

DOES ENVIRONMENTAL EXPOSURE TO CADMIUM REPRESENT
A HEALTH RISK ?
CONCLUSIONS FROM THE CADMIBEL STUDY.

R. Lauwerys, A. Bernard, J.P. Buchet, H. Roels*
P. Bruaux, F. Claeys, G. Ducoffre, P. De Plaen**
J. Staessen, A. Amery, R. Fagard, P. Lijnen, L. Thijs***
D. Rondia, F. Sartor, A. Saint Remy, L. Nick****

SUMMARY

Cadmium is a very dispersive pollutant which has progressively accumulated in the environment mainly in the areas where nonferrous smelters have been in operation. An important toxicological feature of cadmium is its exceptionally long biological half-life in the human body. For the general population mainly exposed to cadmium by the diet and smoking, the kidney is the main target organ. Some studies have also suggested that cadmium might play a role in the pathogenesis of hypertension.

A cross-sectional study (called Cadmibel) was undertaken to assess whether environmental pollution by cadmium in Belgium might represent a health risk. This paper does not present the detailed results of this study which are published elsewhere but simply reports its main conclusions. A total number of 2327 subjects (stratified according to age and sex) was randomly sampled in two urban (Liège and Charleroi) and two rural (Hechtel-Eksel and Noorderkempen) areas, with different environmental pollution by cadmium. After allowing for the various factors known to influence cadmium accumulation, it was estimated that the cadmium body burden of the residents of the most polluted district (Noorderkempen) was 50 to 85 % higher than in the less polluted areas. No statistical association was found between environmental exposure to cadmium and blood pressure elevation or the prevalence of cardiovascular diseases. However, the study has shown that environmental exposure of the general population to cadmium may induce slight renal tubular dysfunction and may probably also affect calcium homeostasis. The probability of tubular dysfunction (as assessed by sensitive tests) is about 10% when cadmium in urine reaches 2 µg/day. The morbidity associated with the changes in the renal proximal tubule and the calcium metabolism observed when the body burden of cadmium exceeds this value remains to be assessed.

*Industrial Toxicology and Occupational Medicine
Unit, Catholic University of Louvain
30.54. Clos Chapelle-aux-Champs,
1200 Brussels

** Institute of Hygiene and Epidemiology
Department of Epidemiology - Toxicology
1050 Brussels

***Hypertension and Cardiovascular Rehabilitation
Unit, Department of Pathophysiology
Catholic University of Leuven
3000 Leuven

****Environmental Toxicology Unit
University of Liège
4000 Liège

INTRODUCTION

Cadmium, a by-product of the refining of zinc ores, is an important environmental pollutant in

industrialized countries (1). Its industrial production has started at the end of the nineteenth century and after the second world war its production and uses (metal plating, pigments, plastic stabilizers, alkaline batteries) have increased exponentially. The opportunities for recycling cadmium are limited in view of the dispersive nature of several of its major uses and therefore the metal progressively accumulates in the environment.

Belgium is the principal producer of cadmium in Europe. Primary zinc smelters have been in operation in the Liège area till 1981 and in the northern part of the Kempen (N-Kempen) from 1888 till presently. Several monitoring programmes have been implemented to assess the impact of this industrial activity on the environment. In particular the cadmium content of soil, grass, sedimented particles and air has been regularly monitored. The results have revealed a higher degree of pollution by cadmium in the suburban area of Engis, near Liège. Measurements performed in N-Kempen, where two primary nonferrous smelters are still in operation, have also confirmed the environmental pollution by cadmium in this rural area. In view of these findings, the residents have been advised to avoid consumption of well water and locally grown vegetables. It is indeed well established that for the general population, the two main sources of cadmium are the diet and smoking. For young children living in a polluted area, direct ingestion of cadmium-containing dust may also be a significant but temporary source of exposure.

An important toxicological feature of cadmium is its exceptionally long biological half-life in the human body (10 to 30 years) (1). The main sites of deposition are the kidneys and the liver. In the tissues, cadmium is mainly bound to a low molecular weight protein (metallothioncin) whose synthesis is induced by cadmium. For the general population mainly exposed by the oral route, the kidney is the critical target organ, i.e. the organ in which the first adverse effects occur. Classically,

the renal dysfunction induced by cadmium involves the proximal tubule (acquired Fanconi syndrome) but the glomerulus may also be affected either directly or secondarily to the development of interstitial nephritis. Renal dysfunction can also lead to disturbances of the calcium metabolism. Experimental studies have suggested that cadmium might play a role in the pathogenesis of hypertension but the clinical data are still controversial.

Cadmium has also been implicated in the development of various types of cancer (2). Although cadmium is carcinogenic in animals under certain exposure conditions and may have favoured the occurrence of lung cancer in workers exposed to high airborne concentration, there is presently no epidemiological and experimental evidence that exposure to cadmium via food may be associated with an increased risk of cancer (3).

Several epidemiological studies carried out in workers exposed to cadmium mainly by inhalation of dust and fume have led to the conclusion that if the cadmium level in the renal cortex does not exceed 200 mg/kg (wet weight), corresponding to a urinary cadmium concentration of about 10 µg/g creatinine, the probability of detecting renal damage is low (4). It is well known, however, that studies performed on occupationally active male subjects may underestimate the risk for other groups in the general population. A few pilot studies carried out in the Liège area between 1975 and 1980 have indeed raised the suspicion that long term environmental exposure to cadmium may also lead to an increased accumulation of the metal in the body and to renal effects (5-7). Although the results of these studies suggested a possible health effect of environmental exposure to cadmium, they had to be interpreted cautiously. All had been performed in the same area and the influence of (an) other unknown factor(s) interfering with both cadmium accumulation and renal function remained a possibility. It was therefore considered necessary to undertake a large scale

cross-sectional morbidity study which was called «Cadmibel» (Cadmium in Belgium) (8).

OBJECTIVES OF THE CADMIBEL STUDY

The main objectives of the Cadmibel study were threefold 1) to determine to which extent environmental exposure to cadmium resulting from industrial emissions may increase the cadmium body burden; 2) to establish whether this elevation of cadmium body burden is associated with changes in the renal function or influences the blood pressure, and possibly the prevalence of cardiovascular diseases; 3) to assess the acceptable internal dose of cadmium for the general population.

In view of the current knowledge of the metabolism of cadmium, the internal dose of the metal can be estimated by measuring its level in urine. Cadmium level in blood is more influenced by the intensity of recent exposure. This paper does not describe the detailed protocol and results of this study, which are published elsewhere (8-11), but simply summarizes its main conclusions.

PRINCIPAL RESULTS OF THE CADMIBEL STUDY

The Cadmibel study was carried out from 1985 to 1989. A stratified random sample of 2327 subjects was identified in two urban (Liège and Charleroi) and two rural (Hechtel-Eksel, N-Kempen) areas. Subjects residing in the Liège area were subdivided into those living near a large zinc and cadmium producing plant that was in operation until 1981 (Engis) and those residing in the city of Liège and the other suburbs. These areas were selected so that the study population included urban and rural populations with different environmental exposure to cadmium (8). The results of several environmental monitoring programmes carried out during the last 15 years in the selected areas indicate that the

intensity of environmental pollution by cadmium is probably in the following order: Charleroi \leq Liège except Engis $<$ Hechtel-Eksel \leq Engis $<$ N-Kempen. The study in N-Kempen was undertaken in 5 villages (Balen, Lommel, Mol, Neerpelt en Overpelt), where soil analyses had revealed cadmium concentrations exceeding 6 mg/kg. After exclusion of subjects who had been occupationally exposed to heavy metals, those aged under 20 or over 80 years, those who could provide no reliable information on smoking habits or occupational exposure to heavy metals, and those whose 24-h urine collections were not considered reliable, the final cohort used for the statistical analysis was composed of 1699 subjects.

The main conclusions of this epidemiological study can be summarized as follows.

The cadmium burden of the body continuously increases with age, at least until age 60, and is higher in smokers than in nonsmokers (Fig. 1). Nonsmoking premenopausal women have a higher cadmium body burden than nonsmoking men of the same age. In addition to these well known variables (smoking habits, age, sex) influencing the cadmium body burden, we have found that environmental pollution by cadmium also contributes to increase the cadmium body burden of subjects residing in the areas polluted by the emission of nonferrous smelters. After allowance for the various factors known to influence cadmium accumulation, we have estimated that the cadmium body burden of the residents of the N-Kempen was 50 to 85 % higher than in Charleroi. We could not confirm the hypothesis that an increased exposure to cadmium is related to blood pressure elevation and a higher prevalence of cardiovascular diseases (9).

We have found, however, that environmental exposure of the general population to cadmium may induce renal tubular dysfunction (10). This conclusion is suggested by the finding of statistically significant dose-effect and dose-response relationships between the urinary

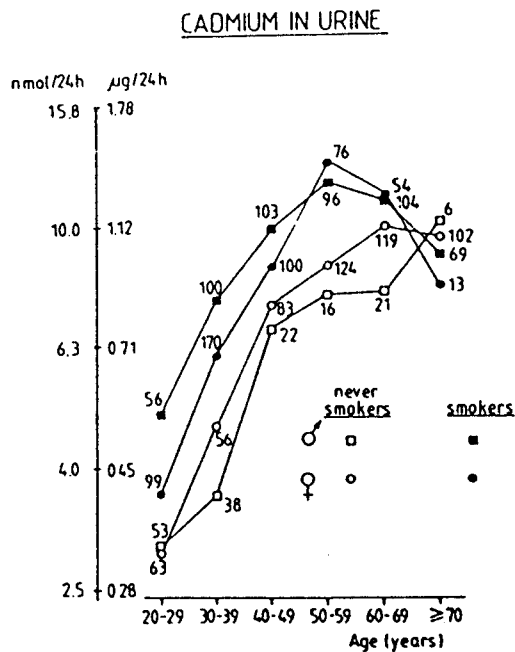


Fig.1 : Geometric average urinary excretion of cadmium by age-group in subjects non-occupationally exposed to heavy metals.

excretion of cadmium (a marker of cadmium body burden) and five effect parameters (urinary excretion of retinol-binding protein, N-acetyl-beta-glucosaminidase activity, beta₂-microglobulin, aminoacids and calcium). These relationships were maintained by taking into account other possible determinants such as exposure to lead, age, sex, smoking habits, diuresis, the presence of diabetes, urinary tract diseases, the consumption of analgesics, the place of residence and the first order interaction terms between cadmium level in urine and the other predictors cited above.

A synergistic effect of cadmium body burden and diabetes was also found on two renal parameters (urinary excretion of N-acetyl-beta-glucosaminidase activity and beta₂-microglobulin).

Serum alkaline phosphatase activity was significantly and positively correlated with

urinary cadmium. Allowance for several possible interfering factors (liver diseases, alcohol consumption, menopause, treatment with diuretics and contraceptive pills) did not abolish the associations between serum alkaline phosphatase activity, calciuria and cadmium body burden. These results suggest that environmental exposure to cadmium may be of sufficient intensity to influence calcium homeostasis and bone metabolism (11).

HEALTH SIGNIFICANCE OF THE FINDINGS

The morbidity associated with the changes in the renal proximal tubule and the calcium metabolism, mainly when they are isolated findings, remains presently unknown. From a public health perspective, it seems reasonable to propose that the exposure of the general population to cadmium should be kept at a level preventing the occurrence of such dysfunction. It has been estimated that the risk of tubular effects and calciuria is about 10% when cadmium in urine reaches 2 µg/day (Fig. 2). The risk, however, may be higher for diabetic patients.

In the total study population (excluding occupationally exposed subjects) about 10% of the subjects excrete more than 2 µg Cd/24 h in urine (Table 1). In women, the prevalence of cadmiuria of at least 2 µg/24 h is similar in smokers and in nonsmokers confirming that environmental exposure to cadmium also plays a significant role in this increased accumulation of cadmium in the human body. Since cadmium is a cumulative toxin, it is not surprising that the subjects excreting more than 2 µg Cd/24 h are mainly found above 40 years of age. The comparison of their distribution between the different areas reveals that the highest prevalences of increased urinary cadmium are found in N-Kempen where, in each age group, the percentage of subjects excreting more than 2 µg Cd/24 h is about twice than in the other areas. Several pilot studies carried out before launching the Cadmibel

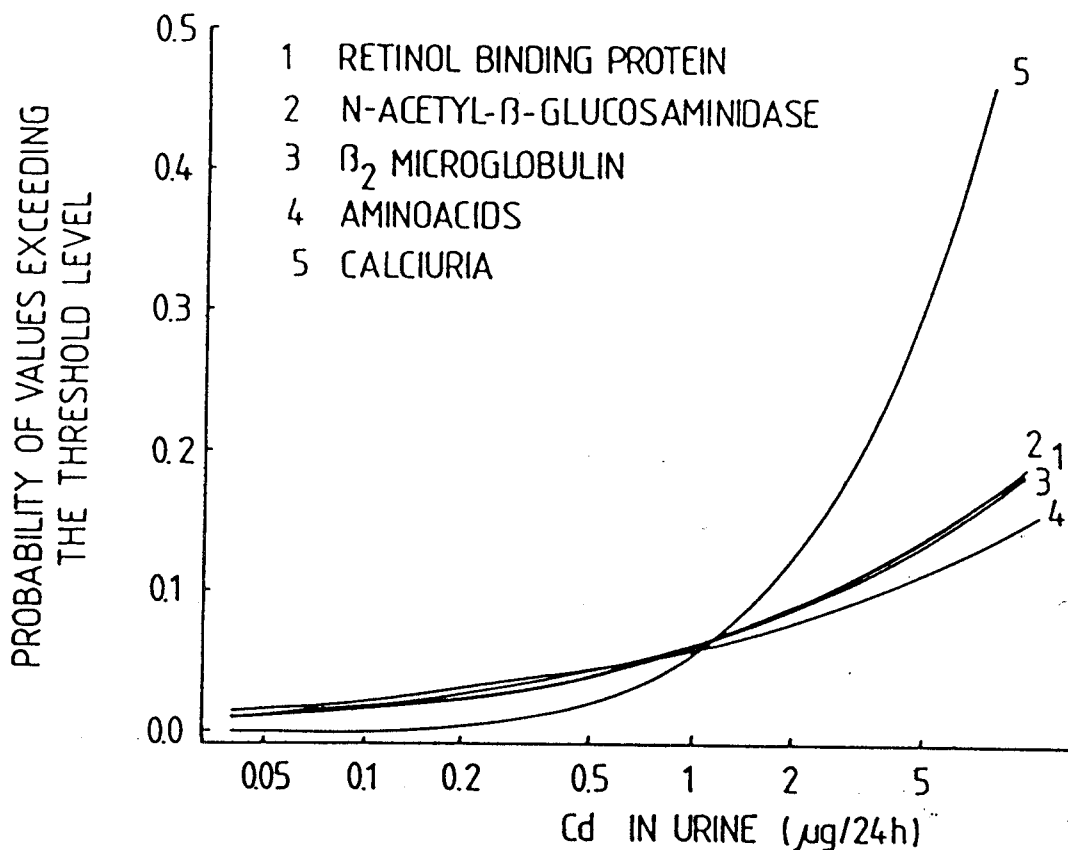


Fig. 2 : Probability of renal dysfunction assessed by five urinary variables as a function of the urinary cadmium excretion. The curves were derived from a logistic regression analysis. Abnormal values : > 338 µg/24 h for retinol-binding protein; 3.6 IU/24 h for N-acetyl-beta-glucosaminidase, 283 µg/24 h for beta₂-microglobulin, 357 mg alpha-NI/24 h for aminoacids, and 9.8 mmol/24 h for calcium.

study have shown that the distribution of the urinary cadmium levels in Charleroi is representative of the non-contaminated districts of the country. Hence, it can be concluded that about 10% of the general population of Belgium have a cadmium body burden sufficient to cause slight renal tubular dysfunction. In order to prevent its occurrence, the urinary excretion of cadmium should not exceed 2 µg/24 h.

RESUME

Le cadmium est un polluant très dispersif qui s'est progressivement accumulé dans l'environnement notamment dans les régions où sont implantées des

fonderies de métaux non ferreux. Une caractéristique toxicologique du cadmium est sa très longue demi-vie dans l'organisme humain. Pour la population générale, principalement exposée au cadmium par l'alimentation et éventuellement la consommation de tabac, l'organe cible critique est le rein. Certaines études ont aussi suggéré que le cadmium pouvait jouer un rôle dans la pathogénie de l'hypertension.

Une étude épidémiologique transversale (appelée Cadmibel) a été entreprise pour apprécier si la pollution de l'environnement par le cadmium dans certaines régions du pays pouvait avoir des répercussions sur la santé des habitants. Cet article ne contient pas les résultats détaillés de l'étude, publiés ailleurs, mais résume ses principales conclusions. Au total, 2327 personnes ont été examinées; elles constituent un

TABLE 1 : PERCENTAGE OF SUBJECTS NON-OCCUPATIONALLY EXPOSED TO CADMIUM AND EXCRETING MORE THAN 2 µg Cd/24 h IN URINE

	AGE (YEARS)			
	20-39	40-59	60-79	TOTAL
<u>Hechtel-Eksel</u>				
Never smokers	0	8.3	9.3	6.3
Past and current smokers	2.1	17.4	14.0	10.7
Total	1.4	13.9	11.5	9.0
<u>N-Kempen</u>				
Never smokers	7.0	25.0	41.8	26.0
Past and current smokers	2.9	30.7	28.6	14.9
Total	4.1	28.1	38.2	19.8
<u>Charleroi</u>				
Never smokers	2.8	9.1	8.6	7.0
Past and current smokers	1.5	13.6	13.5	8.9
Total	1.9	11.7	11.5	8.1
<u>Liège (excluding Engis)</u>				
Never smokers	2.9	0	3.9	2.2
Past and current smokers	0	16.5	15	10.9
Total	1.2	10.9	10.7	7.6
<u>Engis</u>				
Never smokers	0	4.3	10.3	5.9
Past and current smokers	5.5	20.0	29.2	14.7
Total	4.2	13.2	18.9	11.3
<u>Total study population</u>				
Never smokers	2.9	9.4	16.1	9.6
Past and current smokers	2.2	18.9	17.2	11.6
Total	2.4	15.1	16.6	10.8

échantillon représentatif de la population résidant dans deux zones urbaines (Liège et Charleroi) et deux zones rurales (Hechtel-Eksel et Noorderkempen) présentant différents degrés de pollution par le cadmium.

La charge corporelle en cadmium, des sujets habitant dans la zone la plus polluée (Noorderkempen), dépasse d'environ 50 à 85 % celle des sujets résidant dans les régions les moins contaminées. Contrairement à ce que suggèrent certaines données expérimentales, l'accumulation de cadmium dans l'organisme n'est pas associée à une élévation de la tension artérielle ou à une fréquence accrue d'affections cardiovasculaires. L'étude a cependant révélé que l'exposition environnementale au cadmium peut induire un léger dysfonctionnement tubulaire rénal et probablement aussi une perturbation du métabolisme calcique.

Le risque d'un dysfonctionnement tubulaire (détecté à l'aide de tests sensibles) est d'environ 10% quand la quantité de cadmium excrétée dans les urines atteint 2 µg/24 heures.

Il reste à évaluer si dans la population générale en Belgique les perturbations au niveau du tubule rénal et du métabolisme calcique peuvent entraîner une augmentation de la morbidité par affections rénales et/ou osseuses.

SAMENVATTING

Cadmium is een vervuilende stof die zich gemakkelijk verspreidt en die zich geleidelijk aan opgestapeld heeft in het leefmilieu vooral rond non-ferrometaalbedrijven. Een belangrijk toxicologisch

kenmerk van cadmium is zijn uitzonderlijk lange biologische halfwaardetijd in het menselijk lichaam. In de algemene bevolking gebeurt de blootstelling aan cadmium hoofdzakelijk via de voeding en het roken; de nier is hierbij het voornaamste doelwit-orgaan. Sommige studies hebben ook gesuggereerd dat cadmium een rol zou kunnen spelen in de pathogenese van hypertensie.

Een transversale epidemiologische studie (Cadmibel genoemd) werd uitgevoerd in verschillende streken om na te gaan of milieuvervuiling door cadmium in België een gezondheidsrisico inhoudt. Dit artikel geeft geen gedetailleerde beschrijving van de bevindingen van de studie, die werden elders gepubliceerd, maar beperkt zich tot een samenvatting van de voornaamste besluiten. In het totaal werden 2327 personen onderzocht die een toevallige steekproef vertegenwoordigen van de bevolking van twee stedelijke gebieden (Charleroi en Liège) en twee rurale gebieden (Hechtel-Eksel en Noorderkempen) die verschillen in cadmiumvervuiling. Wanneer rekening wordt gehouden met de verschillende factoren die de cadmiumaccumulatie kunnen beïnvloeden, komt men tot de vaststelling dat de cadmiumbelasting van het lichaam bij de bewoners van de meest vervuilde streek (Noorderkempen) 50 tot 85 % hoger was dan in minder vervuilde gebieden. In tegenstelling tot wat verwacht werd op grond van dierexperimentele studies, ging een toegenomen cadmiumbelasting van het lichaam niet gepaard met verhoogde bloeddruk of met verhoogde prevalentie van cardiovasculaire aandoeningen. De Cadmibel-studie heeft echter wel aan het licht gebracht dat cadmiumvervuiling van het leefmilieu bij de algemene bevolking een lichte dysfunctie van de niertubuli en vermoedelijk ook een stoornis in het calciummetabolisme met zich kan meebrengen.

Er is ongeveer 10 % kans dat tubulaire dysfunctie (opgespoord met gevoelige testen) zich voordoet wanneer de urinaire excretie van cadmium minstens 2 µg/24 h bedraagt. Of een dergelijke cadmiumbelasting van het lichaam een reële toename van nier- en botmorbiditeit met zich meebrengt in de algemene bevolking van België moet nog aangetoond worden.

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