BioMetals **17:** 485–489, 2004.

Cadmium and health in the 21st Century – historical remarks and trends for the future

Gunnar F. Nordberg
Environmental Medicine, Department of Public Health and Clinical Medicine, Umeå University, SE-90187 Umeå, Sweden (E-mail: gunnar.nordberg@envmed.umu.se)

Key words: cadmium, health effects, history, humans

Abstract

The first health effect of cadmium (Cd) was lung damage, reported in workers already in the 1930's, while bone effects and proteinuria were reported in the 1940's. After World War II, a bone disease with fractures and severe pain, the itai-itai disease, a form of Cd-induced renal osteomalacia, was identified in Japan. Subsequently, the toxicokinetics and toxicodynamics of Cd were described including its binding to the protein metallothionein. International warnings of health risks from cadmium pollution were issued in the 1970's. WHO, 1992, identified renal dysfunction as the critical effect and a crude quantitative evaluation was presented. In the 1990's population groups in China exposed to Cd via rice were studied and new information on skeletal, renal and reproductive toxicity of Cd was obtained in the ChinaCad project. There was a decrease in Bone Mineral Density (BMD), an increased prevalence of fractures and an increased urinary content of marker proteins of renal dysfunction among persons with long term exposure to Cd. The development of such biomarkers can be seen as a result of applied 'proteomics' research. Variation in metallothionein gene expression was related to development of renal dysfunction, supporting the usefulness of this 'genomic' approach. The ongoing rapid development of 'genomics' and 'proteomics' technologies will improve possibilities for molecular epidemiology studies in the future, providing an even better basis for preventive action. In many countries, Cd exposures are now under better control than in the past. The target for the 21st century is to achieve a totally acceptable exposure situation without adverse health effects from Cd.

Introduction/Historical remarks

When discussing Cadmium and Health in the 21st century, it may be of interest to summarize the first published observations concerning cadmium induced health effects. Damage to the lung in cadmium-exposed workers was the first human health effect related to cadmium (Cd) in a report published already in the 1930's (Bulmer *et al.* 1938). Acute gastrointestinal effects with vomiting and diarrhoea in persons consuming Cd contaminated food and drink were reported in the 1940's (US Publ Health Serv 1942). Nicaud *et al.* 1942 observed a systemic effect, osteomalacia, in a few Cd – workers. Proteinuria and emphysema in Cd battery workers were reported by Friberg 1948. A bone disease with fractures and severe pain, the Itai-itai disease (Japaneese for Ouch – Ouch disease), occurred after World War II in Fuchu, Toyama prefecture, Japan (Hagino 1957). Dr Hagino was a local practitioner who initiated studies concerning this disease. X-ray findings included Milkman's pseudofractures (Looser zones) in the long bones, changes characteristic of osteomalacia. There were also decalcification and fractures of other bones including compression fractures of the spine. In the area where the disease occurred, women had the habit of screening out sunlight by wearing typical dress with wide hats. Biochemical findings were characteristic of osteomalacia with increased serum levels of alkaline phosphatase and decreases in calcium and phosphate. Gastrointestinal- and renal dysfunction were other less prominent findings (Ishizaki 1969, Murata *et al.*

1970). In these cases, elevated levels of Cd in urine were found (Ishizaki 1969) and in 1968 the disease was declared by the Japanese Government to be a disease related to environmental pollution. Cadmium, released from a mine in the mountains was transported by a river into the plain, where the contaminated water was used for irrigation of rice fields. The rice plant takes up Cd from the soil and consumption of contaminated rice. This is the main route of exposure for the general population. Further aspects concerning bone effects in humans exposed to cadmium are given in the following text of the present paper and in other contributions to the present volume by Kazantzis (2004), by Zhu *et al.* (2004), by Järup (2004) and by Nishijo *et al.* (2004).

Advances in cadmium toxicology, early risk estimates

At the time when Itai-itai disease was discovered in Japan, research on cadmium toxicokinetics and health effects were going on in Sweden, initiated by Friberg's (1948, 1950) observations of renal damage in Cd workers. Toxicological studies in animals showed that in long-term exposures, and even after a single exposure, the level of Cd is gradually increasing in the kidneys. The explanation for this phenomenon is that the low molecular weight, Cd-binding protein metallothionein (MT) carries Cd to the kidney (Nordberg 1972). Based on this information on cadmium toxicokinetics, the kidney was identified as the critical organ, crucial for development of other more severe health effects of cadmium. Murata 1970 correctly identified itai-itai disease as a form of renal osteomalacia. The identification of the kidney as the critical organ in combination with an approximate tissue level of Cd in the kidney cortex giving rise to toxicity, made it possible to estimate intake levels giving rise to renal effects. This evidence showed that there were small or non-existing safety margins of environmental and occupational cadmium exposures as they occurred in the 1970's. The risks were pointed out in a number of early publications in English (Friberg *et al.* 1971; Nordberg 1974; Nogawa *et al.* 1975).

Model of cadmium toxicokinetics and kidney damage

Further studies supported the original observations and we advanced a model regarding the kinetics of Cd in humans (Kjellström & Nordberg 1978) and the mechanisms of action of Cd on the kidney (Nordberg *et al.* 1985; Nordberg & Nordberg 2000). After uptake into blood plasma, Cd is mainly bound to albumin and other high-molecular weight proteins. This form of Cd is taken up to a large extent by the liver and may cause liver damage (Faeder *et al.* 1977; Friberg 1950). After uptake in the liver, Cd is released from albumin and the synthesis of metallothionein (MT) is induced. Cadmium-metallothionein (Cd-MT), because of its small molecular size, is efficiently filtered through glomeruli and taken up by renal tubular cells. In long-term exposure there is a slow release of Cd-MT from the liver to blood with gradual uptake of Cd in the kidney (Nordberg 1972; Chan *et al.* 1993). After uptake of Cd-MT into renal tubular cells via pinocytosis (Fowler & Nordberg 1978), MT is catabolised in lysosomes releasing cadmium ions causing membrane damage (Nordberg *et al.* 1994) and perturbation of calcium metabolism, particularly in basolateral membranes (Jin *et al.* 1987, Leffler *et al.* 2000). Based on this model, which was early quantitated and made available in a mathematical form (Kjellström & Nordberg 1978), risk estimates for renal effects in Cd exposures were presented. These calculations based on toxicokinetics and toxicodynamics (also presented by WHO 1992) have now been complemented by an increasing body of epidemiological evidence. Such evidence on Cd exposure and proteinuria are presented in the following text and in other presentations at this symposium by Bernard, by Jin *et al.*, by Järup and Alfvén, and by Oskarsson *et al.*

Reproductive toxicity and carcinogenicity

Reproductive effects of cadmium were shown already in the 1950's, when Parizek and Zahor(1956), reported the occurrence of testicular necrosis after injection of relatively modest doses of cadmium in rats. The toxicity of cadmium to the male reproductive system has been extensively investigated in animals, but very limited data is available in humans. Studies of male reproductive hormones were included in the ChinaCad studies (cf later section of this paper). Cd and testicular and prostatic cancer is reviewed by Goyer *et al.* (2004).

When moderate cadmium doses were injected in prepubertal female rats, or in adult rats in persistent oestrus, ovarian changes are observed (Kar *et al.* 1959). Effects on the placenta and 'toxaemia of pregnancy' can be induced by Cd in pregnant rats (Parizek

1965). Such changes may be the basis for embryotoxic and teratogenic effects of cadmium, first reported by Ferm and Carpenter 1968. Developmental effects in the offspring of animals exposed to low levels of oral Cd during pregnancy were reported and discussed in the present symposium by Oskarsson et al. (2004).

The first observations of cancer in experimental animals as a result of Cd exposure were reported by Haddow *et al.* 1961. They found sarcomata at the site of injection and Leydig cell tumors in the testis. The findings of sarcomata were confirmed by Kazantzis 1963. Later studies have found cancer in other organs including the lung after inhalation (review by IARC 1993). Recently, attention has been paid to the risks of testis and prostate cancer in animals and Man (reviewed in this symposium by Goyer *et al.*, 2004).

In humans, the first report about an increased prevalence cancer was published 1967. Kipling and Waterhouse 1967 found prostate cancer in Cd workers, but no increase in lung cancer. Lung cancer was elevated in relation to Cd exposure in the studies by Lemen *et al.* 1976. Aitio (in press) has summarized the background for the classification by IARC (1993) of cadmium and cadmium compounds as carcinogenic to humans (Group I) as well as other WHO evaluations.

Basis for recent studies on Cd and health in China (ChinaCad)

In an evaluation by WHO 1992, renal dysfunction was identified as the critical effect. Skeletal and reproductive effects as well as cancer were also discussed as possible critical effects, but more quantitative information was considered necessary in order to classify those effects as critical. For the effect on the kidney, a quantitative evaluation of the risks of such dysfunction was presented implying that lifelong exposure to 140–260 micrograms per day or a cumulative intake of $>$ 2000 mg would give rise to increased urinary excretion of low mol wt proteins. However the need for more epidemiological data on renal effects was pointed out.

The questions that seemed urgent to answer in the mid 1990:ies were: 1) Do bone effects occur in Cd-exposed population groups outside Japan? 2) What environmental Cd exposures give rise to renal effects? 3) Do male reproductive effects occur in Cd exposed population groups?

These were the questions that formed the basis for the epidemiological studies funded by the European Commission (ChinaCad) and the results were described and discussed in the present symposium. An area near Wenzhou, previously identified by professor Kong as Cd polluted, was selected for study and an area without pollution 40 km north of Wenzhou was used as control area. Totally 734 persons participated and gave blood and urine samples, their Bone Mineral Density was determined by monophoton densitometry. Only a few results from these studies will be mentioned in this paper. Detailed reports on various findings are given in other papers in this volume.

Some results from the ChinaCad studies

It is known that bone density decreases in women after the menopause and postmenopausal women were thus considered separately. When comparing persons with blood cadmium above 20 microgram/l with other participants, there was a statistically significant increase in the prevalence of low bone density (lower than the tenth percentile) both in men, in women before menopause and particularly in women after menopause. Further details concerning these and other findings on bone density are given elsewhere in this volume by dr Zhu *et al.* (2004).

Renal dysfunction has earlier been described in other cadmium-polluted areas in China by Cai *et al.* 1995. To further elucidate the relationship between renal dysfunction and cadmium exposure, cadmium was measured in blood and urine and determinations of several indicator proteins in urine were performed in the present (ChinaCad) study. An increased prevalence of elevated (exceeding 0.3 mg/g crea) urinary retinol binding protein (RBP) was reported by Nordberg *et al.* 2002. This increase was statistically significant at urinary Cd of 5–10 microgram/g crea and higher. A statistically significant increase in the prevalence of high RBP was also found in relation to high blood cadmium values. Results of determinations of other, more sensitive, indicator proteins and other statistical analyses are reported by Jin *et al.* (2004) and by Bernard *et al.* (2004).

As a part of the ChinaCad project, male reproductive effects were investigated, both in humans and in animal experiments. A dose–response relationship was found (Zeng *et al.* in press) between the level of Cd in urine and the prevalence of high levels of testosterone in serum (exceeding the 95^{th} percentile in the low Cd exposed part of the population). There was also a statistically significant relationship between indicators of Cd exposure (and internal dose) and clinical signs of tissue changes in the prostate (Zeng *et al.*,

this volume). The animal experiments included studies of male reproductive hormones in rats. Zeng *et al.* 2003 showed that in rats with long term oral exposure to Cd, there were higher levels of testosterone in serum than in controls. Gunnarsson *et al.* 2003 showed that there was a decrease of the LH (luteinizing hormone) receptor expression and in the cAMP levels in the testis of rats after single dose exposure. The observations in humans and animals, give some support to the hypothesis that Cd exposure may play a role in relation to the occurrence of prostate cancer. Further aspects concerning effects of Cd on the testis and prostate are given elsewhere in this volume by Goyer *et al.* (2004).

Other studies on proteiuria in cadmium exposed humans – early 'proteomics' research

The first useful epidemiological data on relationships between intake levels of Cd and an increased urinary excretion of RBP or beta-2-microglobulin (B2M) were reported in the 1970:ies based on methods developed at that time allowing specific measurements of these proteins. As mentioned, early such data from Japan was used by WHO/IPCS 1992 in a quantitative assessment of a relationship between cadmium intake and renal effects. The sensitive protein biomarkers now widely used as indicators of cadmium nephrotoxicity – in addition to B2M and RBP, NAG (N-acetyl-D-beta-glucosaminidase) A and its isoform B and protein HC (Human Complex forming glycoprotein) and several other urinary indicator proteins – have been further developed as biomarkers in the 1990:ies and this can be seen as a result of applied 'proteomics' research. By further research in the area of proteomics, even more specific and sensitive markers of renal dysfunction will be developed in the present century. Such achievements will allow an even better and more precise assessment of renal dysfunction in the future and possibly also of other health effects induced by Cd. Compared to the situation before 1990, a number of important studies have now contributed improved data on the relationship between internal dose of Cd and renal dysfunction. Available data are described and discussed in other contributions to the present volume (Bernard, Jin *et al.*; Jarup and Alfvén; Nogawa *et al.* Oskarsson *et al.*).

'Genomics' research in the ChinaCad project and future trends

It is known from animal experiments briefly described previously in this paper, that tissue metallothionein (MT) has a protective role against Cd. In order to examine if interindividual variation in MT gene expression would be possible to relate to development of renal dysfunction, such 'genomics' studies were included in the ChinaCad project. A relationship was found between MT gene expression in peripheral lymphocytes and decreased sensitivity to developing renal dysfunction from Cd. (Lu *et al.* 2001; Lu *et al.*, 2004).The usefulness of this 'genomic' approach was thus supported by the results obtained. Present methodology in the field of 'genomics' and 'proteomics' is under rapid development and improved tests will undoubtedly be available in the near future. Such refined technology will improve our possibilities to perform molecular epidemiology studies in future decades of the 21st century, providing an even better basis for preventive action.

Concluding remarks

Early warnings of human health risks from Cd exposure issued approximately 30 years ago when such risks of occupational and environmentally exposures were first recognized have been of importance for action taken by authorities in various countries all over the World. An improved database on relationships between cadmium exposure and health effects in humans as well as improved tools for further studies are now available and cadmium exposures are now much better controlled than in the past. The target for the 21st century will be to achieve a totally acceptable exposure situation without adverse health effects from cadmium exposure.

References

Aitio A., Tritscher A. 2004 Effects on Health of Cadmium – WHO approaches and conclusions. *BioMetals* **17**, 491.

Bernard A. 2004 Renal dysfunction induced by cadmium: biomarkers of critical effects. *BioMetals* **17**, 519–523.

Bulmer FMR, Rothwell HE, Frankish ER. 1938 Industrial cadmium poisoning. *Can Public Health J* **29**, 19–26.

Chan H, Zhu L-F, Zhong R, Grant D, Goyer RA, Cherian GM. 1993 Nephrotoxicity in rats following liver transplantation from cadmium-exposed rats. *Toxicol Appl Pharmacol* **123**, 89–96.

Cai S, Yue L, Shang Q, Nordberg G. 1995 Cadmium exposure among residents in an area contaminated by irrigation water in China. *Bull World Health Organ* **73**, 359–367.

Faeder EJ, Chaney SO, King LC, Hinners TA, Bruce R, Fowler BA. 1977 Biochemical and ultrastructural changes in livers of cadmium treated rats. *Toxicol Appl Pharmacol* **39**, 473–487.

Ferm VH, Carpenter SJ. 1968 The relationship of cadmium and zinc in experimental mammalian teratogenesis. *Lab invest* **18**, 429–432.

Fowler BA, Nordberg GF. 1978 Renal toxicity of cadmium metallothionein: Morphomeric and microanalytical studies; *Toxicol Appl Pharmacol* **46**, 609–623.

Friberg L. 1948 Proteinuria and kidney injury among workmen exposed to cadmium and nickel dust. *J Ind Hyg Toxicol* **30**, 32–36.

Friberg L. 1950 Health Hazards in the manufacture of alkaline accumulators with special reference to chronic cadmium poisoning. *Acta Med Scand* **138** (suppl 240), 1–124.

Friberg L, Piscator M, Nordberg G. 1971 Cadmium in the Environment. CRC press Cleveland, USA.

Goyer RA, Liu J., Waalkes MP. 2004 Cadmium and Cancer of Prostate and Testis. *BioMetals* **17**, 555–558.

Gunnarsson D, Nordberg G, Lundgren P, Selstam G. 2003 Cadmium-induced decrement of the LH receptor expression and cAMP levles in the testis of rats. *Toxicology* **183**, 57–63.

Haddow A, Dukes CE, Mitchley BCV. 1961 Carcinogenicity of iron preparations and metal carbohydrate complexes. *Rep Br Emp Cancer Campagn* **39**, 74–76.

Hagino N. 1957 About investigations on Itai- itai disease. *J. Toyama Med Ass.* Dec 21, 7.

IARC 1993 *Beryllium, cadmium, mercury and exposure in the glass manufacturing industry*. International Agency for Research on Cancer, Lyon IARC Monographs on the evaluation of carcinogenic risks to humans, Vol 58.

Ishizaki A. 1969 On the so called Itai-itai disease. *J Jpn Med Soc* **62**, 242–249. (in Japanese).

Jarup L, Alfvén T. 2004 Low level cadmium exposure, renal and bone effects – The OSCAR study. *BioMetals*, **17**, 505–509.

Jin T, Wu X, Tang Y, Nordberg M, Bernard A, Ye T, Kong Q, Lundstrom NG, Nordberg GF 2004 Environmental epidemiological study and estimation of benchmark dose for renal dysfunction in a cadmium-polluted area in China. *BioMetals*, **17**, 525–530.

Jin T, Leffler P, Nordberg GF. 1987 Cadmium-metallothionein nephrotoxicity in the rat: Transient calcuria and proteinuria. *Toxicology* **45**, 307–317.

Kar AB, Das RP, Karkun JN. 1959 Ovarian Changes in prepubertal rats after treatment with cadmium chloride. *Acta Biol Med Ger* **3**, 372–379.

Kazantzis G. (2004) Cadmium, osteoporosis and calcium metabolism. *BioMetals*, **17**, 493–498.

Kjellstrom T, Nordberg GF. 1978 A Kinetic model of cadmium metabolism in the human being. *Environ Res* **16**, 248–269.

Lemen RA, Lee JS, Wagoner JK and Blejer HP. 1976 Cancer mortality among cadmium production workers. *Ann NY Acad Sci* **271**, 273–279.

Leffler P, Jin T, Nordberg GF. 2000 Differential calcium transport disturbances in renal membrane vesicles after cadmium-metallothionein injection in rats. *Toxicology* **143**, 227–234.

Lu J, Jin T, Nordberg G, Nordberg M. 2001 Metallothionein gene expression in peripheral lymphocytes from cadmium exposed workers. *Cell Stress and Chaperones* **6**, 97–104.

Lu J, Jin T, Nordberg GF, Nordberg M. 2004 The application of metallothionein (MT) gene expression in peripheral blood lymphocytes (PBLs) as a biomarker of cadmium exposure. *BioMetals*, **27**, 569–570.

Murata I, Hirono T, Saeki Y and Nakagawa S. 1970 Cadmium enteropathy, renal osteomalacia (Itai-itai disease in Japan). *Bull Soc Int Chir* **1**, 34–41.

Nicaud P, Lafitte A, Gros A. 1942 Symptoms of chronic cadmium intoxication. *Arch Mal Prof Med Trav Secur Soc* **4**, 192–202.

Nishijo M, Nakagawa H, Morikawa Y, Kuriwaki J-i, Miura K, Kido T, Nogawa K. 2004 Mortality in a cadmium polluted area in Japan. *BioMetals*, **17**, 535–538.

Nogawa K, Ishizaki A, Fukushima M, Shibata I, Hagino N. 1975 Studies on the women with acquired Fanconi syndrome observed in the Ichi river basin polluted by cadmium. *Environ Res* **10**, 280–307.

Nogawa K, Kobayashi E, Okubo Y, Suwazono Y. 2004 Environmental cadmium exposure, adverse effects and preventive measures in Japan. *BioMetals*, **17**, 581–587.

Nordberg GF. 1972 Cadmium metabolism and toxicity. *Environm Physiol Biochem*, **2**, 7–36.

Nordberg GF. 1974 Health Hazards of Environmental Cadmium Pollution. *Ambio* **3**, 55–66.

Nordberg, GF, Kjellström, T and Nordberg M. 1985: Kinetics and metabolism. In: L Friberg, C-G Elinder, T Kjellström, GF Nordberg Eds.: *Cadmium and Health: A Toxicological and Epidemiological Appraisal. Vol I, Exposure Dose and Metabolism*. CRC Press, Boca Raton FL, pp. 103–178.

Nordberg GF, Jin T and Nordberg M. 1994 Subcellular targets of cadmium nephrotoxicity: Cadmium binding to renal membrane proteins in animals with or without protective Metallothionein synthesis. *Environ Health Perspect* **102** (Supplement 3), 191–194.

Nordberg G, Jin T, Bernard A, Fierens S, Buchet JP, Ye T, Kong Q, Wang H. 2002 Low Bone Density and Renal Dysfunction Following Environmental Cadmium Exposure in China. *Ambio* **31**, 478–481.

Nordberg M and Nordberg GF. 2000 Toxicological Aspects of Metallothionein. *Cellular and Molecular Biology* **46**, 451–463.

Oskarsson A, Lindén A, Olsson I-M, Petersson K. 2004 Cadmium in food chain and health effects in sensitive population groups. *BioMetals*, **17**, 531–534.

Parizek J and Zahor Z. 1956 Effect of cadmium salt on testicular tissue. *Nature* **177**, 1036.

Parizek J. 1965 The peculiar toxicity of cadmium during pregnancy – an experimental 'toxaemia of pregnancy' induced by cadmium salts *J Reprod Fertil* **9**, 111–112.

U.S. Publ Health Serv. 1942 Public Health Report, Cadmium poisoning. *Div Ind Hyg Natl Inst Health* **57**, 601–612.

Zeng X, Jin T, Nordberg GF. 2003 Changes of serum sex hormone levels and MT mRNA expression in rats orally exposed to cadmium. *Toxicology* **186**, 109–118.

Zeng X, Jin T, Buchet JP, Jiang X, Kong Q, Ye T, Bernard A and Nordberg GF. Impact of cadmium exposure on male sex hormones: A population-based study in China. *Environ Res* in press.

Zeng X, Jin T, Jiang X, Kong Q, Ye T, Nordberg GF. in press Effects on the Prostate of Environmental Cadmium Exposure – a Cross-Sectional Population Study in China 2004 *BioMetals*, **17**, 559–566.

Zhu G, Wang H, Shi Y, Weng S, Jin T, Kong Q, Nordberg GF. 2004 Environmental cadmium exposure and forearm bone density. *BioMetals*, **17**, 499–503.

WHO 1992 *Cadmium*. World Health Organisation, Geneva. Environmental Health Criteria 134.