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Health Effects of Environmental Exposure to Cadmium: Objectives, Design and Organization of the Cadmibel Study: A Cross-Sectional Morbidity Study Carried Out in Belgium from 1985 to 1989

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Cadmium is a cumulative environmental pollutant. For the general population mainly exposed by the oral route and through tobacco smoke inhalation, the kidney is the critical organ. Belgium is the principal producer of cadmium in Europe, and certain areas of the country are polluted by cadmium mainly because of past emissions from nonferrous industries. Preliminary studies carried out in one polluted area have suggested that environmental pollution might lead to an increased uptake of cadmium by the human body and possibly to health effects. Thus, a large-scale morbidity study has been initiated to assess the validity of this hypothesis. The present paper describes the protocol of this study. Its main objectives are to determine to what extent environmental exposure to cadmium resulting from industrial emissions may lead to accumulation of the metal in the human organism; to establish whether or not environmental exposure may induce renal changes and/or influence blood pressure; and to assess the acceptable internal dose of cadmium for the general population. The study design takes advantage of the fact that biological indicators of exposure, body burden, and early nephrotoxic effects of cadmium are available, which increase the likelihood of detecting a cause-effect relationship.

Introduction

Cadmium Metabolism and Toxicity

Cadmium is an occupational and environmental pollutant that has raised great concern during the last decade. Its industrial production started at the beginning of this century, and since then it has almost doubled every 10 years at least up to 1970 (*1*). The opportunities for recycling cadmium are limited in view of the dispersive nature of several of its major uses; therefore, the metal progressively accumulates in the environment. In Sweden, the average concentration of cadmium in winter wheat has increased during the twentieth century by 100% (*2*). An important toxicologic feature of cadmium is its exceptionally long biologic half-life in the human organism (10 to 30 years).

Excessive exposure to cadmium has been linked with the development of respiratory insufficiency (occupational exposure), renal disturbances and osteomalacia (environmental and occupational exposure) (*3*). The role of cadmium in the development of hypertension remains uncertain.

Cadmium has also been implicated in the development

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of various types of cancer. Although cadmium is carcinogenic in animals under certain exposure conditions and may enhance the occurrence of lung and possibly prostate cancer in workers exposed to high airborne concentrations, there is no current epidemiologic or experimental evidence substantiating that exposure to cadmium via food may be associated with an increased risk of cancer (*4*).

It is generally accepted that for the general population mainly exposed by the oral route and possibly through inhalation of tobacco smoke, the kidney is the critical organ (i.e., the organ in which the first adverse effects occur). One of the earliest signs of cadmium nephropathy is an increased proteinuria resulting from a decreased tubular reabsorption of low molecular weight proteins (e.g., β_2-microglobulin, retinol-binding protein) and possibly also an increased glomerular filtration of high molecular weight proteins (e.g., albumin, transferrin) (*3,5*).

Studies carried out in workers exposed to cadmium mainly by inhalation have led to the proposal that if the level in the renal cortex does not exceed 200 mg Cd/kg (wet weight), corresponding to a urinary cadmium concentration of about 10 μg/g creatinine, the probability of detecting renal damage is low (*6,7*). It should be stressed, however, that this conclusion, based on studies performed on occupationally active male subjects, might underestimate the risk for other groups in the general population, particularly for older persons with declining renal function. The results of a few preliminary epidemiologic studies carried out in Belgium and summarized later in this paper tend to support this hypothesis.

Environmental Pollution by Cadmium in Belgium

Belgium is an important producer of cadmium (about one-fourth of the European production), and certain areas of the country (e.g., the Meuse valley near Liège and the rural northern part of the Kempen) are polluted by cadmium, mainly because of past emissions from nonferrous industries. For example, in Liège, between 1972 and 1977 when three large zinc and/or cadmium producing plants were still in operation, the 50 and 95 percentiles of the daily airborne concentration of cadmium near the urban center amounted to 18 and 165 ng/m^3, respectively (*8*). In an industrial area with low environmental cadmium contamination (Charleroi), the 95 percentile of the daily airborne concentration of cadmium never exceeded 30 ng/m^3. Between 1978 and 1987, the cadmium concentrations in soil and in grass in the Liège area ranged from 4 to 39 mg/kg (dry weight) and from 0.5 to 25 mg/kg (dry weight), respectively; whereas the corresponding values in the control industrial area (Charleroi) ranged from 0.5 to 1 mg/kg (dry weight) and from < 0.5 to 2 mg/kg (dry weight). Recent measurements have been performed in the northern part of the Kempen (N-Kempen) where two important primary zinc smelters have operated since 1888 and one zinc smelter was in operation from 1904 to 1972. These findings confirmed the environmental pollution by cadmium in this rural area (measurements performed by the Institute of Hygiene and Epidemiology, Brussels; Institut de Recherches Chimiques, Tervuren; Lisec-Studiecentrum voor Ecologie en Bosbouw, Bokrijk).

For example, between 1984 and 1987, the 50 percentile of the daily airborne concentration of cadmium was below 10 ng/m^3, but the 95 percentile amounted to 40 ng/m^3. Between 1981 and 1986 the cadmium concentrations of grass ranged from 0.13 to 29 mg/kg (dry weight). The cadmium contamination of the top-layer soil (0–25 cm) from 155 kitchen-gardens was measured in the years 1983 and 1984; the levels ranged from 0.5 to 24 mg/kg (dry weight), and 41% of the samples had cadmium levels > 3 mg/kg (dry weight). Well water from that area was also found to be contaminated by cadmium. During the years 1983 to 1984, the cadmium concentration of water samples from 2410 wells (> 95% used as drinking water) ranged from 0.05 to 400 μg/L (50 and 90 percentiles amounting to 4.3 and 25 μg/L, respectively); 45% and 25% of the samples had cadmium levels exceeding 5 and 10 μg/L, respectively. In Belgian rural areas that are not polluted the 95 percentile of daily airborne cadmium level is lower than 10 ng/m^3, and the background cadmium contamination of grass and soil does not exceed 0.2 and 1 mg/kg (dry weight), respectively.

Preliminary Studies on Environmental Exposure to Cadmium in Belgium and Its Health Effects

The environmental exposure of the Belgian population to cadmium is high compared with other countries (*9*). In a World Health Organization (WHO) collaborative study carried out in 1981 involving teachers from 10 countries, the median cadmium concentration in blood ranged from 1.2 μg/L for Japan and Belgium to less than 0.5 μ/L in Israel. Also, three studies were undertaken in the Liège area to assess whether or not the environmental pollution by cadmium led to an increased uptake by the inhabitants and possibly to health effects.

In the first study carried out in 1978 and 1979 (*10*) it was found that the blood and urine levels of cadmium in a group of nonsmoking elderly women (n = 60), who had spent most of their life in the Liège area and had never been occupationally exposed to cadmium, were higher than those found in a group of women (n = 70) of the same age and socio-economic status who had lived in the control industrial area (Charleroi) that was less polluted by this metal. The urinary excretion of total protein, aminoacids, β_2-microglobulin and albumin followed the same trend as that of cadmium.

Following these preliminary observations, a mortality study was undertaken (*11*). It was found that although the overall mortality was not markedly different, the standardized mortality ratios (SMR) and the

proportional mortality rates (PMR) from nephritis and nephrosis for the years 1969 to 1976 were higher in Liège than in Charleroi or in Belgium as a whole (SMR: Belgium 100, Charleroi 102, Liège 196; and PMR: Belgium 3.3, Charleroi 3.0, Liège 6.0). Since the increased mortality rate for renal diseases was observed in both males and females, the influence of environmental factors other than occupation was suggested. Furthermore, a 1980 epidemiologic study on analgesic nephropathy (a frequent cause of end-stage renal disease in certain areas of Belgium) did not show a difference in the prevalence of the disease between Liège and Charleroi (*12*), suggesting that the higher SMR by nephritis and nephrosis in Liège did not result from a difference in the consumption of analgesics between the two regions.

To confirm that the cadmium body burden of the Liège inhabitants was really increased, as suggested by the results of the urinary excretion of cadmium, a study of autopsies was undertaken (*13*). It was found that in all age groups, the persons who had lived in the Liège area had accumulated more cadmium in their renal cortex and liver than did residents from other areas of Belgium (mainly from the southern provinces). The same trend was found in males and females. Examination of the medical records and/or an inquiry to the next of kin indicated that this difference did not result from differences in occupational exposure or smoking habits between the groups.

Although the results of these three studies (*10,11,13*) suggest a possible health effect of environmental exposure to cadmium, they must still be interpreted cautiously. These studies have been performed in the same area (Liège), and the influence of another unknown factor interfering with renal function remains a possibility. To further assess the hypothesis that environmental pollution by cadmium in Belgium may have led to health effects, it was considered necessary to undertake another morbidity study of larger scale than the preceding one which involved several areas of the country. The present report describes the methodology of this collaborative study.

Objectives of the Present Study

The main objectives of the study were to determine to what extent environmental exposure to cadmium resulting from industrial emissions may lead to accumulation of the metal in the human organism; to establish whether or not environmental exposure may induce renal changes and/or influence blood pressure; and to assess the acceptable internal dose of cadmium for the general population. In view of our current knowledge of the metabolism and the nephrotoxic effects of cadmium, the internal dose of cadmium was assessed by measuring its levels in blood and urine, while the determination of creatinine clearance and of urinary excretion of specific proteins were used as indicators of renal effects.

The study was designed so that additional objectives complementary to those cited above could be pursued, i.e., the assessment of the possible impact of environmental exposure to lead on renal function and blood pressure; the identification of endogenous and exogenous factors that influence the internal dose of lead and cadmium, blood pressure, and renal function; and eventually an assessment of the health significance of the morbidity data collected in the framework of this study by an independent analysis of the mortality from cardiovascular and renal diseases in the areas investigated.

Selection of the Areas

Attempts were made to select areas differently polluted by cadmium and also to match each polluted area with at least one less polluted or control area with regard to the socioeconomic environment. Four areas were selected: *a*) One industrial area (Liège) was polluted mainly because of industrial emissions of cadmium (the last cadmium producing plant was closed in 1981); the area has a surface of about 100 km^2 and a population density of 2272 persons/km^2, and steel production remains an important industrial activity in this area. *b*) A second industrial area (Charleroi) was not polluted by cadmium but had iron foundries in operation; the area is spread over 130 km^2 and has a population density of 2014 persons/km^2. *c*) A rural area (N-Kempen), located near two nonferrous smelters, has a surface approximately 200 km^2 with a population density 280 persons/km^2. *d*) A control rural area (Hechtel-Eksel) has a surface area approximately 75 km^2 with a population density of 125 persons/km^2 (Fig. 1).

Population Selection

In view of the distribution characteristics of the various measurements, the examination of 250 to 300 per-

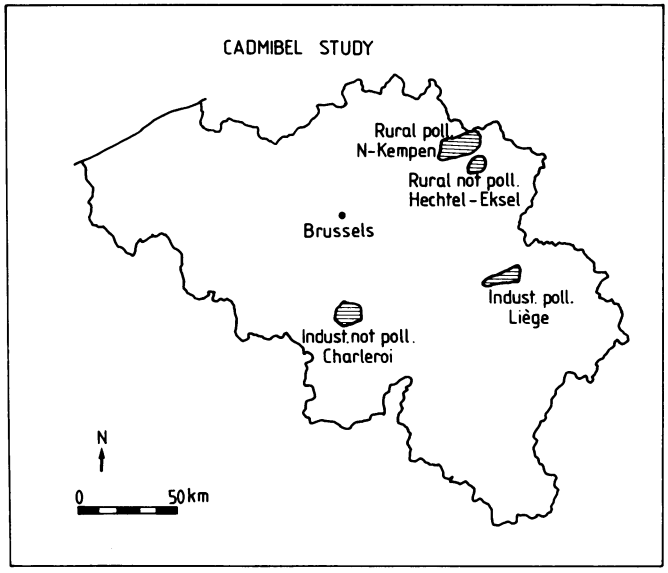

FIGURE 1. Areas selected for the study of the health effects of environmental exposure to cadmium in Belgium.

sons in each of the four areas was considered sufficient to detect with an α error of 5% and a β error of 10%, a 10% difference in the protein excretion, a 5% difference in creatinine clearance, or a 5 mm Hg difference in systolic pressure and a 3 mm Hg difference in diastolic pressure.

Hence, it was finally decided to examine at least 300 subjects (150 males and females) in each area, equally distributed over the three age groups 20 to 39, 40 to 59, and 60 to 79 years, respectively. At least 600 subjects have thus been examined in the polluted areas (Liège and N-Kempen) and 600 in the less polluted areas (Charleroi and Hechtel-Eksel). Although it was intended to select a similar number of male and female individuals in each age group, for practical reasons sampling was based on households defined as all subjects living at the same address.

In each area a sample of at least 200 households was randomly selected. All family members between the ages of 20 and 80 were eligible for the study as long as the number of individuals (n = 50) needed in each sex and age group had not been reached. When 50 individuals had been identified in one or more of the six sex-age strata, only the family members belonging to the subgroups whose quota had not yet been satisfied were selected. Households whose head members were not of Belgian nationality were excluded from the sample.

Several methods were used to gain local support for the study and motivate the participants. All local civil authorities (mayor and aldermen), health inspectors, general practitioners, and health professionals were approached. Advertisements appeared in local newspapers and were broadcasted on radio and television. A letter of invitation was sent to all eligible families. All participants were informed of their personal results via their general practitioner.

Experimental Protocol

Field Study

The field study was spread over 4 years and was carried out by ten specially trained observers (nurse or social worker). Two areas were always examined at the same time.

Each household was visited twice by the same observer. The first home visit consisted of five consecutive blood pressure readings (phase 5 diastolic pressure), obtained with a standard sphygmomanometer in the sitting position followed by a pulse rate count and a measurement of height and body weight. The participants were given a self-administered questionnaire and a wide-neck metal-free polyethylene container for a 24-hr urine collection. They were carefully instructed, in writing, about the procedure for collecting the urine and storing the containers between voidings in order to prevent metal contamination. The questionnaire inquired about the participants' medical history, their current and past occupations, smoking habits, consumption of alcohol, locally grown vegetables and well water, and drug intake. (A translation of the questionnaire in English is available on request.)

At the second visit 1 week later, the questionnaire and a recent 24-hr urine sample were collected, and the measurements of blood pressure, pulse rate, height, and body weight were repeated. Each subject was thus characterized by the mean of ten blood pressure measurements and by two determinations of pulse rate, height, and body weight.

At one of the home visits, preferably the first, a fresh urine sample was obtained after the blood pressure and pulse rate measurements had been performed. Four milliliters (for β_2-microglobulin measurement) were immediately transferred to a tube containing 0.4 mL phosphate buffer 1 M, pH 7.6, containing 0.2% NaN_3. For the preservation of the 24-hr urine samples, NaN_3 10% (3 mL/container) was used. The volume and the pH of the 24-hr urine samples and the pH of the spot-urine samples were measured in the field centers and indicated on the containers.

On a separate occasion, but usually within 1 week of the urine collection, a physician visited the participants and withdrew 20 mL venous blood with a syringe. The sample was divided in two aliquots of 4 mL (2 tubes with anticoagulant, 0.1 mL Na_2-EDTA 10%), and the remainder was kept in two empty tubes for separation of serum in the field centers.

All blood and urine samples were kept at 4°C. These samples were transported in cooling boxes from the field centers to the laboratories once a week.

All laboratory materials (tubes, urine containers, syringes, and needles) and solutions (buffer, NaN_3, EDTA) were checked for contamination by cadmium, lead, selenium, zinc, copper or calcium. The acceptable background contamination of materials and solutions had to be < 0.05 μg/L for cadmium, < 2 μg/L for lead, < 2 μg/L for selenium, < 10 μg/L for zinc, < 0.5 μg/L for copper, and < 0.1 mg/L for calcium.

Biological Analyses

The following measurements were performed in the two laboratories involved in the study: on whole blood—lead, cadmium, zinc-protoporphyrin, and selenium; on serum—creatinine, alkaline phosphatase, γ-glutamyltranspeptidase, total cholesterol, HDL cholesterol, calcium, magnesium, zinc, ferritin, and β_2-microglobulin; on 24-hr urine—creatinine, cadmium, calcium, sodium, potassium, copper, total amino acids, total protein, β_2-microglobulin, retinol-binding protein, albumin, N-acetyl-β-glucosaminidase, and reagent strip analysis; on spot-urine—creatinine, cadmium, β_2-microglobulin, and reagent strip analysis.

The determination of cadmium, lead, and selenium in whole blood, and of cadmium and copper in urine were performed by electrothermal atomic absorption spectrometry (Perkin-Elmer Zeeman-3030 or Zeeman-5100) using the stabilized-temperature-platform-furnace (Cd, Pb, Se) or the furnace wall (Cu) techniques coupled with a Zeeman-effect background correction system. The

method of external standard line in a whole blood matrix was used for trace metal analysis in whole blood, while the method of standard addition was used for urine. The concentration of zinc in serum was determined according to Kelson and Shamberger (*14*), using the method of deproteinization with trichloroacetic acid combined with flame atomic absorption spectrometry (Perkin-Elmer Model 305).

Zinc-protoporphyrin (ZPP) in blood was measured using a hematofluorimeter (Aviv Associates, Lakewood, NJ). The concentration of β_2-microglobulin and ferritin in serum and that of β_2-microglobulin, retinol-binding protein (RBP) and albumin in urine were determined using a nonisotopic immunoassay based on latex particle agglutination (*15*).

A colorimetric method was used for the determination of total α-N-amino-aciduria using picrylsulfonic acid (*16*). Total proteinuria was determined on urine, after overnight dialysis, using Folin's reagent and bovine serum albumin as reference protein (*17*). The activity of *N*-acetyl-β-glucosaminidase (NAG) in urine was determined according to the fluorimetric method of Tucker et al. (*18*). Creatinine in serum and urine (*19*), magnesium (*20*), alkaline phosphatase (*21*), γ-glutamyltranspeptidase (γGT) (*22*), total cholesterol (*23*) and HDL cholesterol (*24*) in serum were determined on a COBAS-BIO centrifugal analyzer (Roche Diagnostics). Calcium in serum and urine was analyzed by a complexometric titration method (*25*) on a Corning 940 Calcium Analyser. Sodium and potassium in urine were measured by flame photometry (KLiNa-Beckman Instrument) (*26*).

Quality Control

Training of the Observers and Blood Pressure Measurements

The trainees were explained the rationale and methodology of blood pressure measurements, were shown a videotape (*Measuring Blood Pressure*, Production n° B, 132, The Audio-visual Centre, University of London, 11 Bedford Square, London WC1, 1973) showing a falling mercury column, and they obtained experience using a regular sphygmomanometer at home for 1 week. They were then tested in two phases: they again recorded the pressures from the videotape and were finally tested by using stethoscopes having two pairs of ear pieces on live subjects. To pass the test all videotape readings had to be within 10% of the standard, and all measurements in the live subjects had to be to within 10% of the simultaneous pressure determinations by an experienced observer (*27*).

Biological Analyses

Most of the analyses were performed in duplicate using internal calibration standards and, when available, certified reference standards were run along with each series of study samples. Acceptable limits for precision were defined for duplicate measurements, and a series of measurements was repeated when the precision or the results of the corresponding standards (accuracy) fell outside the limits specified in Table 1.

Before the start of the study and during its course, the two laboratories participated in several external quality control programs that concerned the following measurements: cadmium and lead in blood (UK External Quality Assessment Scheme organized by the Wolfson Research Labs, Queen Elisabeth Medical Centre, Birmingham, England); zinc and selenium in serum, lead, and cadmium in blood and cadmium in urine (Trace Element Quality Control Scheme organized by the Robens Institute, University of Surrey, Guildford, UK); and creatinine, alkaline phosphatase, γ-glutamyltranspeptidase, total cholesterol and calcium in serum (Belgian Quality Control Scheme supervised by the Ministry of Health).

Furthermore, for some analyses (lead, cadmium, and ZPP in blood; zinc, ferritin, and β_2-microglobulin in serum; cadmium, copper, creatinine, β_2-microglobulin, and retinol-binding protein in urine), 10% of the samples were analyzed in the two study laboratories. When the results of one sample deviated more than 10%, the whole series was reanalyzed in both laboratories.

Data Processing and Statistical Analysis

Coding the questionnaire and clinical examination sheet was performed by trained technicians who also entered the data into the computer. For the purpose of

Table 1. Acceptance limits for precision of duplicate measurements and accuracy.

Sample	Analyte	Precision, %	Accuracy, %
Whole blood	Cd (≤ 2 μg/L)	< 10	± 15
	(> 2 μg/L)	< 5	± 10
	Pb	< 5	± 5
	Se	< 5	± 10
	ZPP	< 5	± 10
Serum	Zn	< 5	± 5
	Creatinine	< 4	± 5
	β_2-Microglobulin	< 10	± 10
	Alkaline phosphatase	< 3	± 5
	Ca	< 2	± 2
	γ-GT	< 3	± 5
	Ferritin	< 10	± 10
	Cholesterol	< 4	± 4
	Magnesium	< 3	± 5
Urine	Cd	< 5	± 5
	Cu	< 5	± 5
	Amino acids (total)	< 5	± 10
	Proteins (total)	< 10	± 10
	β_2-Microglobulin	< 10	± 10
	RBP	< 10	± 10
	Albumin	< 10	± 10
	Na	< 2	± 4
	K	< 2	± 4
	Ca	< 2	± 2
	Creatinine	< 2	± 3
	NAG	< 5	—

quality assurance, 10% of the questionnaires coded by one technician was selected at random and coded again by another technician and vice versa. All results of the biological measurements, questionnaires, and clinical examination that were entered into the computer were verified against the original data. Algorithms based on the answers to the questionnaire have been defined to characterize smoking habits and alcohol consumption and to identify subjects with current or past occupational exposure to heavy metals, those under current and/or past medication known to interfere with blood pressure or renal function (e.g., antihypertensive drugs, diuretics, analgesics, contraceptive pill), and those with recent and/or past history of diabetes mellitus or of diseases of the cardiovascular or renal systems. The statistical analysis will be performed using the procedure of multivariate analysis provided by the SAS system (*28*). If necessary, comparisons of group means and regression analyses will be performed after normalizing the distribution of biological measurements by a logarithmic transformation.

Practical Organization of the Study

The progress of the field and laboratory work was supervised by a scientific committee composed of scientists belonging to the four research units. Three-month-interval reports were submitted to a steering committee composed of representatives of the agencies that funded the study.

Discussion

With a few exceptions the majority of epidemiologic studies on the health effects of environmental pollutants have attempted to assess the relationships between various external indicators of pollution (presence of emission sources, results of environmental monitoring network) and morbidity (clinical signs) and/or mortality data. This kind of approach suffers from many limitations. Indeed, current and/or past exposure to pollutants can only be estimated on a population basis. Furthermore, diagnosed clinical entities are late manifestations of physio-pathological processes, the evolution of which to diseases may have been influenced by various exogenous and endogenous factors. With such an approach, environmental pollutants can be identified as etiologic agents of pathologic conditions only when their role is overwhelming by comparison with that of other factors or when the time interval between exposure and diseases (latency period) is not too long. But environmental pollution is rarely of such intensity that its clinical effects are rapidly apparent. Furthermore, since many diseases are multifactorial, the favoring role of environmental factors may be easily overlooked with an epidemiologic approach based on a crude assessment of exposure to environmental pollutants and a search for late effects (diseases, causes of death).

These difficulties can be overcome if assessment of exposure is carried out on an individual basis (e.g., through the use of biological monitoring methods) and if early biological effects are selected as health indicators. This individual approach offers the advantage of preventing the dilution effect associated with the use of external exposure parameters (ambient pollution). Biological monitoring markedly reduces the uncertainty in the assessment of individual exposure to pollutants. Furthermore, the usually shorter time interval between the occurrence of an excessive body burden and the development of early biological effects prevents the interference of various factors that subsequently may influence the evolution to clinical disease and mask the contribution of environmental pollution.

Unfortunately, our limited knowledge on the metabolic fate of environmental pollutants in the human body and their mechanism of action restricts the applicability of such an approach. Cadmium is a remarkable exception. Biological indicators are available to estimate current (cadmium in blood) and lifetime-integrated exposure (cadmium in urine) and to detect its early influence on its main target organ, the kidney. The design of the present epidemiologic study has taken benefit of this knowledge and is a good example of the importance of the interplay between epidemiologists and biologists for a better assessment of the potential health impact of an environmental pollutant.

The advantage of measuring early preclinical effects stems not only from the reduction of the latent period, which increases the likelihood of detecting a cause-effect relationship, but probably also from the reduction of selection-bias influence (e.g., sick persons may decide to move from an industrially polluted area). With cadmium, it is possible to assess the body burden of each participant by a biological measure that permits researchers to study the correlation between individual lifetime-integrated exposure and the risk of adverse effects without making any assumption on past environmental pollution, for which monitoring data may not necessarily be available. The method of population selection (sampling on households) also offers several advantages (*29*) over individual sampling: *a*) it is more practical since several persons can be visited at the same address, *b*) it usually has a higher participation rate, *c*) it permits investigators to perform blood pressure readings in more basal conditions, and *d*) it allows them to study, in a subset of the examined population, the influence of familial aggregation on certain measurements (e.g., blood pressure) and environmental factors on cadmium exposure (e.g., consumption of well water).

One must, however, recognize that the design of the present study has also some limitations that must be kept in mind when interpreting the results. If the biological measures of exposure are specific for the pollutant under study, the early indicators of effect are usually organ specific but not pollutant specific. This approach, therefore, should take into account other possible interfering factors. Depending on our current knowledge, these factors may be assessed through biological measurement (e.g., exposure to lead) or, more classically, through the use of a detailed questionnaire

(e.g., consumption of drugs and tobacco, occupation). Furthermore, the health significance of the early markers of nephrotoxicity is not yet fully established. However, there is some evidence from a study carried out on cadmium workers that a persistent increased urinary excretion of proteins may be predictive of an accelerated age-related decline of renal function (reduction of glomerular filtration rate), but the level of protein excretion at which the risk is significantly increased is still unsettled (*30*).

An important aspect of a large-scale collaborative study spread over several years is the need for rigorous quality control programs. Great time and effort have been spent before and during the study to define, in detail, all the quality control programs to be implemented and to check that their results meet the set objectives.

The design of this study should allow us to confidently assess whether or not the body burden of cadmium in groups of the general population who have resided in environmentally polluted areas entails some health risk and also possibly determine the internal dose of cadmium at which the risk of adverse effects is increased.

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