

# Review: effect of environmental cadmium pollution on human health

Jing-Xiu Han<sup>1</sup>, Qi Shang<sup>1</sup>, Yu Du<sup>2</sup>

<sup>1</sup>Department of Epidemiology and Health effects, Institute for Environmental Health and Related Product Safety, Chinese Center for Disease Control and Prevention, 29 Nanwei Road, Beijing, 100050, China; Corresponding author: [sqyoux@yahoo.com.cn](mailto:sqyoux@yahoo.com.cn) (Qi Shang)

<sup>2</sup>Yuzhong district centre for disease control and prevention, Chongqing Municipality

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## ABSTRACT

**Based on the available data obtained from the population investigating, the authors reviewed research articles of the study on analytical methods and exposure levels of cadmium (Cd) in population, the injury of target organ, the evolution of sensitive index for surveillance, the study on effects of human disease and death for environmental Cd exposure, and the study on priority surveillance of human health risk.**

**Keywords:** Cadmium Pollution; Population Investigation; Disease Surveillance; Renal Damage

## 1. INTRODUCTION

Cadmium (Cd) is a toxic heavy metal which can be accumulated in human body and environment long-term. The health risks of environmental Cd pollution have caused the concern all over the world since the “itai-itai” disease caused by chronic Cd poisoning appearing in Japan in 1950’s. Series of criteria and guidelines have been developed in many countries and international organizations to guide the study on health effect of Cd pollution. Cd has been ranked at the sixth of toxic substances for significant human health hazard by U.S Poison and Disease Registry [1]. At the same time, this element has been a focus of study on environmental pollution in the United Nations Environment Programs and the International Commission on Occupational Health. It was also put on a priority position of the study on food contamination in the World Health Organization [2]. Cd pollution of industrialization began in the early 1960’s in China and then many studies on popular health effects of environmental Cd pollution have been carried out in 1980’s and early of 1990’s. It was estimated that the total area polluted by Cd in China is more than 11000 hectares, and there were 11 provinces and municipalities, 25 territories production Cd-polluted rice (Cd concentration 1.32~5.43

mg/kg) (Ministry of Farming Animal Husbandry and Fisheries, Beijing, Internal report, 1980). Annual amount of Cd with industrial waste discharged into the environment was more than 680 tons [3,4]. Unfortunately, there were few researches of Cd pollution on human health effects after the 1990s in China besides some follow up investigations of resident’s health effects which were carried out only in a few contaminated areas. It is these studies that showed the Cd-polluted actives have not been efficiently dealt with over last 20 years in China, and the health risk of residents living in contaminated areas has been becoming more serious than those in the 1980’s [5-8]. The environmental Cd exposure occurs mainly in Japan and China. In other countries, the intensity and duration of Cd exposure and the injury occurring in populations are in a relatively low level, with little related literature reported [9,10].

Population exposing to environmental pollutants has a general character of low-dose, long-term, and chronic poisoning, which will cause two different kinds of chronic health effects, damage of target organs and non-specific changes for population such as weakness, ease to suffering from illness and rise of morbidity and mortality etc. In this paper, the information from population-based study on human health effects of environmental Cd pollution was reviewed.

## 2. TARGET ORGANS DAMAGE OF ENVIRONMENTAL Cd EXPOSURE

Main work of study on popular health effects caused by environmental Cd pollution can be divided into different scopes: target organ (kidney, bone, prostate, etc.) damage, biomonitoring, dose-response relationship, investigation of exposure level, mortality, and survival analysis [11]. There were some studies on mortality and survival analysis in recent years in China [8].

### 2.1. Target Organ Damage and Biomonitoring

Based on results of toxicological studies, the researches

on human specific-injury caused by Cd exposure have focused on injury biomonitoring of bones and urogenital system. The main researches were early screening for the early sensitive biomonitoring indices, monitoring and evaluation of target organ damage, and study on the dose-response relationship between Cd exposure and health damage indices. There were a lot of early indices of kidney damage applied in the popular surveys. Some were related to body burden of Cd exposure, such as blood Cd (B-Cd) and urinary Cd (U-Cd); some were sign of bone injury, such as bone mineral density (BMD), urine calcium, urine phosphorus, urine or serum alkaline phosphatase (U-, B-ALP), urine hydroxyproline (U-HOP), and so on. Index commonly used to show Cd accumulation level in renal cortex and the whole body was U-Cd. There are generally two different kinds of groups of biomonitoring indices for renal tubular dysfunction and renal tubular pathological damage: urine protein and urine enzyme. The former included urine  $\beta_2$ -micro-globulin ( $U\beta_2$ -MG),  $\alpha_1$ -microglobulin ( $U\alpha_1$ -MG), retinolbinding protein (U-RBP), metallothionein (U-MT), albumin (U-ALB), amino acids, and so on. The latter were urine N-acetyl- $\beta$ -D-glucosaminidase (U-NAG), alkaline urine (U-ALP), and  $\gamma$ -glutamyltranspeptidase enzyme ( $\gamma$ -GT), etc [5,9,12]. Urine enzyme was mainly from renal tubular epithelial cell, therefore, changes of enzyme activity in urine had been considered as representative indicator of renal tubular injury comparing with urinary protein serving as tubular re-absorption dysfunction indicator. However, the most commonly used indices were U-Cd,  $U\beta_2$ -MG, and U-NAG (U-NAG applying in 3 ways: A-isozyme, B-isozyme and total NAG, renal tubular epithelial cells are rich in B-NAG), among which good correlations have been observed. Early sensitivity of urinary enzymes or urine protein reported in many literatures. It is a result of the survey reported by different authors carrying out at different Cd exposure stages, different accumulating Cd exposure level causing different health effects. Analyzing the progress of chronic Cd poisoning, the urinary protein mainly from the serum did not increase significantly when there was no renal glomerulus and re-absorptive in the early stage. In this period, phenomena of Cd nephrotoxic was a rise in U-Cd and urinary enzymes. With the increase in Cd exposure level, U-Cd, urine enzyme and urine protein would be synchro-increasing, it was a sign of renal tissue injury with renal dysfunction. The renal tubular injury induced by environmental Cd exposure was irreversible even after soil replacement in Cd-polluted rice paddies [13-15]. In the late stage of Cd exposure, it would be seen that U-Cd and urinary protein increased sharply with urinary enzyme active reducing. Therefore, in practice, application of specific biomonitoring indicators and result analysis should consider the levels of U-Cd and cumulative Cd exposure of population in different contaminated areas [16,17]. It was estimated based on literatures that some of above indicators appearing in the urine

in correspondence to 24-hour urinary Cd concentrations were: Ca: 1.9 $\mu$ g, U-NAG: 2.74 $\mu$ g, U-RBP: 2.87 $\mu$ g,  $U\beta_2$ -MG: 3.05 $\mu$ g, amino acids: 4.29 $\mu$ g. In addition, when U-Cd began to rise abnormally, the other biomarks would be at the levels of: U-NAG: 2.74 $\mu$ g, U-RBP: 338 $\mu$ g,  $U\beta_2$ -MG: 283 $\mu$ g [10]. If an individual has synchronized with increasing in the levels of U-Cd,  $U\beta_2$ -MG and U-NAG over national standard value, it would mean that the individual's health had been severely damaged suffering from environmental Cd pollution. And if there were 10% individuals with severe health damage in a contaminated area at the same time, it would be judged to be a contaminated area with popular health damage according to the health standards of China [18]. Government should take action to control environmental pollution and prevent residents in the area from Cd health damage.

The first change of biomark index corresponding to environmental Cd exposure was the increase of U-Cd. When the level of U-Cd arrived at approximately 2.5~5.0 $\mu$ g/g, the indices of renal dysfunction and renal tubular injury began to change [19-22]. However, some researchers [8,23,24] calculated benchmark doses (BMDs) of U-Cd and their 95% lower confidence bounds (BMDLs) for renal effects of Cd in a population with low environmental exposure. Yasushi *et al.* [23] obtained BMDs of U-Cd were lower than the critical concentrations previously reported. For both NAG and protein HC, the BMDs (BMDLs) of U-Cd were 0.5-1.1 (0.4-0.8)  $\mu$ g/L (adjusted for specific gravity of 1.015 g/ml) and 0.6-1.1 (0.5-0.8)  $\mu$ g/g creatinine. But considering age effect, it was important to establish the threshold level of Cd exposure at each age [14,15]. In the late of chronic Cd poisoning, with U-Cd and  $U\beta_2$ -MG significantly increasing [25-27], the bone injury indicators and U-ALB were expected to show a significant change. Usually, bone damage was a delayed sign of severe chronic Cd poisoning. Population-based studies [28-31] showed an association between osteoporosis and low-level environmental Cd exposure. Cd can cause bone demineralization, either through direct bone damage or indirectly as a result of renal dysfunction. Result of a study [32] indicated that excretion of urinary Vitamin D-binding protein (DBP, which binds, transports and activates vitamin D, plays a major role in calcium homeostasis and bone turnover) in urine may be linked to renal tubular dysfunction and possibly bone lesions in the inhabitants of Cd-polluted areas. Nordburg *et al.* [33,34] reported that the BMD decrease in postpartum women with raised levels of U-Cd or B-Cd, and BMD decrease in men with increased levels of B-Cd in Asia excluding Japan. Kido's [35] studies had shown that the urinary indicators of renal function ( $\beta_2$ -MG) and indicator of Cd exposure in male and female were negatively correlated with the central part of the second metacarpal BMD. Cd induced the disorders of normal osteoblasts and bone metabolism through disrupting calcium messenger system, led to osteomalacia, increased the dissolution of

calcium, decreased BMD, and caused osteoporosis [36]. Environmental Cd exposure may also be associated with increased risk of dental caries in deciduous teeth of children [37].

Jin *et al.* [38,39] had reported prostate damage induced by Cd, but little information was provided in population research.

## 2.2. Estimation of Cd Intake Level

Early research on the population Cd intake levels mainly focused on estimating daily intake. It was a static mode and just got a cross-sectional data at surveying day. This method could not get accumulation exposure level, a very important data to observe and research a relationship between Cd intake and chronic health damage. For this reason, many people used total intake (or the cumulative intake) to find out the relationship between accumulative Cd intake and health chronic injury as well as key point of chronic damage at different total intake level, which would be corresponding to different degree of health injury [40,41]. Japanese scholars reported their result that they used the data of daily intake level multiplying by total exposure days to estimate population total intake level [42-44]. This method did not consider a difference in food intake levels at different age stages, generally, and the amount estimated in this method might be greater than actual intake level. There were some scholars who calculated the Cd total intake through way of estimating the cumulative rice consumption. Two different methods were accepted to estimate the cumulative rice consumption. One method is that total rice consumption was calculated using consumption in various age groups, which was estimated based on the curve equation of daily average rice consumption in various age groups [40], the another way, which used coefficient to estimate, the total rice consumption was reckoned according to various coefficients of various age groups. The coefficients were set as follows, 0~9 age group: 0.413, 10~19 age group: 0.885, 20~59 age group: 1, and age group beyond 60: 0.823 [41]. Two kinds of methods both considered the differences in dietary consumption in children and elder population, and the calculated results were also similar (estimated Cd intakes for the 45-year-old group are 161mg and 166mg, respectively). Chiyoda [45] used urine protein and urine sugar as biomonitoring indicators, and estimated that the allowed total intake of Cd in Japanese was less than 1.58g in their life. Due to the lack of continuous monitoring data, the estimating value of population total intake was a relative result, it would be mainly applied in evaluating the group exposure, and considered only as a reference value when used to identify the health damage of individual [40].

## 2.3. Dose-Response Relationship on Cd Exposure

It has been possible to link the total Cd intake with

population health damage dynamically by calculating accumulative Cd intake so that a regress formula could be gotten between population health damage degree and Cd exposure dose. The result of digitizing health damage degree makes it possible to compare all of information from different authors' studies in a dosage scale. Health damage degree corresponding to different accumulative exposure dose could also be used to predict the tendency of population health damage caused by Cd exposure which based on the data of environmental monitoring or biomonitoring. A large number of articles had reported the dose-response relationship between the total Cd exposure and biomonitoring indicator of popular health injury, and explored the level of Cd exposure associated with the degree of health injury. These reports about dose-response relationship focused on the association between Cd exposure and indicators of renal injury, such as: U-Cd and  $U\beta_2$ -MG, U-NAG, U-RBP, and so on. The estimation of total exposure level laid basis on the unit of population group, which corresponded to the incidence of abnormal value of a variety of monitoring indicators, the occurrence of specific chronic diseases, such as fracture morbidity and mortality of "itai-itai" disease. Some authors had used U-Cd as indicator of Cd exposure to that of responsive renal injury indicator to calculate relationship between exposure and response, and observe development trend and degree of renal injury [46-48]. Japanese scholars also used Cd concentration of rice in different regions, corresponding to incidence of abnormal monitoring indicators, to calculate dose-response relationship. Nevertheless, this method which only provided a relationship between different exposure level and indexes of popular health damage just was a static model of dose-response relationship.

## 2.4. Mortality and Survival Analysis of Population Exposed to Environmental Cd

Mortality of people exposed to environmental Cd had been reported in China and Japan. Kawana [49] reported the mortality rate of "itai-itai" disease was 72.6 % (50.4% in control group) from 1967 to 1982, the average survival time was 76.4 year-old (control group: 78.3 year-old) with statistically significant differences. Kobayashi [50] had studied on relationship between the level of urine calcium and life expectancy, as well as the number of female pregnancy and childbirth associating with popular mortality. He found that the lower urine calcium, the shorter life-span. But popular mortality was not associated with the number of pregnancy and childbirth. Death analysis in Japan mainly adopted a method of following-up observation [51,52]. Based on the biomonitor data from past population-based survey, they collected the data of death records from Cd contaminated areas and analyzed mortality and survival time to observe the changes of popular renal injury indicators, such as U-Cd,  $U\beta_2$ -MG, U-RBP and so on, in the areas where populations had exposed to

environmental Cd at different levels. Different from common disease surveillance, there was no cause-specific death or disease-specific mortality reported in those reports. Since the discovery of itai-itai disease, Japanese scholars had observed and studied on the damage of the death in Cd-exposure population. The studies had shown that higher volume of Cd in rice caused population higher Cd exposure, and then could induce population to have a series of health effects, such as more severe renal injury, higher mortality, shorter survival time, and more unfavorable the prognosis [48,50,53-56]. Even if zinc-Cd smelters closed, historical environmental contamination remained a persistent source of exposure. Environmental exposure to Cd increased total, and noncardiovascular mortality in a continuous fashion without threshold [57,58]. One study [59] found that environmental Cd exposure was associated with an increasing risk of all cause, cancer, and cardiovascular disease mortality among men, but not among women. Additional efforts are warranted to fully explain gender differences on the impact of environmental Cd exposure.

### 3. HUMAN NON-SPECIFIC DAMAGE FROM ENVIRONMENTAL Cd POLLUTION

In addition to target organ damage, there were still some non-specific impacts of environmental Cd pollution on the human health. Low IgG level of children with higher Cd body burden suggested that Cd could affect development of children's immune system. According to the detection of immunoglobulin sub-type, IgG<sub>3</sub> was the most sensitive to the inhibitory effect of Cd, followed by: IgG<sub>1</sub>, IgG<sub>2</sub>, IgM and IgG<sub>2a</sub>. Therefore, IgG could be used as the sensitive indicator of immune suppression of children exposed to Cd [60]. EU Toxicology, Eco-toxicology and Environmental Science Committee had agreed with the opinion that Cd exposure could have immunosuppressive effects [61]. Gary [21] reported that the urine Cd in 3 levels of 0~0.99 $\mu$ g/g Cr (control group), 1.00~1.99 $\mu$ g/g Cr and  $\geq$ 2 $\mu$ g/g Cr respectively, its OR for the early stage of diabetes were: 1.48 (95%CI: 1.21~1.82) and 2.05 (95%CI: 1.42~2.95); the OR for type II diabetes: 1.24 (95%CI: 1.06~1.45) and 1.45 (95%CI: 1.07~1.97) [2]. Early diabetes (IFG) and type II diabetes had significant dose-response relationships with urinary Cd concentration, it suggested that the two kinds of human diseases had related to the Cd exposure.

Many literatures reported the impact of Cd on human reproductive system. Falcon [62] reported that pregnant women exposed to environmental Cd might have an adverse effect in perinatal period, e.g. fetal growth retardation, low birth weight, birth deformities and premature. Nishijo *et al* [63-65] reported that mothers with higher urinary Cd concentration would be company with higher levels of Cd and lower calcium concentration in their breast milk. Cd

exposure may be a possible cause of male infertility. A significant negative correlation was observed between serum Cd level and all examined biophysical semen characteristics except sperm volume [66].

Nishijo *et al.* [55,67] reported that there were dose-response relationships between Cd exposure and mortality risks in both male and female in the Cd contaminated areas. Chronic exposure to Cd could increase popular mortality and shorten life expectancy. In recent years, a 15-year-follow-up investigation of 3119 residents living in Cd polluted area had confirmed that Cd exposure was associated with popular mortality [55]. Another survey found the standardized mortality rates of six kinds of diseases in Cd contaminated areas were higher than non-contaminated areas, such as cancer, respiratory disease and cerebrovascular disease. Some population-based studies reported that Cd exposure was associated with increased risk of breast and endometrial cancer [68-70]. These might because that Cd mimicked the function of steroid hormones [71]. Moreover, data suggested that Cd exposure was associated with increasing testosterone levels [72]. High testosterone levels have been associated with the risk of breast cancer. But more experimental and epidemiological studies are required to establish a cause and effect association between the metal and hormone dependent cancers and to verify the mechanism of action. Cd exposure via inhalation might associate with some human cancers, but Verougstraete [73] did not think that it could cause human cancer exposing to environmental Cd. Cd levels in blood were associated with a modest elevation in blood pressure [74]. A 15-year-follow-up study found that mortality for heart failure and cerebral infarction was increased among inhabitants living in a Cd-polluted area in Japan [54]. The incidence of subhealth state of population in Cd pollution area was higher than that of people in non-polluted area, such as dizziness headache, loss of appetite, coughing, shortness of breath, etc. The morbidity of chronic disease was also significantly higher than that of people in non-polluted area, such as stomach and duodenal ulcer, bronchitis, urinary calculi, and so on. The health status of residents in the polluted area had been impacted by the environmental Cd pollution, the infant mortality. The pre-mature deliver rate in the Cd polluted area was higher than those of control area, and the spectrum of popular disease and death in polluted area was significantly high than those of people in control area [75,76].

Some research data [77] indicated that Cd exposure could result in pancreatic dysfunction and the effect appeared at lower urinary Cd level than renal dysfunction. But more studies were needed to prove it.

The research data on non-specific hazards of environmental Cd pollution was not too much, because the health effects of population were characterized by target organ damage in the early stage of chronic Cd poisoning, which had led main studies focusing on effects of renal injury, a

special-effects, in a long time, yet few investigations on the change of popular mortality and morbidity of environmental Cd exposure.

#### 4. MONITORING AND EARLY WARNING STUDIES ON POPULATION HEALTH HAZARDS

Thacker [78] put forward the concept of Environmental Public Health Surveillance (EPHS) in 1996. The U.S. Center for Disease Control and Prevention (CDC) has been laying the groundwork for what was planned to become a nationwide environmental public health track network in 2002 for integrating network to assess local and state data to determine exposures and health effects linked to environmental hazards. CDC also provided the EPHS system with a set of environmental public health indicator (EPHI) in 2003, including: 1) hazard indicators (Conditions or activities that identify the potential for exposure to a contaminate or hazardous condition); 2) exposure indicators (Biological markers in tissue or fluid that identify the presence of a substance or combination of substance that could harm an individual); 3) health effect indicators (Disease or condition that identify an adverse effects from exposure to a known or suspected environmental hazard); 4) intervention indicators (programs or official policies that minimize or prevent an environmental hazard, exposure, or health effect). Project-specific monitoring indicators needed to meet the following requirements: 1) measurable; 2) trackable over time; 3) based on demonstrated links between environment and health; 4) useful and understood by diverse populations; 5) informative to the public and to responsible agencies; 6) tied to public health objectives; 7) action-oriented; 8) incorporated in clear-case definitions [79]. In 2005, the U.S CDC announced the launch of national network-building projects EPHS. Combining with population disease information, EPHS would help to assess hazard factors in the environment, the main exposure routes, the health effects of population and time trends through monitoring environmental harmful factors, investigating the exposure routes and identifying people at risk, timely releasing and delivering relevant information to help high-risk people to avoid the exposure to hazard factors and reducing the incidence of chronic diseases in population. Its basic object was to realize the integration of disease and death data monitored continuously and routinely with the occasional professional investigation of environmental risk factors and the individual-based population health evaluation data. EPHS was different from any other existing monitoring system. Its characteristics included: identify the health effect trend of population exposed to environmental risk factors based on the routine analysis of data on population disease and death; determine the environmental risks and population health status through professional targeted

research [80]. The raise of EPHS concept was the overthrow of conventional route of monitoring and early warning study on population health risks. It was combined with environmental benchmark dose exposure and referred to the EAI (environmental accident index) indicators. The integration of environmental hazard surveys monitoring data and human disease surveillance data provided scientific opportunities for the development of population health hazard monitoring and early warning system studies. EPHS was expected to be an ideal technical platform, which was able to integrate all kinds of disease control tasks and disciplines in the field of environmental health and combine the main tasks of CDC at all levels.

#### 5. RESEARCH OBJECTIVES IN THE FUTURE

It is very important to explore the risk factor for "Itai-Itai" disease exposed to environmental Cd continuously in long time and at high level, which has already existed in China [81]. It is not time to say stop, although great achievement has been made in study on health effect of exposure to environmental Cd. There is a lot of work needed to do for realizing Cd health risk well in the future. The main research objects should focus on: 1) continue to conduct follow-up study on health hazards of all kinds of people, evaluate the population Cd exposure and the severity of health damage related, and analyze its trend; 2) concern about the human disease and death impact due to Cd exposure, collect and screen the information of population disease and death closely related to Cd exposure, and study the link and dose-response relationship between kidney damage and Cd exposure; 3) establish human health hazard monitoring and early warning network of Cd exposure in the framework of environmental public health monitoring; 4) implement prevention and intervention research on population health hazards of environmental Cd exposure to reduce the risk of population Cd exposure and health injury related.

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