation (Takenaka et al. 1983; Glaser et al. 1990), injection (Heath et al. 1962; Gunn et al. 1964; Kazantzis 1963; Waalkes et al. 1988) and diet (Waalkes and Rehm 1992), were established to induce tumors. On the other hand, in mice and hamsters, only a few reports are available for evaluating carcinogenicity, with most of them indicating the non-carcinogenicity of cadmium.

Regarding the apparent discrepancy between the results of human studies and those of laboratory animal studies, it should be clarified whether common mechanisms for the occurrence of carcinogenicity exist, and the apparent discrepancy should be explained at the molecular and cellular levels. This is important since the detection power is low in epidemiological studies on human populations. As described above, because there are reports showing negative findings for carcinogenicity of cadmium, the carcinogenicity of cadmium should be re-evaluated. We propose that at present, it is appropriate that cadmium be clas-

sified under Group 2A, which means that "The agent is probably carcinogenic to humans."

Genotoxicity

It is believed that cadmium compounds do not have mutagenicity, based on the standard mutagenicity test that utilizes *Salmonella* and *E. coli* (IARC 1982; Kazantzis 1987). However, in recent mammalian cell culture studies, it was found that cadmium induced mutation (Oberly et al. 1982; Ochi and Ohsawa 1983; Klein and Rossman 1990; Meplan et al. 1999a, b), DNA chain disruption (Coogan et al. 1994; Hartwig 1994; Misra et al. 1998) and chromosomal aberrations (Ochi and Ohsawa 1985; Bassendowska-Karska and Zawadzkak-Kos 1987; Gibson et al. 1995; Sofuni et al. 1996). Furthermore, cadmium exposure increased genotoxicity by inhibiting the repair mechanism of cadmium-induced injury of the gene (Hartwig 1994).

Reproductive toxicity

In the reproductive organs and fetuses of rats, exposure to cadmium led to exudative damage, edema and necrosis of the testis, reduction of sperm motility, necrosis of the efferent ducts, injury of Sertoli cells, decrease in serum testosterone concentration, abortion and teratogenesis of the fetus (Parizek and Zahor 1956; Ragan and Mast 1990; Goyer 1991; Saygi et al. 1991). It is recognized that sensitivity of the testis to cadmium exposure is dependent upon the mouse strain (Gunn et al. 1965; Taylor et al. 1973; Chellman et al. 1985; King et al. 1999), although the underlying mechanism as to how cadmium causes testicular damage is largely unknown. It is not clear whether fetal toxicity of cadmium is attributable to placental defect or to the accumulated cadmium in the fetus.

In epidemiological studies, no reproductive toxicity of cadmium, such as testicular, gestational and fetal effects, has been observed in male and female human populations. On the other hand, in laboratory animal studies, male and female reproductive disturbances have been clearly observed.

In SPEED98, which is a compilation of chemicals suspected to have endocrine-disrupting activities, by the Environmental Agency (currently Ministry of the Environment), cadmium is one of the 70 suspected chemicals. It should be studied in detail whether a low dose of cadmium, the level of which is equivalent to the exposure level of people in daily lives, acts as an endocrine-disrupting chemical.

Cardiovascular disease (Hypertension etc.)

It has been reported that long-term low-dose exposure to cadmium causes hypertension and arteriosclerosis without renal dysfunction in rats (Perry et al. 1979; Revis et al. 1981; Subramanyan et al. 1992). In addition, those studies have shown that long-term high-dose exposure to cadmium causes renal toxicity but not cardiovascular disease. In the human population, it has been reported that patients afflicted with hypertension tended to excrete larger amounts of cadmium in the urine and that the incidence of arteriosclerosis was higher in people living in cadmium-polluted areas than in those in a reference area in the Netherlands (Perry and Schroeder 1955; Perry and Kopp 1983; Houtman 1993). On the other hand, the incidence of hypertension was found to be low in patients afflicted with 'Itai-Itai' disease, people living in cadmium-polluted areas and cadmium-exposed industrial workers (Kagamimori et al. 1986). These results suggest the possibility that the dysfunction of renal tubular reabsorption is linked to the regulation of blood pressure. This possible association should be evaluated in terms of cadmium exposure level, the degree of renal dysfunction, effects of smoking and medical treatment.

Disruption in cellular signal transduction and involvement of apoptosis

It has been reported that cadmium affects cellular function by perturbing signal transductions, such as protein kinase C (Bagchi et al.

1997), mitogen-activated protein kinase (Templeton et al. 1998; Ding and Templeton 2000), and cyclic AMP pathways (Merali and Singhal 1975; Kacew et al. 1977; Kumar and Bhattacharya 2000); however, how the disruption of these pathways by cadmium leads to the manifestation of toxicity in vivo is largely unknown. On the other hand, it has been shown that apoptosis is involved in the manifestation of cadmium toxicity in various tissues including liver and kidney (Azzouzi et al. 1994; Habeebu et al. 1998; Ishido et al. 1998; Hart et al. 1999; Xu et al. 1999; Zhou et al. 1999). In particular, it has been reported that exposure to cadmium at relatively high and low levels causes necrosis and apoptosis, respectively, which suggests that the mode of cell death by cadmium is dependent upon its exposure level (Azzouzi et al. 1994; Habeebu et al. 1998; Xu et al. 1999; Zhou et al. 1999).

Critical concentrations of cadmium in the manifestation of renal toxicity

According to a report by the Joint Expert Committee of Food Additives (JECFA), organized by the Food and Agriculture Organization and World Health Organization, the accumulated cadmium concentration in the renal cortex (200 μg/g wet tissue) was estimated to cause renal dysfunction in 10% of people who have this amount of cadmium in their renal cortex (WHO 1989, 1993). In the subacute toxicity study in which rats were exposed to cadmium, renal dysfunction was found to occur at 150 μg Cd/g wet tissue (Kajikawa et al. 1981; Dudley et al. 1985; Tohyama et al. 1987; Hiratsuka et al. 1996; Horiguchi et al. 1996). When rats were given 200 ppm cadmium in the diet for two months, renal dysfunction was observed at tissue cadmium concentrations of 100 to 250 μg/g wet tissue (Mitsumori et al. 1998). In contrast, in rats fed 40 ppm cadmium for eight months, no renal dysfunction was observed despite the fact that renal cadmium concentration was found to range from 90 to 200 μg/g wet tissue (Mitsumori et al. 1998). These results suggest that experimental conditions such as the dosing regimen and the duration of exposure affect the critical concentration and that the renal cortex concentration of 150 μg/g wet tissue does not always cause renal dysfunction. Furthermore, it was found in a Rhesus monkey study that cadmium concentration at the time of onset of renal dysfunction was 300 to 500 μg/g wet tissue (Nomiyama and Nomiyama 1982; Umemura 2000). Recent studies revealed that when rats were given diets consisting of 28% purified diet and 72% ordinary rice containing cadmium-polluted rice (1.01 ppm cadmium) or cadmium chloride (40 ppm cadmium) for eight to 22 months, renal toxicity was not induced and renal cadmium concentration ranged from 50 to 120 μg/g wet tissue (Hiratsuka et al. 1999; Shibutani et al. 2000, 2001).

It is generally thought that proximal tubular dysfunction occurs since the level of cadmium ions that are not bound to metallothionien increases in the kidney when excess amounts of cadmium are accumulated in this tissue (Goyer 1989; Nordberg et al. 1992b; Klaassen et al. 1999). Thus, the balance between metallothionein-bound and -free forms of cadmium is thought to be the key determinant for the onset of renal dysfunction. Chronic cadmium toxicity occurs in metallothionein I/II knock-out mice when cadmium concentration in the kidney is less than 10 μg/g wet tissue (Table 1). Thus, the induction of renal dysfunction by cadmium may be partly dependent upon the biosynthesized amounts of metallothionein in the kidney, and it is plausible to consider that relatively low levels of exposure to cadmium through food and smoking might trigger renal dysfunction in humans who do not have sufficient capability for inducing metallothionein. This aspect of susceptibility in terms of genetic polymorphism warrants further study (Kita et al. 2001).

TABLE 1. *Evaluation of chronic renal toxicity caused by cadmium exposure in the MT-null mice and wild-type mice*

Compound	Mouse Type	Route	Period	Dose	Toxicity indicator	Toxicity evaluation	Cd in kidney (μg/g)	Reference
CdCl2	MT-null	s.c.	10 weeks	0.05 mg Cd/kg	Urinary γ-GTP and NAG	+	<10	Liu, et al. 1998
	MT-null	s.c.	10 weeks	0.1 mg Cd/kg	Urinary γ-GTP and NAG	+	<10	
	Wild-type	s.c.	10 weeks	0.05 mg Cd/kg	Urinary γ-GTP and NAG	−	30	Liu, et al. 1998
	Wild-type	s.c.	10 weeks	0.1 mg Cd/kg	Urinary γ-GTP and NAG	−	60	
	Wild-type	s.c.	10 weeks	1.0 mg Cd/kg	Urinary γ-GTP and NAG	−	120	
CdCl2	MT-null	Oral[1)]	6 months	30 ppm	Urinary γ-GTP	+	5	Liu, et al. 2000
	MT-null	Oral[1)]	6 months	100 ppm	Urinary γ-GTP	+	<10	
	MT-null	Oral[1)]	6 months	300 ppm	Urinary γ-GTP, BUN	+	<10	
	Wild-type	Oral[1)]	6 months	30 ppm	Urinary γ-GTP, BUN	−	5	Liu, et al. 2000
	Wild-type	Oral[1)]	6 months	100 ppm	Urinary γ-GTP, BUN	−	10	
	Wild-type	Oral[1)]	6 months	300 ppm	Urinary γ-GTP, BUN	−	50	
CdCl2	MT-null	Oral[2)]	6 months	100 ppm	Urinary γ-GTP	+	5	Liu, et al. 2000
	Wild-type	Oral[2)]	6 months	100 ppm	Urinary γ-GTP, BUN	−	50	
CdCl2	MT-null	Oral[2)]	4 months	50 ppm	Urinary γ-GTP and NAG, BUN	−	10	Himeno et al. 2000
	Wild-type	Oral[2)]	4 months	50 ppm	Urinary γ-GTP and NAG, BUN	−	35	

[1)]drinking water, [2)]feed.

+, toxic effect; −, nontoxic effect; γ-GTP, γ-glutamyltranspeptidase; NAG, β-N-acetyl glucosaminidase; BUN, blood urea nitrogen.

Life expectancy of people in cadmium-polluted areas

In 1993, JECFA recommended a provisional tolerable weekly intake (PTWI) of cadmium of 7 μg/kg/week (which is tantamount to 1 μg/kg/day), the amount of which should not be exceeded to avoid the possible adverse effects of cadmium (WHO 1993). This value is based upon the estimation that the lifetime exposure to cadmium by intake does not exceed 50 μg/g tissue in the renal cortex.

Regarding the life expectancy of cadmium-exposed people, the mortality of people living in cadmium-polluted areas was significantly lower than that in reference areas, suggesting that the life expectancy with regard to cadmium exposure is better in cadmium-polluted areas (Shigematsu 1984). In contrast, it was reported that the life expectancy was significantly shorter in patients afflicted with renal dysfunction than in people without renal dysfunction, when people with or without renal dysfunction and living in a cadmium-polluted area were compared (Kawano et al. 1986; Nakagawa et al. 1990, 1993; Nishijo et al. 1994, 1995).

In order to decrease cadmium levels in food and to avoid exceeding the PTWI in daily life, it is recommended that proper environmental management of cadmium, such as the reduction of the input of cadmium into the environment and the removal and treatment of contaminated soil are carried out.

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