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Cadmium in human population

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Introduction

Due to man's activity, trace metals are slowly being redistributed in the environment. During the last decades, concentrated metal deposits that are confined in the earth's crust and which are usually harmless to living beings, have been exploited at an increasing rate and discharged partly in the environment. Among these metals, cadmium has raised the most concern because of its high toxicity coupled with an exceptional tendency to accumulate in the human organism.

Although the acute toxicity of cadmium on the lung and the gastrointestinal tract has been known for a long time[91,102], it was only in the 1950's that one first became really aware of the danger resulting from long term exposure to this metal.

In 1942, Nicaud et al.[66], when examining French workers in an alkaline accumulator factory, found several cases of severe osteoporosis with pseudofractures of the bones, associated with an impairment of the general health. A few years later, in Sweden, Friberg[25,26] conducted a toxicological study on workers exposed to CdO dust in an electrical battery plant. He reported emphysema and renal damage characterized by a proteinuria rich in low molecular weight proteins.

However, the greatest concern over cadmium pollution was triggered when it appeared that chronic cadmium poisoning was not restricted to industrial workers, but could constitute a health hazard to the general population. In Japan, contamination of water and rice by cadmium was responsible, in combination with other nutritional factors, for the outbreak of a severe bone disease (Itai-Itai disease)[30]. In industrialized countries, the cadmium body burden of the general population has increased during the 20th century[18,94]. In some population groups, the mean concentration of cadmium in the kidney cortex at the age of 50 is only 2–5 times lower than the critical level for renal damage[27,100]. The potential health effects of the current environmental pollution by cadmium remain largely to be clarified. Whether cadmium plays a role in the occurrence of frequent diseases, such as hypertension or various types of cancer remains a matter of controversy.

The aim of this review is to summarize our current knowledge on the metabolism and toxicity of cadmium in man. Because this field is so large and continues to develop rapidly, a comprehensive review of all published data is impossible. For more details, the reader is referred to several monographs on this subject[27,51,69,101].

Exposure

Working environment

In industry, cadmium enters the organism mainly by inhalation. However, oral intake, namely through contaminated hands, may sometimes be significant. Smoking at one's place of work may also increase the cadmium intake.

Exposure to cadmium may occur in conjunction with a number of industrial processes: production of cadmium and its compounds, fabrication of alloys and solders, plating of metals, use of cadmium in pigments and stabilizers for plastics, fabrication of Cd-Ni batteries, etc. Because of the relatively high volatility of this metal (boiling point: 765 °C), the hazard is particularly high for people welding cadmium-plated materials.

The total airborne cadmium concentration may vary considerably depending on the type of industry and also on the efforts made to reduce the emissions. But, usually, values currently observed in cadmium-using or producing factories range from 5 to 200 μg Cd/m^3. In the past, and also in plants where cadmium emissions are not yet controlled, values as high as 10,000 μg Cd/m^3 have been reported[26,55].

It is likely that cadmium constituted a health hazard long before its industrial use and even before its discovery. Since cadmium occurs in nature together with zinc, lead and copper, the use of these metals over several thousand years, has necessarily been a source of human exposure to cadmium. Some toxic effects (such as proteinuria and emphysema) attributed in the past to lead[87], were probably caused by cadmium.

Occupational exposure to cadmium is limited in space and is normally amenable to adequate control by well-designed preventive measures. Furthermore, it concerns a limited number of adult workers, who are in good clinical health and are kept under medical surveillance. The situation is different for the general population, which is continuously exposed to moderate doses of a widely dispersed contaminant, and certain groups may be more susceptible than others to the toxicity of cadmium.

General environment

For non-smokers, food constitutes the principal environmental source of cadmium. Basic foodstuffs such as wheat or rice can accumulate relatively high amounts of cadmium when grown on a cadmium-polluted soil. Internal organs of mammals, such as liver and kidneys, may also contain high amounts of cadmium. The daily intake depends on both the dietary habits and the concentration of cadmium in

foodstuffs. In the United States, it has recently been calculated that, even assuming an increase of cadmium levels in food between 1945 and 1975, the intake of cadmium has remained fairly constant because of profound changes in eating habits[98]. On the other hand, in Japan, where rice represents the basic staple food, the cadmium intake has, at least in some areas, drastically increased as a result of cadmium pollution.

Friberg et al.[27] have estimated the daily intake of cadmium in an uncontaminated area to be 25-60 µg for a 70 kg person. Values of 10-30 µg/day in the United Kingdom[64] and of 26-61 µg/day in the United States[60] have been reported.

The more recent estimates are lower. A mean daily intake of 16 µg Cd was found in Sweden[20] and a very similar value was obtained in Belgium (15 µg/day)[9].

The most dramatic example of detrimental health effects resulting from environmental exposure to cadmium is the Itai-Itai disease, which broke out in Japan during the early half of the 20th century. This unusual disease was characterized by pain and bone fractures (hence the name of the disease 'Ouch-Ouch'), proteinuria, aminoaciduria and severe osteomalacia. It was first diagnosed among the inhabitants in the Jintzu River basin in Toyama Prefecture[30]. The patients had been exposed to cadmium as a result of contamination of water and rice by discharges from a zinc mine. The average daily intake of cadmium in the endemic area was estimated at 500-800 µg whereas outside the area, the intake amounted to about 30-50 µg[28]. Several other areas in Japan have been found polluted by cadmium[49,67,83]. In these areas, the incidence of tubular protenuria in the general population is significantly higher than in non-polluted areas.

Excessive environmental exposure to cadmium is, however, not restricted to Japan. In 1979, a national geological survey carried out in England indicated a substantial contamination of soil by cadmium at Shipham, a Somerset village. Cadmium originated from nearby extinct calamine workings. The cadmium level in the liver of inhabitants was found to be on the average 5 times higher than in control subjects[33]. After examining 32 residents of the village, Carruthers and Smith[14] concluded that some of the abnormal biological findings observed (namely at the kidney level) could be attributed to cadmium. Their conclusion is certainly premature since the study was based on volunteers and did not include a control group. At about the same time, studies were carried out on the general population in Belgium; these suggested that industrial pollution by cadmium in one area of this country may exacerbate the age-related decline of the renal function, and even increase the proportional mortality rate from nephrosis and nephritis[52,53].

In a recent mortality study carried out at Shipham[39], slight increases in the standardized mortality ratios from nephritis, genito-urinary disease, hypertensive and cardiovascular disease were found by comparison with a nearby control village. However, no definitive conclusion can be drawn from this study, because of the small size of the population examined and of the low number of deaths from specific causes.

Tobacco

Tobacco smoking, too, may significantly increase man's exposure to cadmium. Cigarettes contain generally 1-2 µg cadmium, of which about 10% is absorbed by the lung. Hence, heavy smokers have at age 50-60 a cadmium body burden on the average twice higher than that of non-smokers[21,57].

Metabolism

The main feature of cadmium metabolism is its very long biological half-life and hence its progressive accumulation in the organism. Evolution seems to have provided man with no effective homeostatic mechanism to deal with an increasing intake of this heavy metal. No metabolic pattern allowing its elimination from the organism has evolved. Although the synthesis of metallothionein - an intracellular cadmium-binding protein - corresponds to a defence mechanism, it is also responsible for the selective accumulation of cadmium in the kidney and thus indirectly for its toxic effect on that organ.

Absorption

Inhalation. Depending on the size of the particles, 10-50% of the inhaled cadmium is deposited in the alveolar compartment of the lungs. A part of the deposited cadmium is eliminated by the lung clearance mechanisms. The absorption of the retained cadmium depends on its chemical form. For CdO, it has been estimated at about 60%[51].

Ingestion. In man, the average oral absorption of cadmium amounts to about 5%[63,76]. However, the absorption by the gastrointestinal tract - the main route of exposure for the general population - is influenced by several nutritional factors.

Animal experiments have shown that a low intake of calcium and protein may considerably increase the intestinal absorption of cadmium[50,93]. It is very likely that the low calcium and protein intake in Japan at the end of World War II contributed to the accumulation of cadmium in Itai-Itai disease patients. The study of Flanagan et al.[24] has demonstrated that subjects with low iron stores (low ferritin levels in serum) absorb significantly more cadmium (up to 15% of ingested cadmium) than persons with normal iron stores. Oral absorption of cadmium is therefore higher in females than in males.

It should be stressed that, independent of the absorption rate, age may also influence the cadmium intake through food. Since the greatest caloric intake occurs between the ages of 10 to 20 years, it can be expected that the rate of cadmium accumulation in the organism is the greatest in this age group. The amount of cadmium absorbed via food range from about 0.2 to 5 µg/day[51,69]. However, in view of the nutritional factors mentioned above, it is clear that the intake may be much higher in certain groups of the general population.

Distribution. In blood, more than 90% of cadmium is found in cells. In vitro experiments[35] have shown that

red blood cells accumulate little cadmium, whereas lymphocytes - which synthetize metallothionein - can concentrate cadmium at a level 3000-fold greater than in the cadmium medium.

The two main sites of storage of cadmium are the liver and kidneys. The amount of cadmium accumulated in the liver and kidneys represents about 50% of the total body burden. In the kidney, the concentration of cadmium in the cortex is about 1.5 times higher than in the whole organ[58].

The concentration of cadmium in the liver increases continuously with age; that in the kidney increases also with age at least until age 50-60. From that age, cadmium concentration in kidney levels off and/or decreases. Several explanations have been proposed for this phenomenon, e.g. the effect of age-related functional and morphological changes in the renal cortex[98], an effect due to a lower environmental pollution by cadmium in the past and a decreased food intake with age.

The cadmium body burden of non-occupationally exposed adults in Europe and the United States ranges from 5 to 40 mg[51]. Smokers have on the average a higher cadmium body burden than non-smokers. Ellis et al.[21] have measured by the neutron activation technique the absolute amounts of cadmium stored in the kidney and the liver of 20 adult male Americans. They estimated that the average body burden of cadmium at age 50 is 19.3 mg for non-smokers and 35.5 mg for smokers.

Many studies were carried out to measure the concentration of cadmium in the human kidney cortex. The highest values at age 50 were observed in Japan (60-120 ppm)[99]. In Europe and in the USA, mean values between 15 and 50 ppm were reported[31,74,86].

Recently, a study[100] was carried out to assess the human exposure to cadmium in different areas of the world. The concentration of cadmium was measured in samples of kidney cortex from deceased teachers. The highest values were observed in Japan in the age group of 50 (geometric mean = 67.0 ppm). Values obtained in other countries using the same age group were 2-4 times lower, with geometric means ranging from 15.7 ppm (India) to 39.3 ppm (Belgium). Since these values are average estimates, it can be assumed that in certain countries as in Japan and Belgium, a small fraction of the population has already reached the critical level (around 200 ppm; see toxic effects on the kidney).

In industrial workers, the concentration of cadmium in the kidney cortex may be much higher (e.g. up to 300 ppm)[27,81]. However, when renal damage has occurred, the cadmium level in kidney decreases. This explains why, in most severely poisoned workers and also in patients with Itai-Itai disease, the concentration of cadmium in kidney cortex may be relatively low and sometimes not markedly different from that observed in normal subjects. However, in these persons, the concentration of cadmium in liver remains elevated.

The levels of cadmium in the liver are generally much lower than those in renal cortex. Because of its weight, however, the liver contains a significant fraction of the total body burden. In non-occupationally exposed adults, the concentration of cadmium in the liver ranges approximately from 0.5 to 5 ppm[69]. In cadmium-exposed workers, hepatic cadmium levels may exceed 150 ppm[81]. The ratio between cadmium concentration in liver and in kidney increases with the intensity of exposure[27]; it is therefore much higher for occupationally exposed persons than in the general population. A significant accumulation of cadmium also takes place in other tissues, namely in the pancreas, the thyroid and the salivary glands. The placenta barrier is effective against the transfer of cadmium to the fetus.

In tissues, cadmium is mainly bound to metallothionein, a low molecular weight protein (mol. w 6600) rich in cystein residues but deficient in aromatic aminoacids. The synthesis of this protein corresponds very probably to a defence mechanism against the toxic cadmium ion. One has also hypothesized[27] that metallothionein is involved in the transport of cadmium from the liver to the kidneys. Because of its small size, the cadmium-metallothionein complex released from the liver is freely filtered through the glomeruli to be reabsorbed by the tubular cells. Such a mechanism could explain the selective accumulation of cadmium in kidney cortex.

The cadmium stored in tissues is released very slowly. The biological half-life of cadmium in the liver has been estimated to be 5-10 years and that in the kidney to be about twice as long as in the liver[99]. The total biological half-life of cadmium in the body has been estimated up to 30 years[27].

Excretion

As can be expected from a cumulative toxic, only a small part of absorbed cadmium is excreted. This excretion occurs mainly via the urine. An important fraction of urinary cadmium is probably bound to metallothionein. A closed relationship between both parameters has been reported[15,80] (fig. 1).

On a group basis, the urinary excretion of cadmium is proportional to the body burden and thus increases with age, at least up to 50-60 years[19]. When renal damage has occurred, cadmium excretion by urine increases drastically and the relationship with body burden disappears.

Evaluation of cadmium exposure

The determination of cadmium concentration in liver and kidney samples collected at autopsy or by biopsy provides a direct assessment of the internal integrated dose of cadmium of population groups. Another approach, more directly useful on an individual basis, consists in measuring in vivo by a neutron activation technique the amount of cadmium accumulated in the liver[97] or the kidney[1]. This technique has been applied with occupationally exposed workers[81] and with the general population[21]. For various practical reasons, its routine use cannot be envisaged.

So far, in the health surveillance programs of workers in industry, or in large scale studies on the general

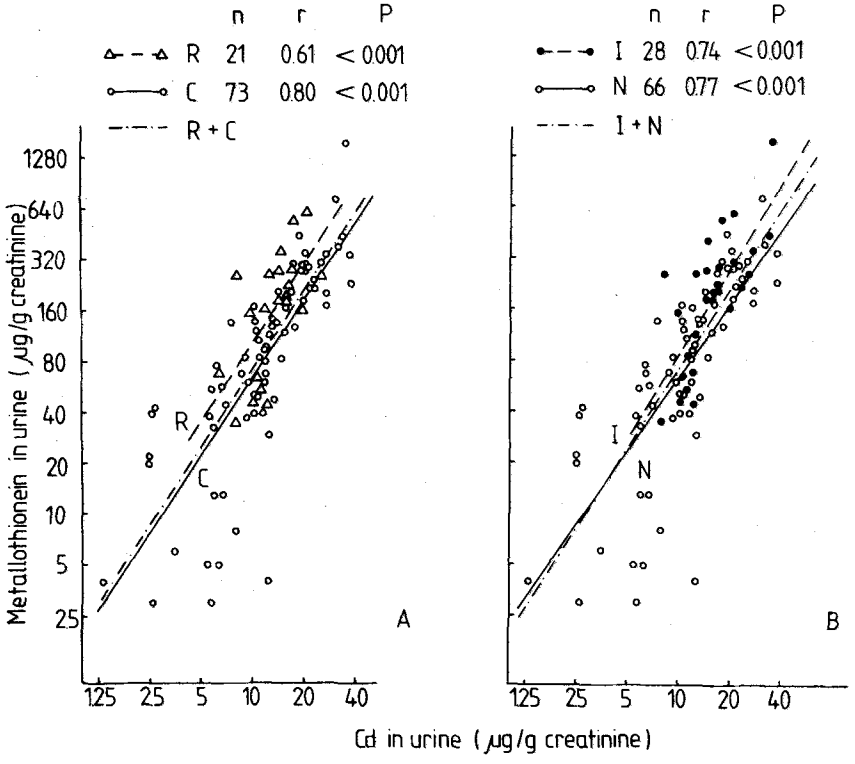

Figure 1. Relationship between urinary metallothionein and urinary cadmium. *A* Workers currently exposed to Cd (n = 73, group C) and workers removed from Cd exposure (n = 21, group R). *B* Workers with normal (n = 6, group N) and increased (n = 28, group I) β_2-microglobulinuria. The regressive line for the total population is shown (reproduced from Roels et al.[80]).

population, the exposure to cadmium has usually been evaluated indirectly by measuring the metal in easily accessible biological samples such as urine or blood.

It is now well established that the concentration of cadmium in blood reflects mainly the average intake of the past few months[47,55]. In non-occupationally exposed people, the cadmium level in whole blood is normally below 5 µg/l.

The significance of urinary cadmium is somewhat more complex[55]. Under moderate exposure (environmental or moderate industrial exposure) and as long as the cadmium-binding sites in the kidney are not saturated, the amount of cadmium excreted in urine is a relatively good indicator of the amount of cadmium stored in the organism. In the absence of occupational exposure, the concentration of cadmium in urine is usually lower than 1 µg/g creatinine.

A urinary excretion of cadmium higher than 10 µg/g creatinine indicates that the saturation of cadmium-binding sites of the organism is occurring and hence that renal dysfunction, if not already present, may develop if exposure is pursued. At this stage, urinary cadmium may also be significantly influenced by recent exposure.

There is now sufficient evidence to suggest that metallothionein level in urine has the same significance as urinary cadmium. As shown in figure 1, good correlations have been observed between both parameters whatever the status of renal function.

Toxic effects

Acute exposure. Ingestion. Acute oral intoxication by cadmium has been observed after the ingestion of acidic food or beverage stored in cadmium-plated containers. For instance, a poisoning incident among Swedish school children was caused by fruit juice contaminated in a vending machine which had a cadmium-plated reservoir[68]. Cases of acute oral intoxication have also been reported in workers exposed to cadmium dust who had eaten or smoked at their place of work. The use of cadmium-plated cooking utensils, currently prohibited in many countries, was in the past frequently a cause of acute cadmium poisoning.

Following acute ingestion of cadmium the target organ is the gastro-intestinal tract. Symptoms are severe nausea, vomiting, salivation, abdominal cramps and diarrhea. In the case of fatal intoxication, these symptoms are followed up by shock due to the loss of liquid or by acute renal failure and cardiopulmonary depression. The no-effect level of cadmium administered at a single oral dose to adults has been estimated at 3 mg and the lethal doses range from 350 to 8900 mg[51].

Inhalation. Acute inhalation of CdO fume generated by heating cadmium metal (in welding, smelting or soldering operations) has been responsible for most fatal or near-fatal accidents in the industry. Between 1958 and 1976, 24 cases of acute exposure to CdO were reported in the literature, involving 100 workers of whom 17 died[59]. It is likely that many more cases were not reported. Symptomatology is that of severe bronchial and pulmonary irritation appearing several hours after exposure. The lethal concentration of CdO for man has been estimated to be around 5 mg/m^3 for a 8-h exposure[51].

Although acute - and sometimes fatal - cadmium poisoning still constitutes a hazard in industry, it is much less frequent than the chronic intoxication.

Chronic effects

Following long term exposure, cadmium may exert various toxic effects, such as renal disturbances, lung insufficiency, osteomalacia, anemia and anosmia. The hypothesis has also been put forward that cadmium is carcinogenic for man and plays a role in the development of cardiovascular diseases, in particular hypertension. Although the lung may be the organ first affected after repeated subacute exposure to cadmium fume, there are presently sufficient data to conclude that under present exposure conditions in industry, the kidney is usually the critical organ. This is also the case when exposure occurs by ingestion.

Effects on the kidney

Cadmium nephropathy was first described in occupationally exposed workers[25,26]. Classically, the functional disturbances induced by cadmium involve the proximal tubule, giving rise to a tubular type proteinuria as in the Fanconi syndrome[12,44,72,90]. The urinary excretion of low molecular weight proteins (mol. wt below 40,000) such as β_2-microglobulin, lysozyme and retinol-binding protein, is markedly increased (up to 1000-fold). Cadmium affects the tubular reabsorption of these proteins which are freely filtered through the glomeruli and taken up by the proximal tubule cells. Currently, the determination of urinary β_2-microglobulin is the most widely used test for the early detection of cadmium proteinuria. It has been shown, however, that because of its greater stability in urine, retinol-binding protein is a more practical and reliable parameter[4].

In cadmium-exposed workers, the low molecular weight proteinuria is often accompanied by an increased urinary excretion of high molecular weight proteins like albumin, transferrin or IgG (mixed type proteinuria)[5,6,32,54]. In some workers, only a glomerular type proteinuria with an enhanced excretion of high molecular weight proteins may be observed (fig. 2). Therefore, an increased urinary excretion of both low and high molecular weight proteins should be regarded as critical effects and thus should be looked for concurrently in order to detect at an early stage renal damage induced by cadmium.

Increased levels of β_2-microglobulin and creatinine in serum, generally accompanied by a reduction in creatinine clearance, have been observed in cadmium-exposed workers, which is suggestive of a glomerular dysfunction[5,73]. Cadmium proteinuria may be also associated with enzymuria, aminoaciduria, glucosuria, impaired acid excretion, decreased concentration capacity of the kidneys and increased excretion of calcium and phosphates. The disturbances in calcium and phosphorus metabolism may lead to the formation of kidney stones and/or to a demineralization of the bones.

These signs of renal damage, observed in cadmium workers, are commonly found in Itai-Itai patients. A higher incidence of proteinuria, glucosuria and β_2-microglobulinuria has been observed in the Jintzu river basin in Toyama Prefecture, where Itai-Itai disease was first seen, and also in other areas where high concentrations of cadmium were found in rice. In the endemic area of Toyama, the increased urinary excretion of β_2-microglobulin was strongly related to the residence time in that area as well as to the purposes for which contaminated river water was used[48]. β_2-Microglobulin concentration in urine was also correlated with the cadmium level in urine and blood. It has been suggested that farmers who usually eat rice containing 0.6 ppm Cd may develop renal damage in their fifties.

It seems however that Japan is not the only country where environmental exposure to cadmium may adversely affect the health of the general population. Recently, a study was carried out in Belgium, suggesting that environmental exposure to cadmium in an industrialized area polluted by this metal may exacer-

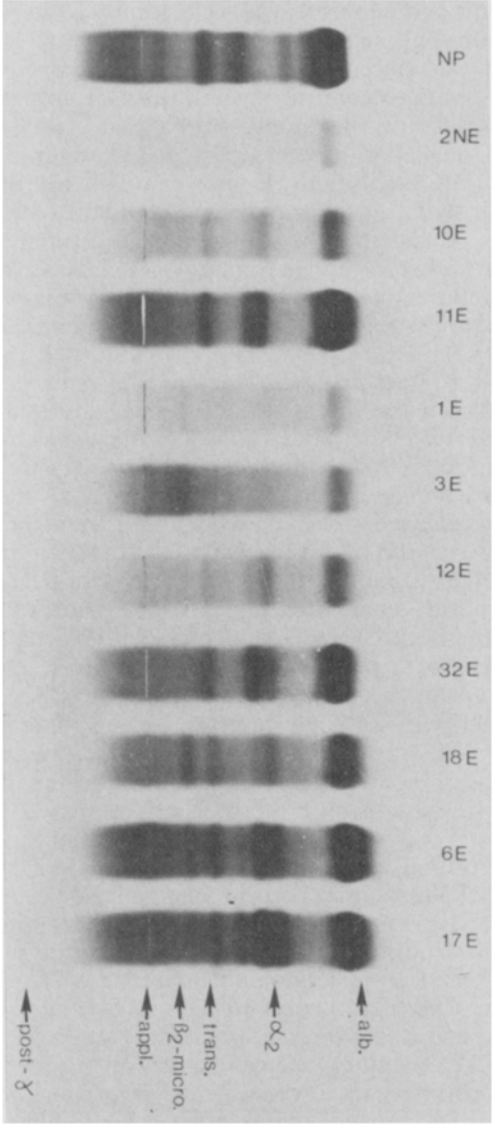

Figure 2. Electrophoresis on agarose gel of about 100-fold concentrated urinary proteins from non-exposed (NE) and cadmium-exposed (E) workers. 2NE: normal pattern; 10E and 11E: glomerular type patterns; 1E and 3E: tubular type pattern; 12E, 32E, 18E, 6E and 17E: mixed type patterns. NP: reference plasma (reproduced from Bernard et al.[5]).

bate the age-related decline of renal function in elderly resident groups[53,78]. The renal function of a group of 60 women over 60 years who had spent the major part of their lives in the cadmium-polluted area, was compared with that of 2 groups of aged women from areas less polluted by this heavy metal. The group of aged women from the contaminated area had, on the average, a higher cadmium body burden (as reflected by a higher urinary excretion of cadmium) than the groups from the other areas. The parameters selected for evaluating renal function (total protein, aminoacids, β_2-microglobulin and albumin in urine) followed the same trend. Significant correlations were observed between the urinary excretion of cadmium and that of the 4 renal function parameters. Furthermore, a retrospective mortality study carried out shortly after these observations[52] revealed that the standardized mortality ratio from nephritis and nephrosis was significantly higher in the cadmium-polluted area than in other areas. The increase was observed for both males and females, which tends to confirm the influence of an environmental factor. An autopsy study is presently under way in our laboratory, comparing the cadmium body burden of inhabitants in Liège area with that of persons living in other parts of Belgium. Preliminary results indicate that the cadmium concentration in the kidney cortex in the age group 40–60 years is, on the average, nearly twice as high in the Liège area (geometric mean 37 ppm) as in other areas of the country.

The latency period before the onset of renal damage depends on the intensity of exposure and generally exceeds 10 years. After removal from exposure, the signs of renal dysfunction may not be reversible[79]. On the basis of the results of cadmium analysis in renal tissues collected from about 30 autopsies or biopsies in persons who had been exposed to cadmium, Friberg et al.[27] has suggested that the critical level of cadmium in renal cortex for the appearance of tubular proteinuria is about 200 ppm. In 1977, a WHO task group[104] concluded that the critical level of cadmium in the kidney cortex may be between 100 and 300 ppm with 200 ppm as the most likely estimate. With the development of neutron activation analysis, the critical levels of cadmium in the human organism have been more precisely estimated. Roels et al.[77,81,82] have measured by this technique the concentrations of cadmium in the liver and the kidney cortex of 309 male workers in 2 Belgian zinc-cadmium plants. The renal function of these workers was evaluated at the same time by determining the urinary excretion of β_2-microglobulin, albumin and of total protein. The critical concentration of cadmium in the kidney cortex has been estimated between 215 and 385 ppm (assuming a mean kidney depth of 8 cm), which corresponds to concentrations in liver from 30 to 60 ppm. The minimal critical body burden of cadmium has been estimated to be around 180 mg. On the basis of the relationship between urinary and renal cortex cadmium, the authors estimated the critical concentration of cadmium in urine between 10–15 µg/g creatinine, a value in agreement with that derived previously from the relationships between urinary cadmium and prevalences of signs of renal dysfunction[4,6,10]. The conclusions of Roels et al.[77,81,82] were confirmed by Ellis et al.[22] who performed a similar study on American cadmium workers.

By using an 8-compartment kinetic model, Kjellström and Nordberg[47] have calculated that a daily intake via food of 440 µg was necessary for a European-American population to reach an average renal cortex concentration of 200 ppm. In 1979, a WHO task group[103] concluded that a daily food intake of cadmium of 200–400 µg may be associated with the appearance of renal critical effects.

It should be stressed, however, that these estimates are derived from data obtained in cadmium-exposed workers. They do not necessarily apply to the general population in which some groups may be more susceptible to the toxic effects of cadmium.

On the other hand, the health significance of an increased urinary excretion of specific low or high molecular height proteins (the effect regarded as critical) is still a matter of discussion. The Subcommittee on Cadmium of the British Occupational Hygiene Society's Committee on Hygiene Standards[8] does not consider as an adverse effect an increase in the excretion of proteins which is not detectable by classical tests for proteinuria (clinical proteinuria). More information is required on the disturbances before it can be concluded whether they must be considered adverse health effects. Meanwhile, it is reasonable to try to indicate at which levels of exposure these disturbances do not occur.

Effects on the lungs

Impairment of lung function has been described only among workers exposed to cadmium by inhalation. Studies performed in the 1950's[2,7,26,43,44] have reported emphysema in workers exposed to cadmium dust and fume. However, in these investigations, the influence of tobacco was not always taken into account so that it is likely that all the pulmonary changes described were not due to cadmium alone. More recent investigations[54,92] on workers currently exposed to cadmium indicate that because of improved working conditions, the pulmonary changes are mild and occur with a much lower incidence and probably at a later stage than the biological signs of renal damage.

Effect on the bones

Bone lesions are usually a late manifestation of a severe chronic cadmium poisoning. They are characterized by osteomalacia, osteoporosis and spontaneous fractures. The patient complains of pain in the back and in the extremities, difficulties in walking and pain on bone pressure. It is generally thought that these bones changes are secondary to renal tubular dysfunction (increased urinary loss of calcium and phosphorus) eventually associated with an altered metabolism of vitamin D. Indeed, it has been shown experimentally that in the chicken kidney, the hydroxylation of vitamin D was inhibited by cad-

mium, which leads to a deficiency in the active form of the vitamin[23].

An extreme manifestation of the toxic effect of cadmium on the bones, is the Itai-Itai disease, which broke out at the end of World War II in the cadmium-polluted area of Toyama in Japan. The etiology of this disease is not yet fully elucidated. A few authors[46,96] have suggested that it was not related to cadmium-pollution but resulted from vitamin D-deficiency. However, a task group of international experts convened by WHO in 1977 concluded, after a review of the epidemiological data regarding Itai-Itai disease, that the close epidemiological association between cadmium exposure and the disease, the accumulation of cadmium in tissues, the finding of osteomalacia in cadmium-exposed workers[66] and the occurrence of renal tubular dysfunction among both Itai-Itai patients and cadmium-exposed persons indicate that cadmium was a necessary factor in the development of Itai-Itai disease.

Itai-Itai disease struck mainly aged women who have had several children and had suffered from calcium and phosphorus deficiency. It is now believed that this severe bone disease resulted from the combination of nutritional deficiencies and cadmium-induced nephropathy.

Carcinogenic effects

Several epidemiological studies have suggested that inhalation of cadmium might increase the incidence of prostate and probably lung cancer in occupationally exposed workers[36,37,45,75]. No firm conclusion can yet be drawn because of the relatively small number of workers examined and also because of the difficulty, in many studies, to evaluate the possible role of other carcinogenic agents such as tobacco. Conflicting results have also been obtained regarding the induction by cadmium of chromosome anomalies in lymphocytes from cadmium-exposed workers (see other effects).

In animals, the injection of cadmium can induce local sarcoma. However, the significance of these tumors can be questioned since it is well known that tumors can be produced by the repeated injection of normally noncarcinogenic substances. Animal experiments have not shown any incidence of prostatic carcinoma. The only indirect tumors which have been induced in different animal species are Leydig cell tumors, but such tumors have not been observed with a higher incidence in cadmium-exposed persons.

There is presently no clinical or experimental indication that exposure to cadmium via food favors the development of cancer, even in Japan where the intake is relatively high.

The association between cancer and exposure to cadmium in man thus appears to be tenuous. Nevertheless, in 1976, the International Agency for Research on Cancer[40] classified cadmium among chemicals which are probably carcinogenic for man. However, new concern about cadmium carcinogenicity has been generated recently by the report of Takenaka et al.[95] on lung cancer in rat chronically exposed to cadmium chloride by inhalation. The animals were continuously exposed to cadmium concentrations in air (aerosols) of 12.5, 25 and 50 $\mu g/m^3$ for a period of 18 months. 13 months after the end of the exposure histopathological examination revealed a dose-dependent incidence of lung carcinoma (71% in the highest, 53% in the middle and 15% in the lowest concentration group).

Hypertension

Schroeder[84] was the first to suggest that cadmium might contribute to the development of essential hypertension in man. He showed that long-term oral administration of cadmium to rat may induce a systolic hypertension which persists throughout their life. He reported also that patients dying from cardiovascular diseases had higher concentrations of cadmium or higher cadmium to zinc ratios than those dying for other causes. This association between hypertension and cadmium levels in tissues was confirmed by some authors[42,56], but not by others[62,65]. Similarly[27,101], the hypertensive action of cadmium in animals was reproduced by some investigations while others failed to show any effect. Carroll[13] and later Hickey et al.[34] found a correlation between the cadmium concentration in the air of more than 20 American cities and the death rate from cardiovascular diseases. However, Hunt et al.[38], in a study involving 77 cities in the USA, failed to show a correlation between cadmium fallout and mortality from cardiovascular diseases. Furthermore, reanalyzing Carroll's data, they were able to demonstrate a higher correlation between population density and hypertension than between hypertension and the cadmium level in the air.

A significant negative correlation between total water hardness and cardiovascular diseases has been fequently reported[61]. Since hard water usually contains fewer heavy metals - in particular, cadmium - than soft water, this explains why one may find a correlation between cadmium in water and prevalence of hypertension[85]. However, with regard to this relationship between hypertension and cadmium in water and also that between hypertension and cadmium in air, it should be remembered that the cadmium intake by the general population through air and water is lower than through food. So far, there is no report of hypertension in industrially exposed workers nor in Itai-Itai disease patients. In Japan, the determination of blood pressure in more than 10,000 persons living in cadmium-polluted areas did not reveal any difference in blood pressure with the degree of pollution[41]. A recent epidemiological study[88] confirms this observation.

These negative findings under conditions of relatively high exposure to cadmium do not disprove that cadmium, at a low environmental level, plays a role in the etiology of hypertension. As suggested by Perry and Erlanger[71], the relationship between cadmium and blood pressure may not be linear and the potential action of cadmium on blood pressure may be divergent according to the intensity of exposure.

Indeed, these authors have observed in animals that at low doses cadmium exhibits a pressor action while at higher doses, it decreases systolic blood pressure. There also have been some speculations that factors such as age, sex, smoking habits, individual susceptibility or mineral content of the diet interfere with the hypertensive action of cadmium. In summary, the role of cadmium in the development of hypertension remains uncertain but the failure, after more than 15 years of epidemiological and experimental studies, to show a clear relationship between cadmium and hypertension casts some doubt on the validity of Schroeder's hypothesis.

Other effects

Among other effects reported in persons chronically exposed to cadmium, one can mention: anosmia, ulceration of the nasal mucosa, yellowing of dental necks, mild anemia and occasionally some signs of liver damage. So far, no report on teratogenic effects in populations exposed to cadmium has been published. In a study on cadmium-exposed women in USSR[16], congenital malformations were not observed, but the birth weights of newborns were lower than those of newborns from control mothers. Data on genetic effects of cadmium are conflicting. One study[89] on Itai-Itai patients showed some chromosomal aberrations, but this was not confirmed by another study[11]. Bui et al.[11] did not find any chromosome anomaly in 5 cadmium-exposed workers. By contrast, Deknudt and Leonard[17] and Bauchinger et al.[3] found a slight but significant increase of the chromosomal anomalies in workers exposed to cadmium. However, in these 2 studies, the workers had also been exposed to other metals, such as lead, zinc or arsenic so that the anomalies observed can not be firmly attributed to cadmium exposure. O'Riordan et al.[70] found no increased aberration yields in blood lymphocytes of cadmium workers. They suggest that the aberrations described previously result from a synergistic action of heavy metal with some environmental mutagens. Recently, Gasiorek and Bauchinger[29] studied the effect of lead, cadmium and zinc separately and in combination on the incidence of chromosomal aberrations in human lymphocytes. They observed a significantly increased incidence of anomalies exclusively with cadmium, an observation the authors relate to the metabolism of cadmium in lymphocytes (synthesis of metallothionein).

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Cadmium in foods and the diet

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Summary. Information on the sources of cadmium in food are presented and the effects of raised environmental levels of cadmium on the concentration of cadmium in plant based foods, fish and shellfish, meat and offals, and dairy produce are discussed. Information is also presented on normal dietary intakes of cadmium and how these intakes may be elevated by environmental pollution or atypical dietary habits. The estimation of dietary intakes of cadmium using data about extreme intakes of specific foods is described.

Introduction

Cadmium is naturally present in all parts of the environment; it is present in all soils and sediments at concentrations which are generally < 1 mg/kg[31] and its total concentration in unpolluted seawater, where it exists mainly as chlorocomplexes, is generally < 1 µg/kg[27]. The concentration of cadmium in air in non-industrialized areas rarely exceeds 2.5 ng/m^3 which is equivalent to 3 ng/kg[5]. Consequently, all food, whether it be of plant or animal origin, is exposed to and contains cadmium. Unlike many other metals, cadmium has come to be used by man only relatively recently. It was identified as an element in 1817; its large scale use dates from the 1940s; and it is only in the last 3 decades that serious consideration has been given to cadmium as a food contaminant.

The use of cadmium may increase, in several ways,