GLOBAL ENVIRONMENT MONITORING SYSTEM

EXPOSURE MONITORING OF LEAD AND CADMIUM

An international pilot study within the WHO/UNEP Human Exposure Assessment Location (HEAL) Programme

Technical report edited by

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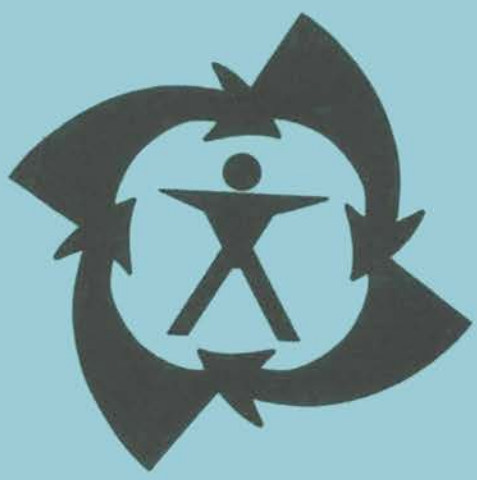

WORLD HEALTH ORGANISATION

UNITED NATIONS ENVIRONMENT PROGRAMME

UNEP

For bibliographic and reference purposes this publication should be referred to as:

Vahter, Marie and Slorach, Stuart (1990). Exposure Monitoring of Lead and Cadmium: an international pilot study within the WHO/UNEP Human Exposure Assessment Location (HEAL) Programme, pp. 82.

Global Environment Monitoring System.

Nairobi: World Health Organisation and the United Nations Environment Programme.

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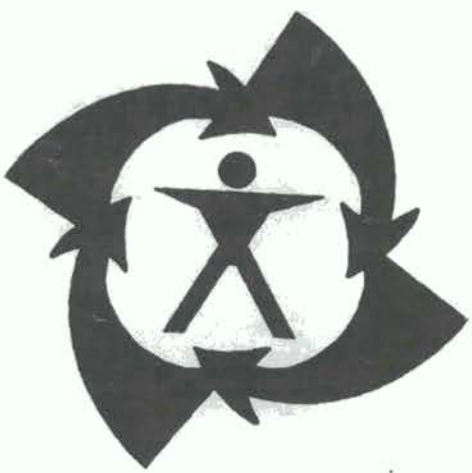

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PREFACE

Human exposure to a pollutant occurs when a person comes in contact with that pollutant through the air they breathe, the water and food they consume or through skin absorption. Knowing the degree of exposure is necessary to study the effects on health and to devise appropriate control strategies. In recent years new techniques have been developed directly to monitor such exposures, assess them accurately and evaluate contributions from the individual sources. An increasing number of countries are using this technology in a multidisciplinary approach to multi-media human exposure and assessment.

To assist the further development and application of the technique currently being applied in several countries, the WHO and UNEP through the GEMS are co-operating in a coordinated effort - Human Exposure Assessment Location Studies (HEALs). This programme aims to improve exposure monitoring and assessment internationally leading to better protection of human health. Direct measurements of human exposure using established methodology, coupled with human activity patterns and social and cultural conditions provide the basic data enabling exposures in a given population to be determined. Accurate risk assessment studies can then be undertaken and cost effective strategies developed if required to further protect human health.

For each study in the HEAL programme, one of the participating institutions in a particular country is designated as a Technical Co-ordinating Centre (TCC). The Centre is responsible for monitoring protocols, design and implementation of quality control programmes and other technical support to help participants implement the project. Each country has, however, a major responsibility for conducting their own study.

In the pilot phase seven countries were involved: Brazil, China, India, Japan, Sweden, U.S.A. and Yugoslavia, and three groups of chemicals were monitored by some of them, namely the heavy metals lead and cadmium, the organic chemicals hexachlorobenzene (HCB) and dichlorodiphenyltrichloroethane (DDT) and the gaseous substance nitrogen dioxide. The substances were chosen for they may pose health risks and the participants were interested in determining exposure to such substances.

Reports of the three pilot phase studies are published separately. This report presents the results from the monitoring of lead and cadmium co-ordinated by a TCC in Sweden as described in the section Institutions and Investigators. Laboratories in China, Japan, Sweden and Yugoslavia completed the project, while Brazil, India and U.S.A. participated in part of the analytical training programme.

INSTITUTIONS AND INVESTIGATORS

The HEAL Pilot Project on Exposure Monitoring of Lead (Pb) and Cadmium (Cd) was coordinated by a Technical Co-ordinating Centre (TCC) in Sweden in close collaboration with the network of national institutions participating in the project. The TCC was organized as a committee with representatives of the Institute of Environmental Medicine and the Department of Environmental Hygiene at the Karolinska Institute (Dr Lars Friberg, chairman, M Sc Marika Berglund, rapporteur, Dr Marie Vahter and Mr Birger Lind), the National Food Administration (Dr Stuart Slorach and Mr Lars Jorhem), the National Board of Health and Welfare (Dr Håkan Wahren), the National Environmental Protection Board, and the Department of Environmental Medicine and Infectious Disease Control, Stockholm County Council, Karolinska Hospital (Dr Carl Fredrik de Ron).

The HEAL pilot Pb/Cd project included an analytical training programme and an exposure monitoring study. Initially, China, Japan, Sweden, USA and Yugoslavia participated in the project, Brazil and India joined at a later stage. China, Japan, Sweden and Yugoslavia completed the pilot project. Brazil, India and USA participated in part of the analytical training programme only. The following national institutions participated in the project:

BRAZIL: Ministry of Health, National Division of Human Ecology and Environmental Health, Brasilia; Oswaldo Cruz Foundation, Rio de Janeiro; State Secretariat of Health and Environment, Rio Grande do Sul; Environment Division, Porto Alegre
Principal investigators: Dr Nestor da Costa Borba and Luiz Augusto Cassanha Galvao
Responsible analyst: Dr Maria Lucia Koslowski Rodrigues

CHINA: Institute of Environmental Health Monitoring, Beijing
Principal investigators: Dr Zheng Xingquan and Dr Zhuang Li
Responsible analysts: Mr Cia Shilin and Ms Gao Ilui

INDIA: National Institute of Occupational Health, Ahmedabad; Air Quality Monitoring and Research Laboratory, Bombay
Principal investigators: Dr S.K. Kashyap, Dr D.J. Parikh and Dr S.R. Kamath
Responsible analysts: Dr C.B. Pandya, Mr N.G. Sathawara and Mr G.M. Shah for NIOH; Mr J.M. Deshpande for Air Quality Monitoring and Research Laboratory

JAPAN: Institute of Public Health, Tokyo;
Yokohama City Institute of Public Health, Yokohama
Principal investigator: Dr Masahiko Fujita
Responsible analyst: Dr Taro Kawamura

SWEDEN: Karolinska Institutet, Institute of Environmental Medicine and Department of Environmental Hygiene, Stockholm; National Food Administration, Uppsala
Principal investigators: Dr Marie Vahter, Dr Stuart Slorach and M Sc Marika Berglund
Responsible analysts: Mr Birger Lind and Mr Lars Jorhem

USA: U.S. Environmental Protection Agency, Washington D.C.
Principal investigator: Dr Michael Dellarco
Responsible analyst: Dr David McNelis, Environmental Research Center, University of Nevada

YUGOSLAVIA: Institute for Medical Research and Occupational Health, Zagreb
Principal investigator: Dr Marko Šaric´
Responsible analysts: Dr Maja Blanuša and Dr Spomenka Telišman

UNEP/WHO SECRETARIAT:
Mr Guntis Ozolins, WHO, Geneva
Dr Henk de Koning, WHO, Geneva
Dr Michael Gwynne, UNEP, Nairobi

SUMMARY

An international integrated human exposure monitoring study for lead (Pb) and cadmium (Cd), involving the sampling of duplicate diets, airborne particles, blood and faeces, was implemented. The first phase of the project consisted of an analytical training phase, which was completed by participating institutions in China, Japan, Sweden and Yugoslavia. Institutions in Brazil, India and the USA participated in part of this phase. The second phase, which consisted of a pilot exposure monitoring study for Pb and Cd including an extensive quality control (QC) component, was performed in China, Japan, Sweden and Yugoslavia.

The experience gained in the QC programme shows that good analytical performance for one type of medium is no guarantee of good analytical results with other types of media. Furthermore, the QC samples have to cover the range of concentrations expected to be found in the monitoring samples. Although major analytical problems were encountered, especially with the duplicate diet and air filters, the analytical performance improved during the training phase.

Exposure monitoring of Pb and Cd was carried out during February - May, 1988 on small groups of non-smoking women, 23-53 years of age, at four HEAL sites: Beijing (12 subjects), Yokohama (3 subjects), Stockholm (15 subjects) and Zagreb (17 subjects). Airborne particles (TSP, personal sampler) and duplicate diets were collected by each subject during 7 consecutive days. Faeces were collected during 4-7 days and blood samples at the end of the monitoring period (day 8). Food consumption records and activity diaries were kept during the whole sampling period. Determinations of the concentrations of Pb and Cd in the collected samples were carried out by the participating institution in each country. For validation of the results, external QC samples (air filters, dust, diets, faeces and blood) were analysed together with the collected samples and the results were evaluated by the technical coordinating centre in Sweden.

Evaluation of the total exposure to Pb and Cd was based on the concentrations in blood. The average blood Pb level was 73 ug/l in Beijing, 29 ug/l in Stockholm, 31 ug/l in Yokohama and 50 ug/l in Zagreb. The corresponding figures for Cd in blood were 0.6, 0.3, 1.6 and 0.7 ug/l. The Pb data from Beijing, when compared with previous results from similar studies, could be considered to indicate increased exposure, while those from the other HEAL sites indicate a decrease in Pb exposure. The Cd data are in reasonable agreement with earlier data from these cities.

The results indicate that the diet is an important route of exposure to Pb and Cd. In general, airborne Cd contributed only a few percent of the total exposure, and airborne Pb 5-15% in Beijing, Stockholm and Yokohama. In Zagreb the uptake of lead from air was about twice that from the diet. High content of Pb and Cd in faeces indicated other sources of oral exposure than the diet. There were large day-to-day and inter-individual variations in Pb/Cd intake, indicating that certain foodstuffs can have a profound effect on the total exposure to Pb/Cd. The average dietary lead intake at the different HEAL sites varied from approximately 4 to 11% of the Provisional Tolerable Weekly Intake (PTWI) proposed by an FAO/WHO Expert Group. The corresponding cadmium intake ranged from about 12 to 33% of the PTWI. On a group basis, the content of Pb and Cd in faeces was found to

reflect the dietary intake, except in Zagreb, where the content of Pb and Cd in faeces exceeded the content in the collected duplicate diets for most women.

This pilot study was one of the first to be developed and implemented as part of the HEAL project. The experience gained shows that, although costly and complicated, it is possible to make comparable measurements on an international scale. It was possible to identify a number of problems in the collection and analysis of different types of exposure monitoring samples, as well as to identify the major routes of exposure. Such information is valuable for the design of a full-scale study on a representative sample of the general population.

1. INTRODUCTION

1.1. UNEP/WHO HEAL project: background and objectives

The UNEP/WHO Human Exposure Assessment Location (HEAL) project was developed as part of the WHO Health-Related Monitoring Programme, which was started in 1973 and originally comprised urban air monitoring, water quality monitoring and food contamination monitoring. These three monitoring projects form part of the Global Environment Monitoring System (GEMS).

Between 1970 and 1980 several reports showing that data from outdoor air monitoring stations do not reflect the total human exposure appeared (e.g. Yocom, 1971; Ott and Mage, 1975; Fugas, 1976; Cortese and Spengler, 1976). In 1977 a Government Designated Expert Group recommended that more attention should be given to human exposure assessment (WHO, 1977). Two pilot projects were developed, one dealing with health-related air pollution monitoring (WHO, 1982 a, b, c; WHO, 1985) and the other with biological monitoring of lead, cadmium and certain organochlorine compounds (Vahter, 1982; Friberg and Vahter, 1983; Slorach and Vaz, 1983; Bruaux and Svartengren, 1985). In 1981 a consultation on health-related monitoring (WHO, 1981) reviewed the ongoing activities and concluded that source-oriented monitoring was not providing adequate information to estimate human exposure and that there was a need to develop and agree on acceptable methodology to determine exposure to environmental pollutants. Therefore, ongoing exposure-oriented monitoring activities within the UNEP/WHO Human Exposure Assessment Location (HEAL) project were initiated (WHO, 1982d; WHO 1983).

The main objectives of the HEAL project are (UNEP/WHO, 1985):

-to improve, field test, harmonize and demonstrate methods for the integrated monitoring and assessment of human exposure to environmental pollutants;

-to promote the assessment of human exposures to pollutants as a basis for the development of environmental control strategies for the protection of public health;

-to provide an overview of existing exposures of selected populations to pollutants and, if possible, to observe trends in this regard;

-to improve national capabilities for environmental monitoring and human exposure assessment, particularly in the developing countries.

Initially, exposure to Pb, Cd, DDT, HCB and NO_2 has been studied. Technical Coordinating Centres (TCCs) have been appointed for various types of pollutants (UNEP/WHO, 1986a). For the time being, seven countries are participating in the HEAL project: Brazil, China, India, Japan, Sweden, USA and Yugoslavia.

For many commonly occurring environmental pollutants there is only a small difference between "normal" exposure levels and the exposure level at which the first

signs of adverse health effects occur. Therefore, it is important to be able to detect small differences in exposure between different populations or groups of subjects, or small changes in exposure within a population over time. This requires sensitive methods for the detection of systematic errors in the analytical results. The analytical quality control programme that has been recommended by UNEP/WHO (1986b) and Friberg (1988) is based on the methods developed in the UNEP/WHO project on biological monitoring of lead and cadmium (Vahter, 1982; Friberg and Vahter, 1983) and involves the analysis of sets of 4-6 quality control (QC) samples and the evaluation of the results using linear regression analysis.

The main objective of the pilot HEAL Pb/Cd study was to develop and test methods for monitoring of exposure to lead and cadmium. The design of the pilot study was decided at a meeting in Stockholm in October, 1986 (Vahter and Slorach, 1986), with representatives of the participating institutions. It included a first phase of analytical training and a second phase of exposure monitoring studies. Monitoring studies on exposure to lead and cadmium were carried out in Beijing, Stockholm, Yokohama, and Zagreb. Short descriptions of the HEAL sites are given in Annex A. Basically, the monitoring involved measurements of the exposure to lead and cadmium via air and diet during one week in a small group of women at each HEAL site.

In order to assure the reliability and comparability of the monitoring data, an extensive quality assurance programme was implemented. It included the sampling and sample handling (preanalytical quality control), as well as the analytical procedures (analytical quality control).

1.2. Health effects and environmental exposure to lead and cadmium

1.2.1. Health effects of lead and cadmium

Inorganic lead may affect heme synthesis, erythrocyte survival, the nervous system, the kidneys, and reproduction (for review see e.g. Skerfving, 1988). Lead exposure has also been associated with cardiovascular effects and cancer. An early effect of lead exposure, the disturbances in heme synthesis, is seen at blood lead levels of about 100 ug/l, but has not been shown to be detrimental to health (see e.g. Mushak and Crocetti, 1988; Skerfving, 1988). The critical organ is the nervous system, especially the fetal and the developing brain. Recent studies suggest that neurobehavioural defects in the first years of life may result from fetal exposure at maternal or cord blood lead levels as low as 100 ug/l (Bellinger et al, 1987; Davis & Svendsgaard, 1987; Dietrich et al, 1987).

The critical effect of long-term low level exposure to cadmium is kidney cortex damage, giving rise to urinary excretion of low molecular weight proteins (for review see e.g. Friberg et al, 1986a). It has been calculated that an average daily intake of about 200 ug Cd will result in an average renal cortex concentration of about 100 mg Cd/kg (Friberg et al, 1986b). In such a population about 10% of the individuals would have exceeded their critical concentrations and can be expected to develop renal tubular damage.

1.2.2. Total exposure to lead and cadmium

Both lead and cadmium may be found in ambient air, dust, food, drinking water, tobacco smoke and in the working environment. Therefore, biological monitoring is the best means of estimating total human exposure and the risk for adverse health effects (Lauwerys, 1983; Nordberg et al., 1985; Friberg, 1985; Clarkson et al., 1988). Available information on the metabolism of lead and cadmium indicates that it is possible to relate the concentrations in blood to the exposure (Skerfving, 1988; Nordberg and Nordberg, 1988). In order to identify the main sources and routes of exposure, integrated exposure monitoring is needed.

1.2.3. Exposure to airborne lead and cadmium

The concentration of lead in air may vary from less than 0.1 ng Pb/m^3 in remote areas to over 10 ug Pb/m^3 near point sources (Fachetti and Geiss, 1982; Elias, 1985; UNEP/ WHO, 1988). In areas with heavy motor traffic (urban areas) air lead levels from 0.13 ug Pb/m^3 to 5.3 ug Pb/m^3 have been reported. In Tokyo and European cities the average concentration of cadmium in air normally varies between 0.002 and 0.05 ug Cd/m^3 (Friberg et al, 1986a).

Airborne lead is often associated with small particles (Chamberlain et al, 1978; Chamberlain, 1985). For example, in London 60% of the airborne lead was found in particles less than 0.3 um and only 1% above 10 um (Chamberlain et al, 1978). In Zagreb the mass median diameter of particles containing lead was found to be 0.3 um, while in a lead smelter area it was 2.1 um (Fugas, 1977). This shows that the size distribution depends on the origin of the lead particles. It has been shown that large lead-containing particles from motor vehicles exhaust settle in the immediate vicinity of the road, while small particles are transported much further (Voorinen, 1983). Studies on the size distribution pattern of cadmium particles in rural, suburban and urban areas have shown that 40-65% of the particles are smaller than 2 um (Lee et al, 1968; 1972; Dorn et al, 1976).

Air is inhaled both via the mouth and the nose, even during low physical activity (Camner and Bakke, 1980). For particles larger than about 1 um the deposition is more efficient in the nose than in the mouth and throat. For particles between 0.01 and 5 um, inhaled via the mouth, the fraction deposited in the alveolar tract may range from 10 to 60% (Task Group on Lung Dynamics, 1966; EPA, 1986). For particles inhaled via the nose the fraction deposited in the alveolar tract may range from 10 to 20%. Most of the metals deposited in the alveolar part of the lung are probably absorbed sooner or later (Lundborg et al, 1985; Nielsen et al, 1988). Thus, it can be estimated that 10-60% of the inhaled lead and cadmium associated with small particles is absorbed. The majority of particles larger than about 10 um are deposited in the tracheobronchial, head and neck regions, cleared and swallowed and thus contribute in a minor way to ingested components.

1.2.4. Exposure to lead and cadmium via the diet

The amounts of lead and cadmium ingested will depend mainly on the levels of these

metals in staple foods, such as cereal products, fruit and vegetables, dairy products, meat and fish. However, the intakes can be markedly elevated by the consumption of relatively small amounts of certain foodstuffs which contain high levels of these metals. For example, the lead levels in foods packed in lead-soldered cans are often five to ten times higher than those in the corresponding fresh or frozen foods (Jorhem and Slorach, 1979; Slorach and Jorhem, 1982) and wine usually contains higher lead levels (50-100 ug/l) than other beverages (Jorhem et al, 1988). In areas with soft and/or acid water the use of lead in plumbing systems may result in very high lead levels in drinking water (Moore, 1985; Sherlock and Quinn, 1986). Relatively high levels of cadmium have been found in some shellfish and in liver and kidney (Jorhem et al, 1984).

The absorption of ingested lead and cadmium in adults is normally relatively low - in the order of 10% for lead and 5% for cadmium (Rosen, 1985; Friberg et al, 1986a). However, the absorption is influenced by the presence of various nutritional factors, inter alia other metals (for review see Bruaux and Svartengren, 1985; Nordberg et al, 1985). Furthermore, the absorption of dietary lead in infants is much higher than in adults (Alexander et al, 1974).

2. MATERIALS AND METHODS

2.1. Selection of subjects

The main objective of the pilot study was to test exposure monitoring methodologies on small groups of women at each HEAL site. By selecting women employed at the participating institutions the identification and evaluation of problems involved in the extensive sampling was facilitated. It was recommended to select 10-15 women at each HEAL site, and that the women should be between 25 and 50 years of age and non-smokers, since smoking may be a significant source of exposure to cadmium (Vahter, 1982 ; Elinder, 1985). For various reasons it was not possible to follow the recommendations completely in all the participating countries. A description of the subjects studied at the various HEAL sites is given below.

Beijing: 12 non-smoking women, 33-48 years of age, working at Beijing Antiepidemiology and Sanitary Station (urban area). All of the women lived in urban areas, 10 of them near the work place (about 10 minutes walk).

Stockholm: 15 non-smoking women, 27-46 years of age, working at the Karolinska Institute (urban area). Two of the women lived in central Stockholm, one in an urban area outside central Stockholm, nine in suburban areas and three in rural areas.

Yokohama: 3 non-smoking women, 44-47 years of age, housewives of staff of the Yokohama Institute of Public Health, living in Yokohama City (urban area). Blood samples were collected from 9 additional non-smoking women, 24-54 years of age, working for the Yokohama City Institute of Public Health, living in Yokohama City (urban area).

Zagreb: 17 non-smoking women, 23-53 years of age, working at the Institute for Medical Research and Occupational Health, Zagreb. Seven of the women lived in urban, old residential areas, four in urban, new residential areas and six in suburban areas.

2.2. Questionnaires

Each participant completed a questionnaire concerning personal data and different life-style factors. Daily activity and food records (Vahter and Slorach, 1986) were kept during the entire sampling period.

2.3. Sample collection

The sample collection scheme is summarized in table 1. Detailed guidelines for the sampling procedures (Annex B) were prepared by the TCC and distributed to the participating institutions.

Table 1. *Sampling scheme for exposure monitoring of lead and cadmium.*

	Days of sampling								
Sampling	1[a]	2	3	4	5	6	7	8	9
Blood								x	
Air	.....	.....	.....	.....	.....	.....	.....	>	
Diet[b]	.....	.....	.....	.....	.....	.....	.....	>	
Faeces[c]			.....	.....	.....	.....	.....	>.....	.....

a) Half of the study group should start their sampling period on a Monday, and the others on a Thursday
b) Duplicates of food and beverages, including drinking water
c) Faeces corresponding to the food and beverages ingested

Blood samples (10-20 ml) were collected in the morning after the last day of the test period (day 8), using evacuated blood collecting tubes (Venoject VT-100H, Terumo Corp., Tokyo, containing heparin), provided by the TCC. In Stockholm blood was collected also on day 1. In Zagreb blood was sampled using Safety-Monovette blood collecting tubes (Sarstedt, Numbrecht, with colourless caps), containing 1.5 mg K_2EDTA/ml. The blood samples were stored deep-frozen prior to analysis.

Total suspended particles (TSP) in the breathing zone of each subject were sampled during a period of 7 consecutive days, using low-volume personal air samplers (Beijing: Dupont model P2500A, Stockholm: T 13350 Casella personal sampling pump AFC 123, Zagreb: Casella, Model T 13050) with a flow rate of approximately 2 litres/minute. The sampling period was 24 hours per filter. The filter holders, equipped with 37 mm membrane filters of 0.45 um pore size (Millipore HAWP 03700, provided by the TCC), were kept as close to the breathing zone as possible. Most of the time at home and in the office the pumps were connected to the mains to recharge the batteries. In Zagreb membrane filters of 0.8 um pore size were used in order to obtain a high enough flow rate. Determination of lead in samples collected simultaneously with 0.45 um and 0.8 um pore

size filters showed no significant difference in collection efficiency over 24 hours. In Yokohama air was sampled (24-h samples) using stationary low volume samplers (Tokyo Dylec Co. low noise type; air flow 20 litres/minute), equipped with 55 mm quartz fibre filters (Pallflex 2500 QAST). The samples were collected at a height of 1.5 m above the floor in the living room during the whole test period of 7 consecutive days.

The dietary intake of lead and cadmium was determined using the duplicate diet technique. Duplicate portions of all foods and beverages, including drinking water, consumed during each 24-h period of the seven day study were collected in acid-washed plastic containers. The only items not collected were special medicines. Each 24-h duplicate diet was thoroughly homogenized and stored deep frozen prior to analysis. Separate collection of drinking water and beverages prepared from tap water was not performed. However, earlier studies have shown that the concentrations of lead and cadmium in drinking water at the HEAL sites studied were low.

Due to the low gastrointestinal absorption of lead and cadmium most of the ingested lead and cadmium will be recovered in the faeces. The lead and cadmium contents of faeces were determined to validate the duplicate diet procedure. Faeces corresponding to the food intake during the 4 first days (in Stockholm 7 days) of the food sampling were collected. In Stockholm and Zagreb a coloured marker (Carmine red) was ingested to indicate the start and the end of the faeces collection period. In Beijing and Yokohama, the faeces collection started 48 hours after the start of the food collection. The faeces was collected in specially designed plastic bags, which were provided by the TCC.

2.4. Analytical procedures

The laboratories could use any analytical procedure, as long as the results obtained were acceptable according to the quality assurance programme. The methods used for the determination of lead and cadmium in the collected samples and the quality control samples are summarized in this section. The procedures used in the different countries are described in detail in Annex C.

In most laboratories lead and cadmium in blood were determined using graphite furnace atomic absorption spectrophotometry (GFAAS) with background correction (BC) after nitric acid deproteinization or wet digestion. One laboratory used the Delves' cup flame AAS technique with BC and one laboratory used an ammonium pyrrolidine dithiocarbamate/methylisobutylketone (APDC/MIBK) extraction method followed by flame AAS. The latter method was not sensitive enough for the determination of cadmium. Calibration solutions were prepared by the addition of known amounts of lead and cadmium to bovine or human blood.

For the determination of lead and cadmium in air filters and dust most of the laboratories used GFAAS and BC after acid digestion of the samples with nitric and perchloric acids. In one institute the slotted tube atom trap (STAT) flame AAS system and BC was used, in order to obtain a high enough sensitivity.

The diet samples were homogenized and treated by wet digestion (nitric and perchloric acids) or dry ashing at 450°C. For the dry ashing, crucibles of platinum or

quartz were used and the ash was dissolved in nitric acid. All laboratories used GFAAS with the BC system in operation. However, for cadmium, one of the laboratories used flame AAS with BC.

The faeces samples were treated in about the same way as the diet samples, but glazed porcelain crucibles were used for the dry ashing. Three of the participating laboratories used flame AAS with BC for the metal determinations and two used GFAAS with BC.

2.5. Quality assurance

In order to ensure the reliability and comparability of the monitoring data, an extensive quality assurance programme was implemented. It covered the sampling and sample handling (preanalytical quality control), as well as the analytical procedures (analytical quality control). Quality control (QC) samples for each matrix involved were analysed both during the training phase (see section 3.1.) and together with the monitoring samples (see section 3.2.1.).

2.5.1. Preanalytical quality control

A crucial point in the monitoring project was to ensure correct sampling, i.e. that the collected air particles, food and faeces really represented the whole sampling period, and to avoid contamination of the samples. The TCC prepared detailed guidelines for the sampling procedures (Annex B), which were distributed to the participating institutions. The sampling procedures and the risk for contamination were also discussed with the participating women prior to commencing the sampling. As mentioned in section 2.3., lead and cadmium in faeces were used for validation of the duplicate diet collection.

In order to avoid contamination, all containers and other equipment used for sampling and storage were checked for lead and cadmium content before sampling. Some of the sampling equipment, i.e. membrane filters, evacuated blood collection tubes and plastic bags for faeces sampling, was distributed by the TCC after control of the metal content in a suitable number of samples of each type of equipment.

2.5.2. Analytical performance evaluation

In order to guard against systematic analytical errors in the range of concentrations likely to occur, the regression lines of reported versus "true" values for a set of external QC samples were evaluated (Vahter, 1982; UNEP/WHO, 1986b; Friberg, 1988). A QC set consisted of 1-2 internal quality control (IQC) samples, the metal concentrations of which were known to the laboratories, and 3-6 external quality control (EQC) samples, the metal concentrations of which were not known to the laboratories. The Maximum Allowable Deviation (MAD) of the empiric regression line from the ideal line $y = x$ was decided on separately for each pollutant and for each medium. In general the MAD was set to $\pm(5\text{-}10\%+2\sigma)$, where σ is an estimated error of the method, based on several QC runs (UNEP/WHO, 1986b; Friberg, 1988). The MAD criteria used for the different HEAL QC samples are given in Table 2.

Table 2. MAD intervals used for the evaluation of analytical performance in the pilot HEAL lead/cadmium study.

Type of sample	MAD-interval
Blood	
Cd (ug/l)	$y=x\pm(0.05x+0.2)$
Pb (ug/l)	$y=x\pm(0.05x+10)$
Spiked air filters	
Cd (ng/filter)	$y=x\pm(0.1x+10)$
Pb (ug/filter)	$y=x\pm(0.1x+1)$
Dust	
Cd (ug/g)	$y=x\pm(0.1x+0.2)$
Pb (ug/g)	$y=x\pm(0.1x+5)$
Diets	
Cd (ug/kg, dry weight)	$y=x\pm(0.1x+25)$
Pb (ug/kg, dry weight)	$y=x\pm(0.1x+25)$
Faeces	
Cd (ug/g, dry weight)	$y=x\pm(0.1x+0.5)$
Pb (ug/g, dry weight)	$y=x\pm(0.1x+1)$

Since the regression line, based on the results of a set of QC samples, has a sampling error (the operating error) the decision on acceptance or rejection of the regression line was based on statistical criteria. A total power of 90% was employed, which means that the probability of accepting an unsatisfactory performance (the true regression line falling outside the MAD-interval) was not more than 10 %. Thus, for acceptance the empirical regression lines had to fall not only inside the MAD-interval, but also inside an acceptance interval (AI), which is narrower than the MAD-interval. The distance between the MAD-lines and the acceptance lines is 1.645 times the operating error, $\sigma_{\hat{y}}$, calculated according to the formula:

$$\sigma_{\hat{y}}^2 = \sigma_{y/x}^2 \left(\frac{1}{n} + \frac{d^2}{(n-1) \cdot \sigma_x^2} \right)$$

where
n = number of observations
d = difference between x-value and x-mean
σ_x = standard deviation of x-values
$\sigma_{y/x}$ = error of method or residual deviation (estimated from previous analyses)

It is obvious from the formula that the AI-lines will get closer to the MAD-lines with increasing numbers of data points (QC samples). Also, a decreased error of method will decrease the difference between the MAD-lines and the AI-lines.

2.5.3. Quality control samples

QC samples for lead and cadmium in blood, air filters, dust, diets and faeces were developed at the TCC (Jorhem and Slorach, 1988; Lind et al, 1988). A summary of the procedures used for the preparation of the QC samples and the estimation of the reference values is given below.

Blood QC samples consisted of hemolyzed bovine blood, containing K_2Mg-EDTA (1.5 mg/ml) as anticoagulant, spiked with various concentrations of lead and cadmium nitrates. The samples were dispensed in 5 ml polyethylene tubes, sterilized by gamma irradiation and stored frozen.

The QC samples for lead and cadmium in air consisted of membrane filters spiked with lead and cadmium, as well as samples of homogenized dust for control of the efficiency of the digestion of the collected particles. Air filter QC samples consisted of 37 mm cellulose acetate/cellulose nitrate membrane filters, spiked with various amounts of lead and cadmium nitrate. Dust QC 1 consisted of U. S. National Bureau of Standards' Standard Reference Material 1648 (NBS SRM 1648), urban particulate matter, the other QC samples consisted of dust collected in homes and offices in the Stockholm area. Hair, fibres, stones etc. were removed, after which the dust was homogenized by grinding in liquid nitrogen and dispensed in 5 ml polyethylene tubes. To test homogeneity, subsamples of varying sizes, from different parts of the QC batch, were analysed for lead and cadmium.

Diet QC samples. Simulated human diets were produced from a number of different foodstuffs. Beef, milk, potatoes, wheat-rye flour, swine kidney, white wine and reindeer liver were mixed in different proportions to give diets with varying concentrations of lead and cadmium. Each diet was homogenized, freeze-dried and homogenized again. Finally, the diets were packed in plastic bottles (approximately 10 g freeze-dried diet in each bottle).

Faeces QC samples consisted of freeze-dried human faeces. Freeze-dried horse kidney cortex was added to a few samples in order to increase the cadmium concentration. The freeze-dried materials were homogenized by grinding in liquid nitrogen, dispensed in 5 ml polyethylene tubes and sterilized by gamma irradiation. The homogeneity of the samples was checked by analyses of lead and cadmium in subsamples of varying sizes taken from different parts of the QC batch.

The reference values for lead and cadmium in blood and air filters were based on the spiked amounts of lead and cadmium and the original concentrations in the samples, which for the membrane filters were insignificant compared to the spiked amounts. The concentrations of lead and cadmium in the unspiked blood were calculated from repeated reference analyses of unspiked and spiked blood. Due to the low concentrations of lead and cadmium in bovine blood (about 7 ug Pb/l and <0.1 ug Cd/l), a small error in the

estimation did not influence the final reference value to any significant extent. The dust, diet and faeces QC samples were not spiked and the reference values had to be established for each QC sample by analyses at a number of reference laboratories. Several subsamples from each QC sample were analysed at the TCC in order to check the preparation process and the homogeneity of the samples and to provide the laboratories with tentative reference values. Details on the reference analyses for lead and cadmium in blood, air filters, dust, diets and faeces are given in Annex D.

The concentrations of lead and cadmium in the QC samples were chosen so that they would correspond to the range of concentrations expected to be found in the collected samples (table 3).

Table 3. *Number of QC samples and the concentration ranges for the various QC samples in the HEAL study.*

Type of sample	Number of QC samples per QC set	Concentration range
Blood	6	0.3 - 5.2 ug Cd/l 28 - 366 ug Pb/l
Spiked air filters	6	4 - 113 ng Cd/filter 1 - 30 ug Pb/filter
Dust	4	2 - 8.5 ug Cd/g 41 - 704 ug Pb/g
Diets	3-4	28 - 909 ug Cd/kg, dry weight 35 - 457 ug Pb/kg, dry weight
Faeces	4	0.4 - 6 ug Cd/g, dry weight 0.4 - 13 ug Pb/g, dry weight

3. RESULTS

3.1. Analytical training

The first two years of the project were focused on analytical methods and training in the chemical analyses. The analyses of the collected monitoring samples were not started until satisfactory performance was achieved in the training phase. The training involved the analysis of several QC samples with assistance from technical consultants from the TCC. Some institutes were provided with instrument spare parts and some other items of laboratory equipment.

Analytical performance evaluation was carried out on several occasions during the training phase. The laboratories received sets of EQC samples (4 sets of blood QC samples and 3 sets of the other QC samples) and the results were evaluated at the TCC. The evaluation was reported back to the laboratories in the form of the regression line, based on the reported values versus the reference values, with the acceptance interval indicated. In addition, the reference values, the calculated slope and the intercept of the regression line and the empirical residual deviation were reported to the laboratories. The results of QC-analyses of the training phase are presented in detail in Annex E. A summary is given below.

Several of the participating institutes had long experience of the analysis of lead and cadmium in blood and produced in general satisfactory results. The analysis of cadmium in blood caused more problems than the analysis of lead. In QC 1 only three of eight laboratories produced satisfactory results for cadmium, while five of the eight laboratories produced satisfactory results for lead. Essentially all results of QC 3-4 (four participating laboratories) were satisfactory.

The participating institutions had less experience in the determination of low concentrations of lead and cadmium in air filters and there was an obvious need for analytical training. In QC 1 four of eight participating institutions produced satisfactory results for lead and four of six for cadmium. There was little improvement during QC 1-3.

In QC 1 for dust, which consisted of NBS SRM 1648 with high concentrations of lead and cadmium, seven of the nine participating laboratories produced satisfactory results (the certified value $\pm$10%) for lead and four for cadmium. In QC 2 and 3, which consisted of house dust with low concentrations of lead and cadmium (normal for the general environment), two of three participating laboratories produced satisfactory results.

The results of QC 1 for diets revealed the necessity of further training. Three of the five laboratories produced satisfactory results. In QC 3 the results from one of the four participating laboratories were not quite satisfactory. There was, however, even for that laboratory a great improvement in results after QC 1. The complex matrices of the samples and the relatively low concentrations of lead and cadmium in the samples are probably the reasons for the analytical difficulties.

In the analysis of faeces the matrix problems are about the same as those for diets, but the concentrations of lead and cadmium are normally higher. In QC 1 three of four participating laboratories produced satisfactory results for lead and cadmium. Analytical improvements during the training phase could be seen. In QC 3 essentially all results were satisfactory.

3.2. Monitoring of exposure to lead and cadmium

3.2.1. Quality control

The results of the QC analyses carried out together with the analyses of the monitoring samples are shown in figures 1-9. In general the QC results were in good agreement with the reference values, and it can be assumed that the systematic errors of the monitoring data do not exceed the limits indicated by the MAD criteria applied.

The institutes in Yugoslavia and Sweden analysed 12 blood QC samples together with the blood monitoring samples, while the institutes in China and Japan analysed 6 QC samples only. All the regression lines for lead in blood were within the acceptance interval, except the regression line in the Yokohama analyses, which was slightly outside (above) the acceptance interval in the low concentration range (figure 1). The average error of the method for the accepted lead QC results was 5.2 ug Pb/l. For cadmium in blood (figure 2), the regression line in the Beijing study was slightly outside (below) the acceptance interval in the low concentration range, while the other regression lines were within the acceptance interval. The average error of the method for the accepted QC cadmium results was 0.09 ug Cd/l.

The institute in Sweden analysed all the 12 QC air filters and the 8 dust QC samples together with the air monitoring samples. The institutes in China and Yugoslavia analysed 6 QC air filters only. All the reported QC results met the MAD criteria used (figures 3-5). The institute in Japan did not analyse any QC samples together with the air monitoring samples, so the accuracy of the air monitoring results cannot be properly evaluated. However, based on the good results obtained during the training phase it seems probable that the air monitoring results are accurate. In general, the errors of the method for the accepted QC results were improved compared to the training phase. The errors were 0.55 ug Pb/filter, 4.1 ng Cd/filter, 4.9 ug Pb/g dust and 0.25 ug Cd/g dust.

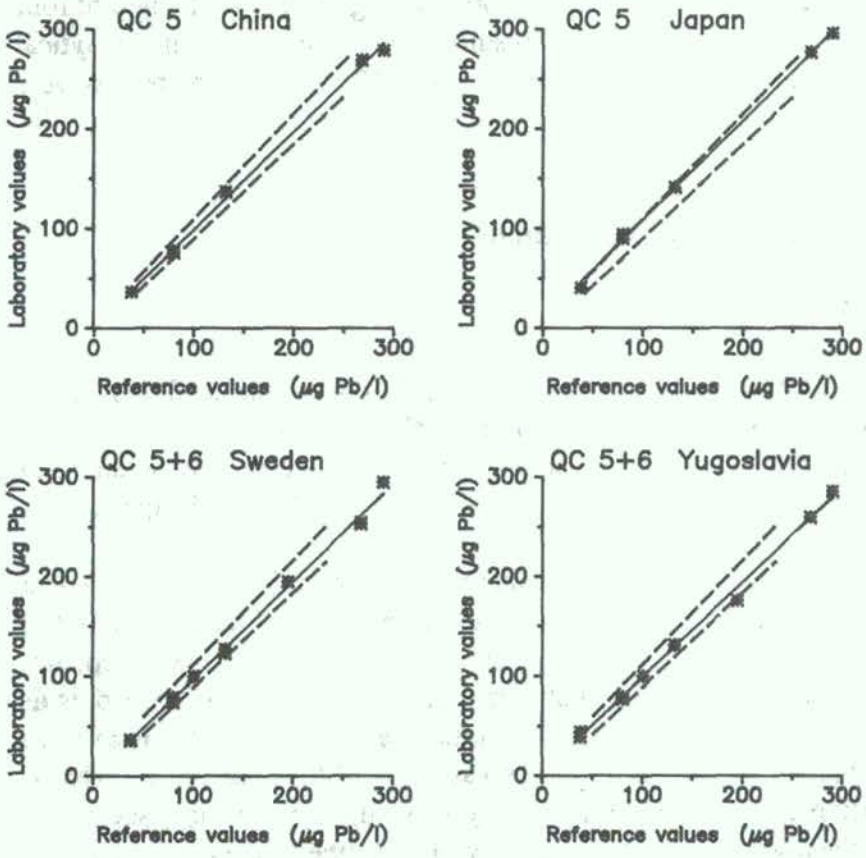


Figure 1. Lead in blood QC samples analysed at national institutes together with the monitoring samples. Acceptance interval indicated by broken lines.

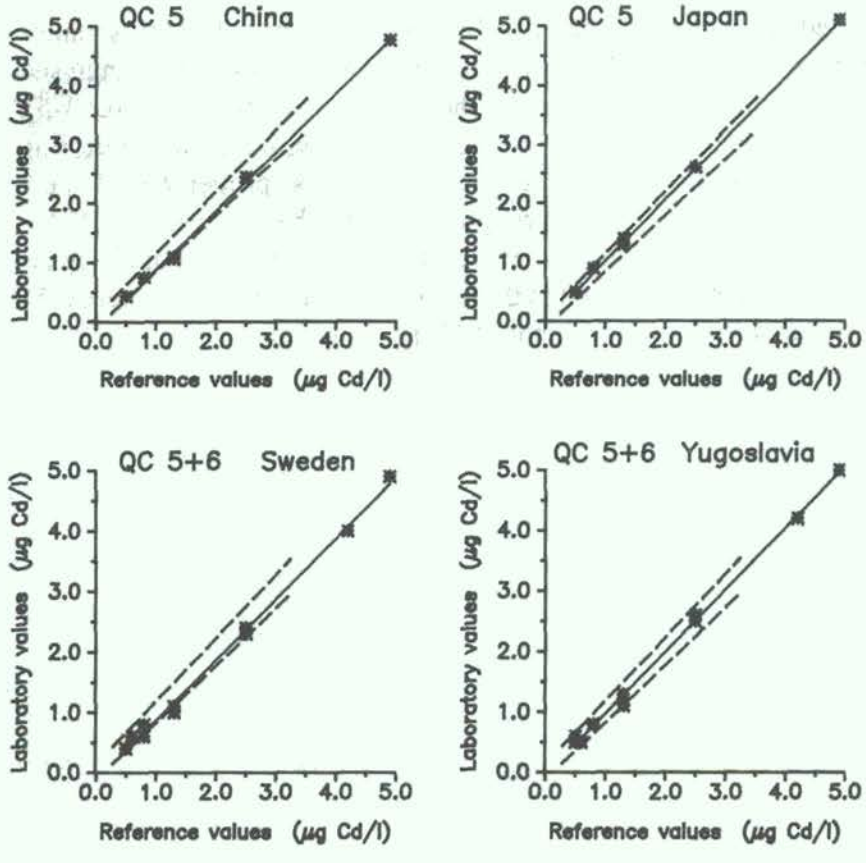
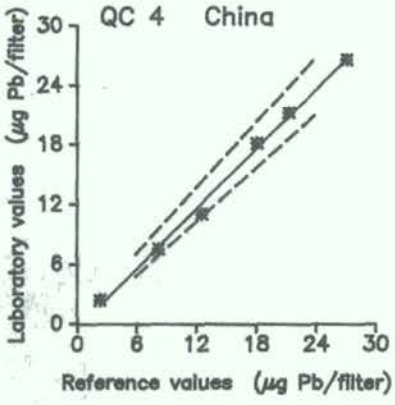
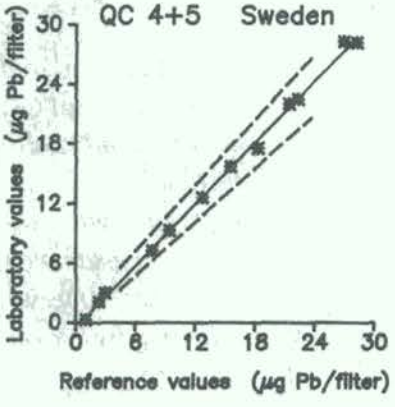


Figure 2. Cadmium in blood QC samples analysed at national institutes together with the monitoring samples. Acceptance interval indicated by broken lines.





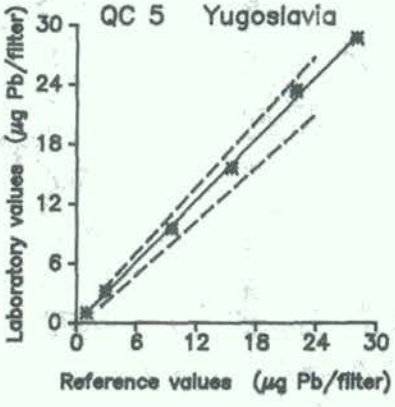
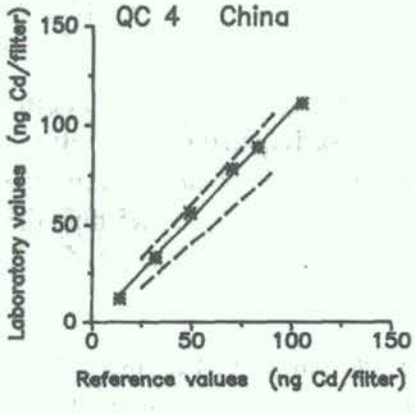
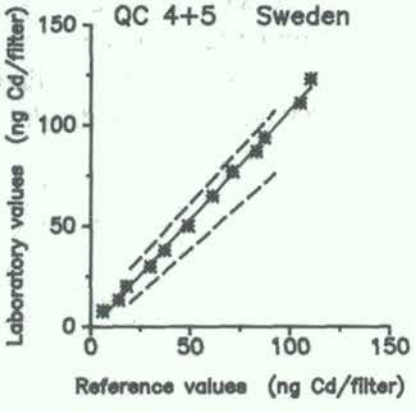


Figure 3. *Lead in air filter QC samples analysed at national institutes together with the monitoring samples. Acceptance interval indicated by broken lines.*





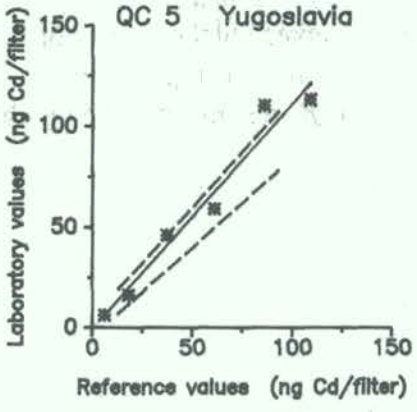


Figure 4. *Cadmium in air filter QC samples analysed at national institutes together with the monitoring samples. Acceptance interval indicated by broken lines .*

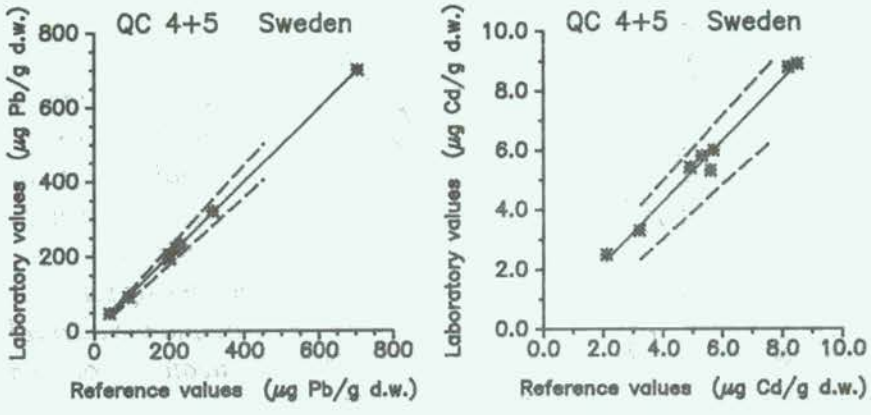


Figure 5. Lead and cadmium in dust QC samples analysed at national institutes together with the monitoring samples. Acceptance interval indicated by broken lines.

All the regression lines for lead and cadmium in the 7 diet QC samples, except the one for lead from the institute in Yugoslavia, were accepted according to the MAD criteria used (figures 6 and 7). The Yugoslavian regression line for lead was outside (below) the acceptance interval in the high concentration range, but the results were better than the results of the three QC rounds of the training phase. The error of the method was 17 ug Pb/kg and 13 ug Cd/kg for the accepted QC analyses.

The regression lines based on the analysis of faeces QC samples (8 samples) from the institutes in China, Sweden and Yugoslavia were accepted according to the MAD criteria used (figures 8 and 9). The institute in Japan analysed 4 faeces QC samples only. The results for lead were accepted but the regression line for cadmium was slightly outside (above) the acceptance interval in the high concentration range. The average errors of the method for all the accepted QC results were 0.5 ug Pb/g dry weight and 0.05 ug Cd/g dry weight.

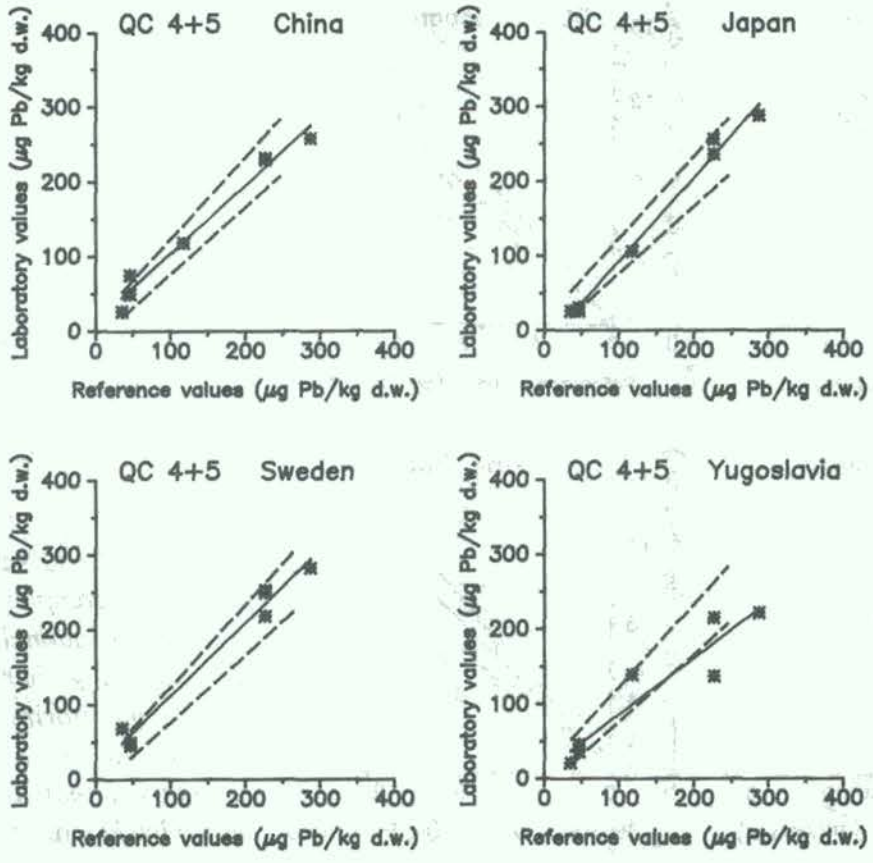


Figure 6. Lead in diet QC samples analysed at national institutes together with the monitoring samples. Acceptance interval indicated by broken lines.

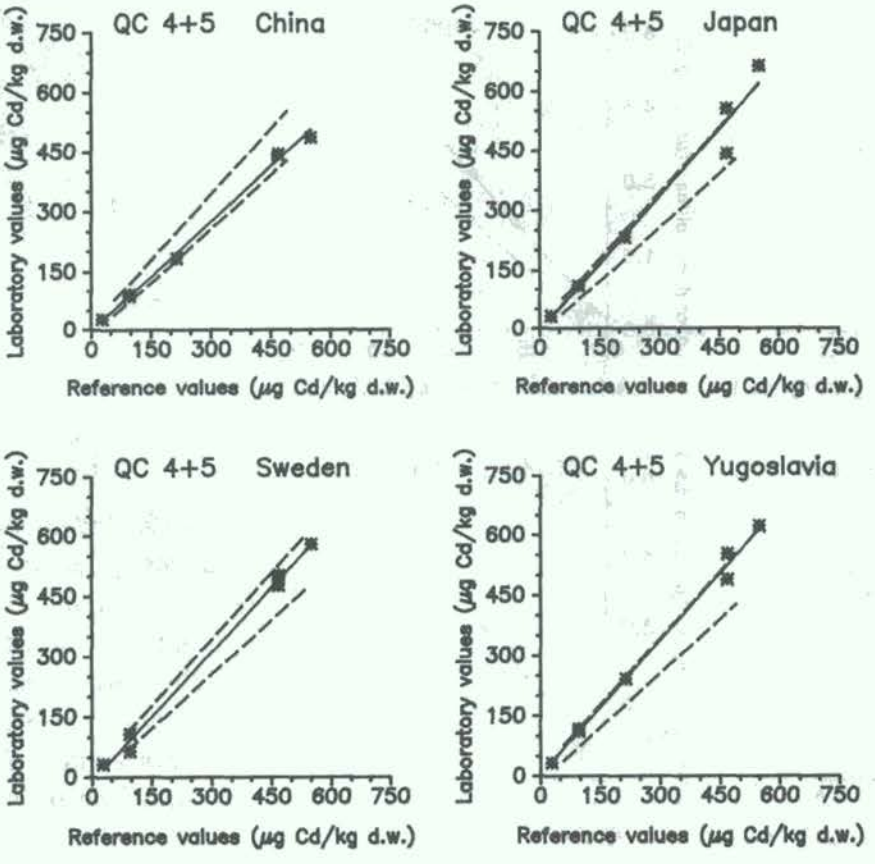


Figure 7. Cadmium in diet QC samples analysed at national institutes together with the monitoring samples. Acceptance interval indicated by broken lines.

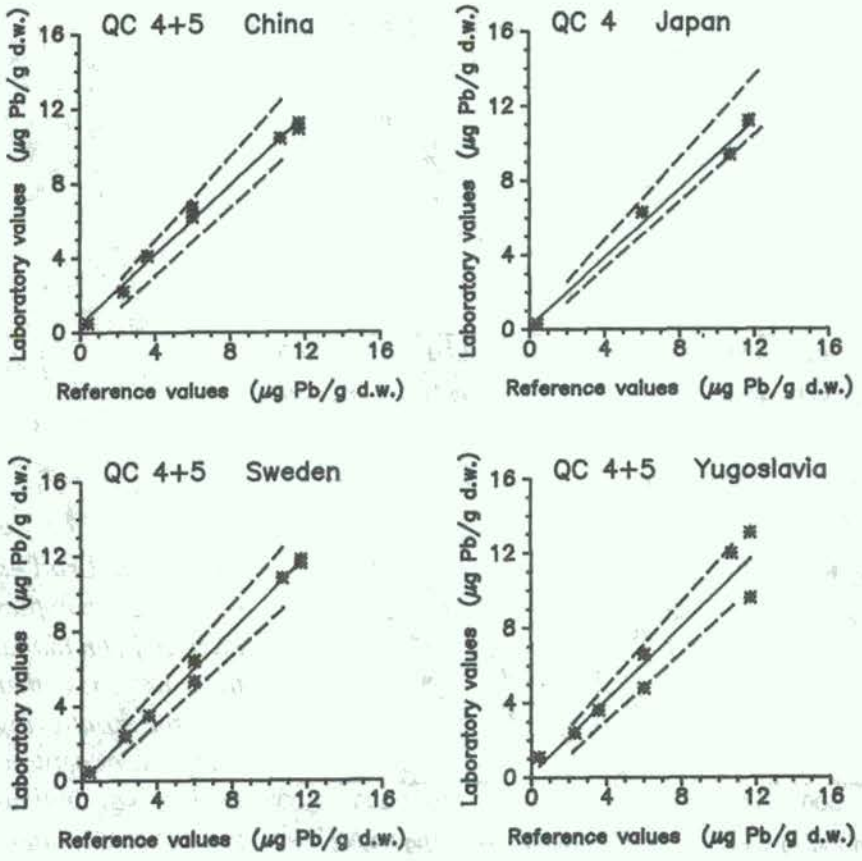


Figure 8. Lead in faeces QC samples analysed at national institutes together with the monitoring samples. Acceptance interval indicated by broken lines.

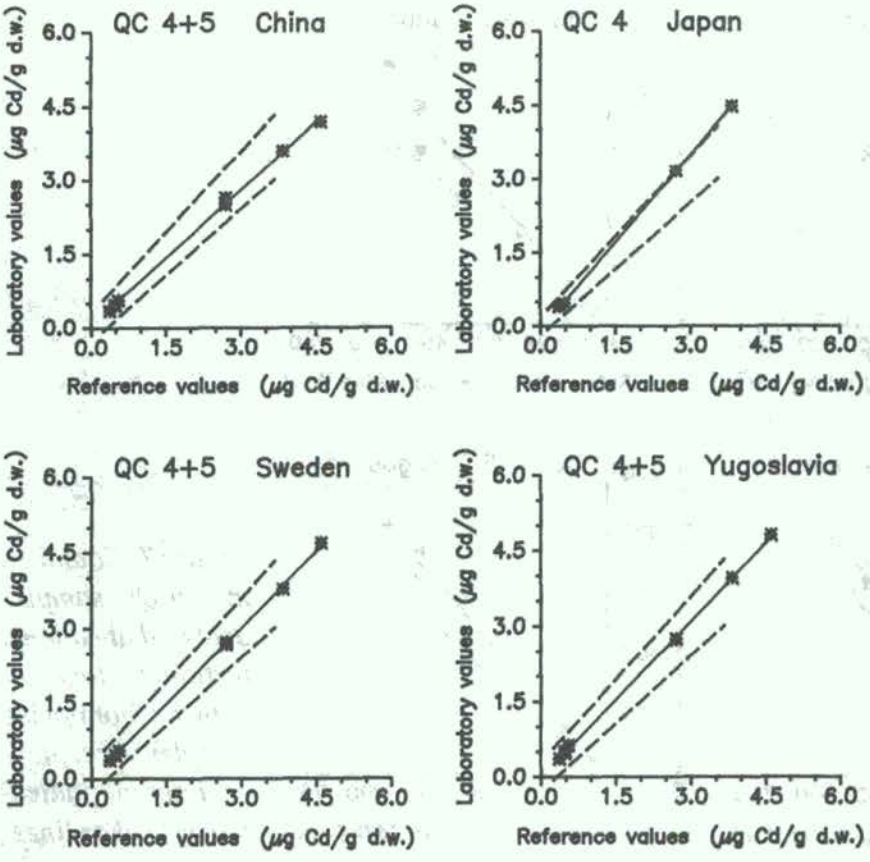


Figure 9. Cadmium in faeces QC samples analysed at national institutes together with the monitoring samples. Acceptance interval indicated by broken lines.

3.2.2. Lead and cadmium in blood

The concentrations of lead and cadmium in the blood samples of the women at the various HEAL sites are given in tables 4 and 5.

Table 4. Concentrations of lead in blood

HEAL site	Number of subjects	ug Pb/l Mean	S.D.	Median	Range
Beijing	12	73	20	69	48 - 124
Stockholm	15	29[a]	8.3	28	15 - 44
Yokohama	12	31	12	32	13 - 60
Zagreb	17	50	17	47	25 - 101

a) Mean of results from days 1 (30 ug/l) and 8 (29 ug/l)

Table 5. Concentrations of cadmium in blood

HEAL site	Number of subjects	ug Cd/l Mean	S.D.	Median	Range
Beijing	12	0.6	0.28	0.5	0.2 - 1.0
Stockholm	15	0.3[a]	0.16	0.3	0.1 - 0.8
Yokohama	12	1.6	0.63	1.5	0.8 - 2.9
Zagreb	17	0.7	0.25	0.8	0.2 - 1.1

a) Mean of results from days 1 (0.3 ug/l) and 8 (0.3 ug/l)

There was no significant difference in the blood lead and blood cadmium concentrations between days one and eight in the Swedish study.

3.2.3. Exposure to airborne lead and cadmium

The concentrations of lead and cadmium in the inhaled air were calculated by dividing the amounts of lead and cadmium on the filters used in the personal air monitors by the total volume (m^3) of air filtered during the 24 hour sampling period. There were large variations in the concentrations of lead and cadmium in breathing zone air both between HEAL sites and between subjects at one and the same HEAL site (tables 6 and 7). There were also large day-to-day variations in the air metal concentrations.

In Yokohama, the air monitoring was carried out using stationary samplers, placed in the living rooms of the 3 subjects. The particles were collected on quartz fibre filters instead of the membrane filters provided by the TCC. The average indoor air concentration of lead was 19 ng Pb/m^3 and the range was 19-20 ng Pb/m^3. The average indoor air concentration of cadmium was 1.9 ng Cd/m^3 and the range was 0.9-2.5 ng Cd/m^3.

Table 6. *Concentrations of lead in the breathing zone air (personal monitoring).*

		ng Pb/m^3				
HEAL site	Number of subjects	Mean[a]	S.D.	Median	Range weekly averages[b]	Range daily averages[c]
Beijing	12	116[d]	20	118	77-153	21-318
Stockholm	15	64	14	66	42- 94	15-169
Zagreb	17	412	195	400	140-840	0-2530

a) Mean of the weekly average air concentrations for all subjects
b) Range of the weekly average air concentrations among subjects
c) Range of all daily average air concentrations measured
d) Six of the subjects were monitored for 4 days only

Table 7. Concentrations of cadmium in the breathing zone air (personal monitoring).

HEAL site	Number of subjects	ng Cd/m³ Mean[a]	S.D.	Median	Range weekly averages[b]	Range weekly averages[c]
Beijing	12	1.2[d]	0.43	1.1	0.8-2.1	0.3-3.7
Stockholm	15	0.8	0.16	0.8	0.5-1.1	0.4-2.6
Zagreb	17	4.5	2.4	3.4	1.7-9.9	0-28

a) Mean of the weekly average air concentrations for all subjects
b) Range of the weekly average air concentrations among subjects
c) Range of all daily average air concentrations measured
d) Three subjects were monitored for 3 days and 3 subjects for 4 days

During periods of low physical activity, e.g. sitting in an armchair, 7-8 m³ of air is inhaled per day (Camner and Bakke, 1980). For persons with moderate physical activity, which was probably the case for most of the subjects involved in the HEAL studies, it is assumed that about 13 m³ of air was inhaled during a 24 hour period. Since the exact size of the lead and cadmium containing particles in the various HEAL studies is not known, it is assumed that 50% are alveolarly deposited and that all the alveolarly deposited lead and cadmium is absorbed.

The estimated average amounts of lead and cadmium absorbed in the body following inhalation of airborne lead and cadmium in the various HEAL study groups are given in tables 8 and 9.

Table 8. Estimated daily absorption of lead following inhalation of lead-containing particles.

HEAL site	Number of subjects	ng Pb absorbed/24 h Mean[a]	S.D.	Median	Range[b]
Beijing	12	760	490	765	500 - 990
Stockholm	15	419	93	428	272 - 613
Yokohama[c]	3	125	-	-	123 - 127
Zagreb	17	2680	1267	2400	900 - 5500

a) Mean of the average daily absorption for all subjects
b) Range of the average daily absorption for all subjects
c) Stationary samplers were used

Table 9. Estimated daily absorption of cadmium following inhalation of cadmium-containing particles.

HEAL site	Number of subjects	ng Cd absorbed/24 h Mean[a]	S.D.	Median	Range[b]
Beijing	12	7.9	2.8	7.2	5.0 - 14.0
Stockholm	15	5.2	1.1	5.2	3.3 - 7.2
Yokohama[c]	3	12.5	-	-	6.0 - 16.5
Zagreb	17	29.2	15.4	22.0	11.1 - 64.2

a) Mean of the average daily absorption for all subjects
b) Range of the average daily absorption for all subjects
c) Stationary samplers were used

3.2.4. Exposure to lead and cadmium via the diet

The average contents of lead and cadmium in the duplicate diets collected by the HEAL study groups are given in tables 10 and 11. Duplicate diet data were missing for two subjects in Beijing.

Table 10. Lead in the daily duplicate diets, including beverages, collected by the HEAL study groups.

HEAL site	Number of subj.	ug Pb in daily diets Mean[a]	S.D.	Median	Range[b]	Range[c]
Beijing	10	46	18	41	29-91	12-174
Stockholm	15	26	7.9	26	13-40	4.4-130
Yokohama	3	31	-	-	26-34	12-60
Zagreb	17	15	7.2	15	6.1-37	2.1-99

a) Mean of average Pb in daily diets (based on 7 daily diets) of all subjects
b) Range of average Pb in daily diets of all subjects
c) Range for all daily duplicate diets

Table 11. Cadmium in the daily duplicate diets, including beverages, collected by the HEAL study groups.

HEAL site	Number of subj.	ug Cd in daily diets Mean[a]	S.D.	Median	Range[b]	Range[c]
Beijing	10	7.1	1.4	7.1	5.4-8.9	3.0-12
Stockholm	15	8.5	2.1	8.1	5.7-14	1.8-56
Yokohama	3	20	2.9	-	17-22	8 -33
Zagreb	17	8.5	3.8	8.0	3.5-19	1.5-37

a) Mean of average Cd in daily diets (based on 7 daily diets) of all subjects
b) Range of average Cd in daily diets of all subjects
c) Range for all daily duplicate diets

Assuming that 10% of the ingested lead is absorbed in the gastrointestinal tract, it can be estimated that on average 4.6, 2.6, 3.1 and 1.5 ug of the daily ingested lead was absorbed by the women in Beijing, Stockholm, Yokohama and Zagreb, respectively. Assuming a 5% gastro-intestinal absorption of cadmium, it can be estimated that on average 0.35, 0.43, 1.0 and 0.42 ug of the daily ingested cadmium was absorbed by the women in Beijing, Stockholm, Yokohama and Zagreb, respectively.

It is obvious from tables 10 and 11 that there were large inter-individual and day-to-day variations in the intakes of lead and cadmium. Figure 10 shows examples of the day-to-day variations in the intakes of lead and cadmium during the study period in Sweden.

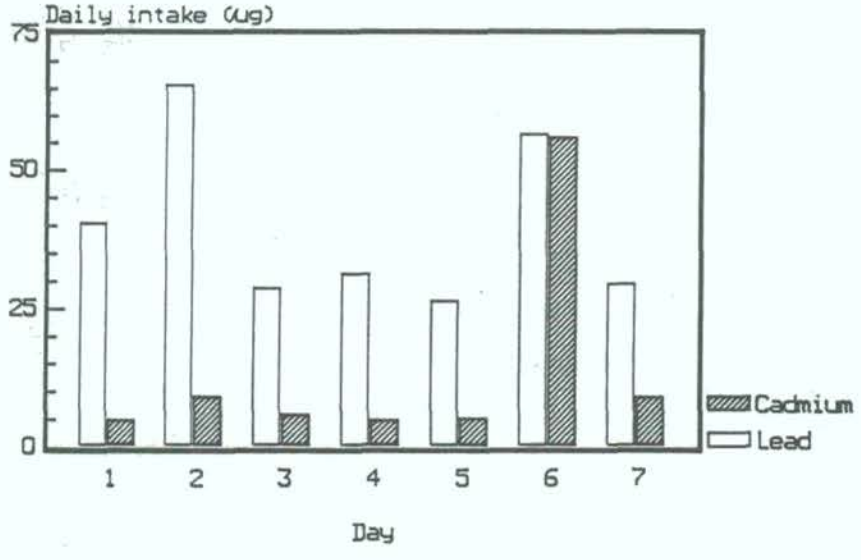


Figure 10. Example of day-to-day variations in the dietary intakes of lead and cadmium by a subject during one week in Sweden.

3.2.5. Elimination of lead and cadmium in faeces

The average daily elimination of lead and cadmium via faeces in the various HEAL study groups is given in tables 12 and 13.

Table 12. Average daily elimination of lead via faeces.

HEAL site	Number of subjects	ug Pb eliminated Mean[a]	S.D.	Median	Range
Beijing	10	42[b]	15	43	17-64
Stockholm	15	23[c]	9.4	21	10- 40
Yokohama	3	30[b]	5.9	-	23- 34
Zagreb	17	49[d]	23	50	8.5-112

a) Mean of the average daily elimination of all subjects
b) Four days per subject. Coloured marker not used
c) Seven days per subject
d) Four days per subject

Table 13. Average daily elimination of cadmium via faeces.

HEAL site	Number of subjects	ug Cd eliminated Mean[a]	S.D.	Median	Range
Beijing	10	7.0[b]	2.3	7.5	2.3-10
Stockholm	15	8.4[c]	2.0	8.7	5.5-12
Yokohama	3	33[b]	11	-	26-46
Zagreb	17	15[d]	6.7	15	5.0-25

a) Mean of the average daily elimination of all subjects
b) Four days per subject. Coloured marker not used
c) Mean of seven days per subject
d) Four days per subject

Some of the first faeces samples collected contained much more lead and/or cadmium than the corresponding first duplicate diets. In the Chinese and the Japanese studies coloured markers were not used. Therefore, the high Pb and/or Cd content in the first faeces samples may indicate that the faeces collected during days 3-6 did not correspond to the diets of the four first days of the sampling period. In the other study groups, the carmine marker may have been mixed in the stomach with food ingested prior to the start of the duplicate diet collection. The Swedish monitoring periods started at 3 p.m., at which time also the carmine marker was ingested. Thus, a high lead and/or cadmium content of the food and/or beverages ingested earlier that day could very well have influenced the first coloured faeces sample. Therefore, the first coloured faeces samples which greatly exceeded the corresponding first duplicate diet with respect to content of lead and cadmium were excluded.

A comparison of the average daily dietary content of lead and cadmium and the average daily faecal elimination is shown in tables 14 and 15. In the study groups in Beijing and Stockholm about 90% of the daily ingested lead and almost all of the ingested cadmium were recovered in the faeces. In Beijing and Yokohama coloured markers were not used in the faeces collection (4 days per subject), which may explain the relatively high standard deviations in the faecal elimination, expressed as a percentage of the daily intake, as well as the high faecal elimination of cadmium in the Japanese study. In the study group in Zagreb the average faecal elimination of lead was more than three times higher than the average lead content of the duplicate diets. The faecal elimination of cadmium was about twice the average cadmium content of the duplicate diets.

Table 14. *Comparison of the average daily dietary intake of lead (based on the duplicate diet analysis) and the average daily faecal elimination.*

HEAL site	Number of subjects	Daily intake, ug Pb	Daily faecal elimination, % of intake			
			ug Pb	Mean	S.D.	Range
Beijing	10	48[a]	42[a]	93	29	65-150
Stockholm	15	26[b]	23[b]	91	18	65-126
Yokohama	3	34[a]	30[a]	87	21	64-106
Zagreb	17	15[c]	49[c]	346	170	118-738

a) Mean of four days for each subject. Coloured marker not used in the faeces collection

b) Mean of seven days per subject

c) Mean of four days per subject

Table 15. Comparison of the average daily dietary intake of cadmium (based on the duplicate diet analysis) and the average daily faecal elimination.

HEAL site	Number of subjects	Daily intake, ug Cd	Daily faecal elimination, % of intake			
			ug Cd	Mean	S.D.	Range
Beijing	10	7.0[a]	7.0[a]	100	31	39-158
Stockholm	15	8.5[b]	8.4[b]	101	21	70-149
Yokohama	3	21[a]	33[a]	154	44	113-201
Zagreb	17	8.9[c]	15[c]	192	123	63-504

a) Mean of four days for each subject. Coloured marker not used in the faeces collection
b) Mean of seven days per subject
c) Mean of four days per subject

3.2.6. Contribution of inhaled and ingested lead and cadmium to the total exposure

The daily absorption of lead and cadmium estimated from the amounts in air, duplicate diets and faeces is shown in figures 11 and 12. The Japanese data are not included since they represented 3 women only.

The results indicate that the diet was the main source of exposure to cadmium at all the HEAL sites. The respiratory absorption of cadmium contributed one or a few percent of the total cadmium absorbed. The respiratory absorption of lead contributed about 14% of the estimated total lead uptake (absorption) in Beijing and Stockholm . In Zagreb the exposure to airborne lead contributed more than the diet to the total uptake. Furthermore, there seemed to be an important source of ingested lead besides the diet.

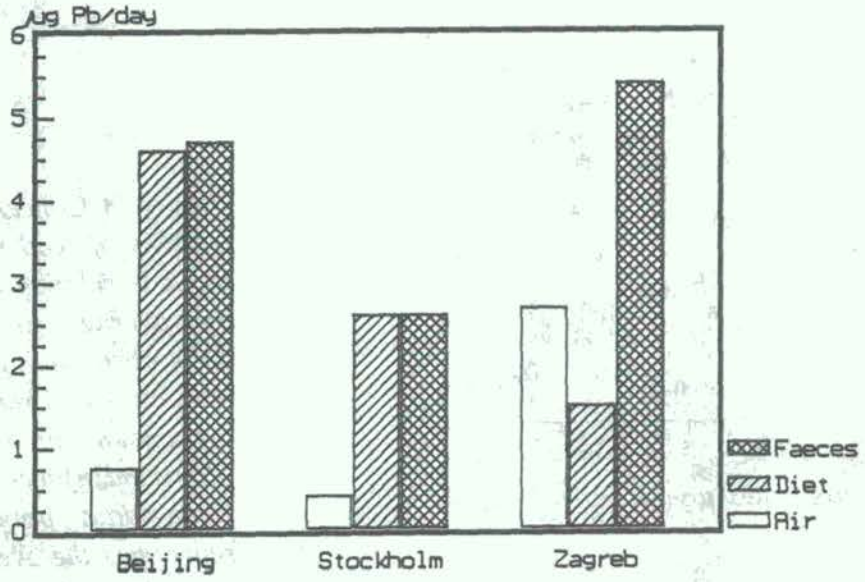


Figure 11. *Daily absorption of lead estimated from the amounts in air, duplicate diets and faeces.*

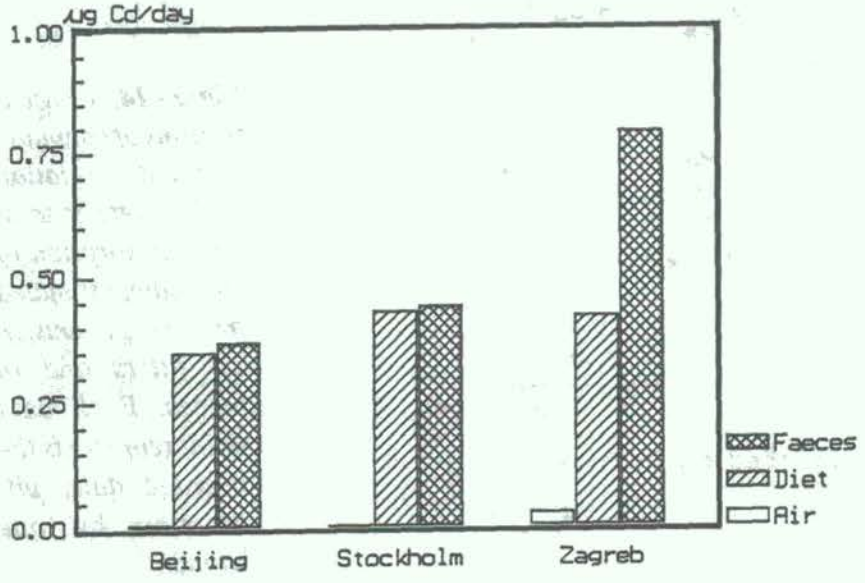


Figure 12. *Daily absorption of cadmium estimated from the amounts in air, duplicate diets and faeces.*

There was no significant correlation between the concentrations of lead and cadmium in blood and the estimated total daily absorbed amounts of lead and cadmium (figures 13 and 14). The absorbed amounts of lead and cadmium were estimated from the amounts of the metals in breathing zone air and in faeces.

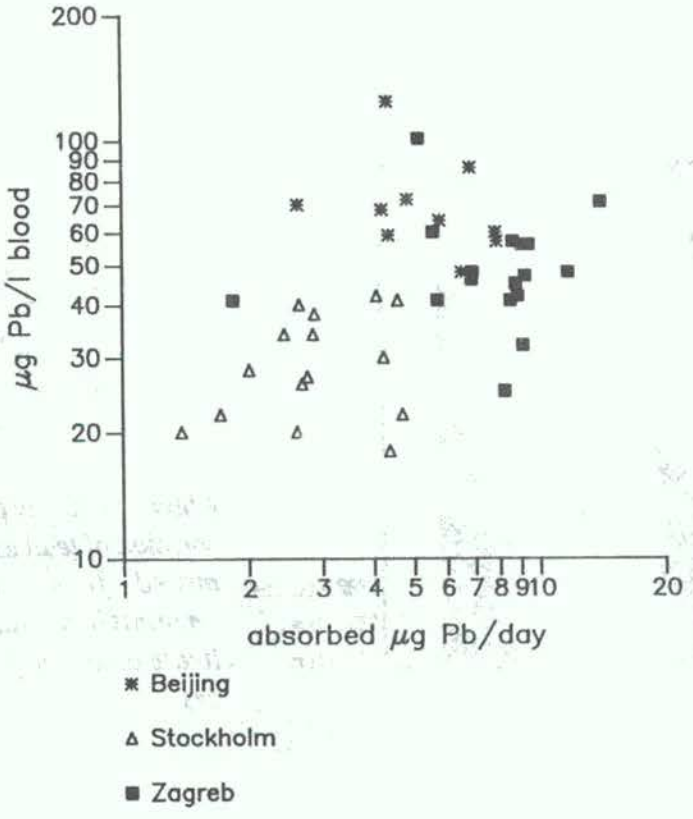


Figure 13. Concentrations of lead in blood in relation to the average total daily absorption of lead, estimated from the amounts on air filters and in faeces. Each data point represents the average daily absorption by one woman.

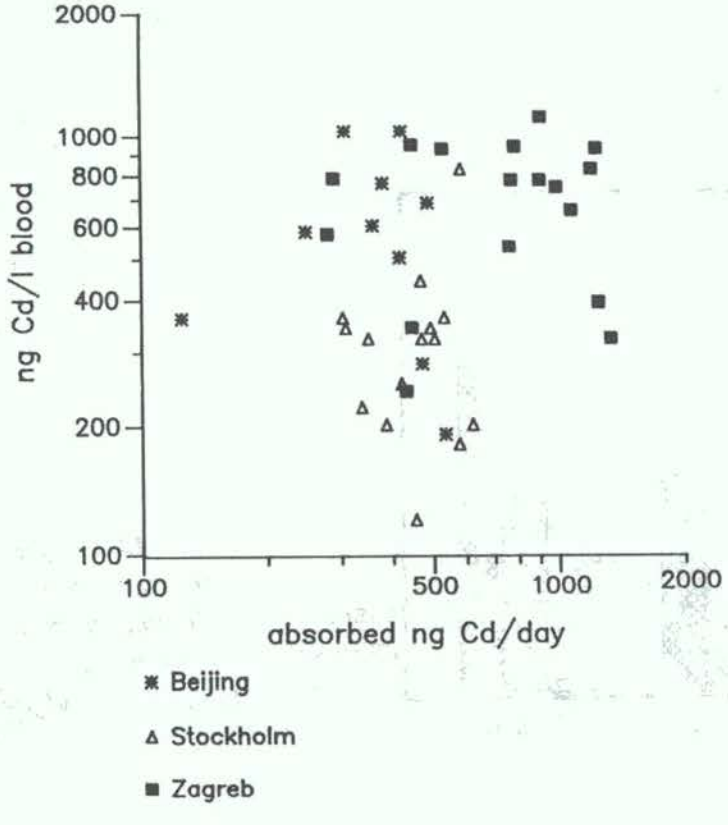


Figure 14. Concentrations of cadmium in blood in relation to the average total daily absorption of cadmium, estimated from the amounts on air filters and in faeces. Each data point represents the average daily absorption by one woman.

4. DISCUSSION

4.1. Methods for exposure monitoring of lead and cadmium

4.1.1. Study design and sample collection

The aim of the present study was to test and demonstrate methods for integrated exposure monitoring of lead and cadmium. The monitoring involved the collection of duplicate diets, airborne particles (personal sampler), blood and faeces during a study period of a week. At most HEAL sites the greatest problems were encountered in the collection of airborne particles. Most commercially available personal air monitoring equipment is designed for measurements of occupational exposure with sampling periods of about eight hours at the most. Therefore, the pump batteries had to be recharged every 6-8 hours. As a consequence, the pumps had to be connected to the mains most of the time when the subjects were at home or sitting in their offices. The noise of the operating pumps also gave rise to some complaints and some of the subjects could not keep the pump near the bed at night, in some cases not even in the bedroom. Attempts to insulate the pumps in order to decrease the noise were not completely successful.

Normally, dietary exposure to pollutants is estimated by analysing duplicate diets or "market baskets", or from the concentrations in individual foodstuffs and food consumption data. The latter requires information on concentrations of pollutants in essentially all foodstuffs. The great day-to-day variation in the dietary intake of lead and cadmium found in this study indicates that a few foodstuffs (probably not staple foods) can contribute a large part of the total intake of lead and cadmium. It has been reported that, in the USA, more than 500 foods must be analysed to cover 90% by weight of the total diet, and almost 1000 foods to cover 95% (Pennington, 1983). Furthermore, the dietary intake calculated from the concentrations in individual foodstuffs and food consumption data may not take into account the differences in concentrations of pollutants in different samples of one and the same foodstuff.

The duplicate diet method will most likely give a better estimate of the dietary intake, especially at the individual level. However, in duplicate diet studies there is a risk that the subjects may decrease their food intake and change their food consumption patterns. In countries like China where, especially at home, food is usually not served as a complete dish on individual plates, as in the western countries, the collection of duplicate diets may be more difficult.

In Beijing and Stockholm about 90% of the lead ingested daily and essentially all of the ingested cadmium were recovered in the faeces. Assuming a 10% gastrointestinal absorption of lead and 5% absorption of cadmium, the data indicate that the duplicate diets really reflected the diets consumed. The situation in Yokohama is difficult to evaluate since only three women participated in the monitoring and coloured markers were not used for the identification of the faeces that corresponded to the collected food. In Zagreb the average daily faecal elimination of lead and cadmium far exceeded the average metal content of the daily duplicate diets. The reason for this discrepancy has not been fully elucidated. A review of the collection of food and beverages did not indicate incomplete duplicate diet collection as a major reason. Also, the concentrations of lead and cadmium in the duplicate diets were confirmed by analyses of some duplicate diet samples at the

TCC. Based on the air measurements of lead and cadmium it can be estimated that only about 5-10% of the faecal lead and less than 1% of the faecal cadmium may have originated from particles which had been inhaled and then cleared from the respiratory tract. Therefore it seems likely that there was a significant peroral exposure to lead and cadmium from other sources than the diet, e.g. dust.

Since the possibility of peroral exposure other than the diet can never be ruled out, the use of faecal lead and cadmium measurement for validation of the duplicate diet collection is limited. The large day-to-day variation in the dietary intake of lead and cadmium and the large variation in the rate of elimination of the metals also make validation difficult. Even with the use of coloured markers the faeces collected did not always correspond exactly to the food ingested during the sampling period.

On a group basis, faecal lead and cadmium may be used as an indicator of the total intake of lead and cadmium. Faeces collection is considerably cheaper and, probably, less inconvenient for the subjects involved than the duplicate diet collection, unless there are cultural reasons speaking against faeces collection. Furthermore, faeces collection will not influence the food consumption pattern to the same extent as the duplicate diet collection. However, there are differences in defaecation habits between individuals and often between days in one and the same individual. For some subjects, defaecation became more irregular than normal during the monitoring period, especially during the first days. Therefore, the longer the faeces sampling period, the better the estimate of the daily amounts ingested.

An evaluation of the questionnaires and records used in this study has not been performed. Evaluation of the monitoring data in relation to the information collected in the food and daily activity records will be made at a national level.

After completion of the sample collection, the participating women were interviewed about the problems encountered, as well as the positive aspects of the sample collection procedure. The importance of motivating the subjects participating in the monitoring, i.e. giving detailed information about the aim and design of the project before the start of the sample collection, was confirmed. The participants also pointed out that the possibilities they had to discuss any problems involved in the sampling, as well as other experiences, e.g. comments from other passengers on the bus/train/subway, made the sample collection less inconvenient. Our impression is that the women participated in the project with great enthusiasm and interest. In Stockholm and Zagreb the local television service covered the monitoring projects, which obviously encouraged the participants to a great extent.

4.1.2. Analysis of lead and cadmium

The external QC programmes during the training phase showed the need for careful choice of analytical techniques as well as analytical training. Several of the participating institutions improved their analytical performance considerably during the 3-4 QC rounds of the training phase. Even institutions with previous experience in the type of analyses involved discovered problems that had to be solved before the analyses of the collected samples could start.

Most problems were encountered in the analysis of diets, due to their complex matrix and the low levels of lead and cadmium. Also the analysis of air filters was complicated due to the the small amounts of metals collected during the 24 h sampling periods with the use of low volume samplers.

4.1.3. Quality control

The method used for the analytical performance evaluation gives the upper limits for the systematic errors in the monitoring data. The maximum allowable deviation of the regression lines of reported versus reference values of the QC samples is often determined by the sensitivity and accuracy of the analytical method. For example, the experience from the QC activities in the HEAL pilot project shows that for lead in blood (ug Pb/l) experienced laboratories can meet the MAD criteria $y = x \pm (0.05x + 10)$, which guarantees that a reported mean blood lead value of, for example, 50 ug Pb/l with 90% probability lies between 37.5 and 62.5 ug Pb/l. For cadmium in blood (ug Cd/l) well experienced and equipped laboratories met the MAD criteria $y = x \pm (0.05x + 0.2)$, which guarantees that a reported mean blood cadmium value of, for example, 0.5 ug Cd/l, with 90% probability lies between 0.28 and 0.72 ug Cd/l.

The regression method may also give valuable information on the type of error. For example, a regression line parallel to the ideal line ($y = x$) indicates an absolute error caused by e.g. a false blank value or inadequate background correction. A slope deviating from 1.0 indicates a constant relative error due to e.g., incorrect standards or errors in the concentrations of the standards.

The experience from the analytical quality control programme within the UNEP/WHO HEAL project shows that good analytical performance for a pollutant in one medium, e.g. lead in blood, is no guarantee for good performance with other media. Thus, it is important that quality control samples have a matrix similar to that of the monitoring samples. Furthermore, the QC samples should cover the range of concentrations expected to be found in the monitoring samples. Good analytical performance at one concentration is no guarantee for good performance at higher or lower concentrations. Results on one or a few reference samples are not sufficient for the evaluation of the analytical performance. This was clearly demonstrated in the analysis of cadmium in air filters.

4.2. Routes and levels of exposure

Although the small number of subjects studied does not allow a complete evaluation of the exposure to lead and cadmium in the general population at each HEAL site, the results of the monitoring studies may give a fairly good estimate of the exposure situation. There is no reason to believe that the selected women differ to any significant extent from the general population with regard to their exposure to lead and cadmium. Furthermore, a comparison of the blood levels of lead and cadmium with those found in previous studies on groups more representative for the general population in the HEAL areas (tables 16 and 17) indicates that the total exposure among the selected women was similar to that of the general population. The average concentration of lead in blood of the women in Stockholm was considerably lower (about 50%) than that found in the UNEP/WHO

Biological Monitoring Project (Vahter, 1982). However, this probably reflects a true decrease in the general population's exposure to lead. Legislative measures taken in Sweden in 1981 lowered the maximum permitted level of lead in petrol from 0.4 to 0.15 g/l, and in 1987 unleaded petrol was introduced. At present about 30% of the petrol used is unleaded. Furthermore, food cans with lead-soldered side seams have to a great extent been replaced by cans with welded side seams or two-piece cans, i.e. cans without side seams (Jorhem and Slorach, 1987). Already in 1984, the blood lead concentrations in the subjects who participated in the UNEP/WHO Biological Monitoring Project had decreased by 30% (Elinder et al, 1984).

The results on lead in blood in Beijing indicate an increased exposure to lead between 1981 and 1988, which may be related to the increased consumption of petrol there.

Table 16. *A comparison of the concentrations of* ***lead*** *in blood (ug Pb/l) with those reported in non-smoking women in previous studies carried out at the various HEAL sites. Arithmetic mean values ±S.D. N= number of subjects.*

	HEAL 1988	National studies	UNEP/WHO 1981-82[1]
Beijing	73±20 (N=12)	64±19[2] (N=110)	59±19 (N=118)
Stockholm	29±15 (N=15)	42±31[3] (N=18)	64±25 (N=45)
Yokohama	31±12 (N=12)		55±18[4] (N=77)
Zagreb	50±17 (N=17)		81±33 (N=84)

1)Vahter, 1982
2) Zheng, unpublished data
3) Elinder et al, 1984
4) Tokyo

Table 17. A comparison of the concentrations of ***cadmium*** *in blood (ug Cd/l) with those reported in non-smoking women in previous studies carried out at the various HEAL sites. Arithmetic mean values ±S.D. N= number of subjects.*

	HEAL 1988	National studies	UNEP/WHO 1981-82[1]
Beijing	0.6±0.28 (N=12)	0.6±0.3[2] (N=110)	0.9±0.54 (N=118)
Stockholm	0.3±0.16 (N=15)		0.3±0.19 (N=45)
Yokohama	1.6±0.63 (N=12)		1.3±0.61[3] (N=77)
Zagreb	0.7±0.25 (N=17)		0.5±0.35 (N=84)

1) Vahter, 1982
2) Zheng et al, 1988
3) Tokyo

The total exposure to cadmium did not seem to have changed significantly during the last few years at most of the HEAL sites studied. The blood cadmium levels were about the same as those reported in the UNEP/WHO Biological Monitoring Project on lead and cadmium (Vahter, 1982). However, in Beijing there seems to have been a decrease in the exposure to cadmium during the last ten years. This may be due to the prohibition on the use of cadmium as a stabilizer and colour pigment.

It is obvious from the results that airborne cadmium contributes only one or a few percent of the total exposure of the general population at all the HEAL sites studied. For lead the contribution from air was somewhat higher, 5-15%, in Beijing, Stockholm and Yokohama, but still low compared to the amount absorbed from the diet. In Zagreb the concentrations of airborne lead were considerably higher than at the other HEAL sites, which is in agreement with the airborne lead levels found both in the present study and in previous environmental air monitoring projects (UNEP/WHO, 1988). The estimated pulmonary uptake of lead was almost twice the uptake of dietary lead, estimated from results of the duplicate diet analysis. However, it was only about half of the total amount of lead ingested, estimated from the analyses of faeces.

The average total dietary intake of lead at the different HEAL sites varied from approximately 4 to 11% of the Provisional Tolerable Weekly Intake (PTWI) proposed by an

FAO/WHO Expert Group (WHO, 1972). The corresponding cadmium values observed ranged from about 12 to 33% of the PTWI (WHO, 1989). The average individual lead intake varied from about 1 to 21% of the PTWI, and the average individual cadmium intake varied from about 6 to 37% of the PTWI. For all the HEAL sites except Zagreb the diet was found to be the major source of exposure to lead and cadmium.

For many of the women studied, there was a great day-to-day variation in the dietary intake of lead and cadmium. One daily diet could contribute more than 50% of the total weekly intake of lead and cadmium. Identification of the food items responsible for the high peaks in the dietary intake of lead and cadmium may help to decrease the exposure substantially.

There was no apparent correlation between the blood levels of lead and cadmium and the estimated average absorbed amounts of the metals. For cadmium, for example, there was a tenfold difference in blood cadmium levels between individuals with about the same estimated average daily uptake. There may be several reasons for this. The study period was only a week, with large day-to-day variations in exposure, while the blood concentration of lead and especially that of cadmium reflect the exposure over several months. Plasma cadmium is probably more related to recent exposure, but the concentrations are often below the detection limit. Furthermore, there may be great variations in gastrointestinal absorption depending on the type of metal compound ingested, the composition and amount of food ingested, nutritional status, especially low iron stores. The chemical form of the metal compound ingested may also influence the blood concentrations. It has been reported that oyster fishermen with high cadmium intake from protein-bound cadmium in the oysters have lower blood cadmium levels than expected (Sharma et al, 1983).

4.3 Conclusions

A pilot study, of the present design and carried out on a small number of selected subjects, may identify the main problems in the collection and analysis of different types of exposure monitoring samples, as well as the major routes of exposure to lead and cadmium. Such information is important for the design of a full-scale study on a representative sample of the general population. Furthermore, the experience gained shows that, although costly and complicated, it is possible to make comparable measurements on an international scale.

The experience from the analytical quality control programme of the project shows that it is important that QC samples have a matrix similar to that of the monitoring samples, that the QC samples should cover the range of concentrations expected to be found, and that one or a few reference samples are not sufficient for the evaluation of the analytical performance.

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ANNEX A. GENERAL INFORMATION ABOUT THE HEAL SITES

BEIJING

Beijing, capital of the People's Republic of China, is located on the north-western edge of the north China plain, between 115.25 and 117.30 east-longitude, 39.28-41.05 north-latitude, with a total area of 16,800 km^2. The total population is 9,796,000 and the population of the urban areas is 2,399,000.

The climate of Beijing is of the temperate-continental type. Spring (April and May) and autumn (September and October) are rather short, while winter (November to March) is rather long. The average annual temperature is 11-12°C, the lowest average monthly temperature is -4 to -5°C in January. The average annual precipitation is around 650 mm. The ground is covered with snow for about 14 days per year.

The occupational distribution in percent of the total number employed is: technical personnel 14.5, public services 20.4, trade 5.5, agriculture 20.5, industry and transport 39.0 and others 0.1. China has complete freedom of religion. There is no special restriction in food habits for the overwhelming majority of the population in Beijing, the inhabitants live primarily on commercially produced food. The main caloric intake is via cereal products.

There are about 193,200 cars in Beijing, corresponding to about 20 cars per 1000 inhabitants. Cycling is the main means of transportation for the inhabitants. Recently, transport with buses, trolleybuses, underground and railway trains, as well as trucks, has been further developed.

In China measures have been taken to limit the emissions of lead and cadmium to the environment. Lead added to petrol is restricted to below 1 g/kg. There is lead-free oil at each petrol station. The consumption of lead-free petrol in Beijing comprises about 80% of the total consumption. The use of cadmium and lead as stabilizers and colour pigments is prohibited. Although lead pipe and lead-soldered tins can be significant sources of lead exposure, it is not a problem in China. Lead-pipes are very rare, and most food cans are not lead soldered. Besides, the annual consumption of canned foods is not high. Wine is another source of lead, but the lead content of all the wine on the Beijing market is below the hygienic standard of food. The average annual consumption of alcoholic beverages in Beijing, calculated from the total sales, is 21.5 litres per person, of which 67% is beer and 6.5% is low alcohol drinks.

STOCKHOLM

The survey was carried out in Stockholm, the capital of Sweden. Stockholm is located at 59° north-latitude and 18° east-longitude on the coast of the Baltic Sea. The total population of Stockholm, including suburbs, is 1,462,000 with 670,000 in the central area. About 20% of the inhabitants in Stockholm are of foreign origin. The total population of Sweden is 8.4 million (1987).

The warm Gulf Stream in the Atlantic Ocean gives Sweden a milder climate than other areas equally far north. The summers are fairly warm, with an average temperature in Stockholm of 17.8°C in July. The average temperature in February is -3.1°C. Annual precipitation is around 550 mm. The ground is covered with snow for about 100 days per year.

The occupational distribution in percent of the total number of gainfully employed persons is: agriculture 3.7, industry 30.4, trade and transport 29.0 and public services 36.9.

About 95% of the population belongs to the Church of Sweden (Lutheran). There are no food restrictions for religious reasons. Mainly commercially produced foods are consumed. The highest calorie intake is via cereals, meat and milk products.

There are about 585,000 passenger cars in Stockholm corresponding to about 400 cars per 1000 inhabitants. In addition, there is a well developed public transportation system with buses, subways and railways, as well as cars and trucks for commercial transport.

In Sweden measures have been taken to limit the emissions of lead and cadmium to the environment. The lead content of petrol has decreased from about 0.8 g/l in 1963 to 0.15 g/l in 1981. Unleaded petrol has been available at most petrol stations since 1987. About 33% of the petrol distributed throughout the country is unleaded.

The use of cadmium in plastic stabilizers and colour pigments is prohibited. In addition, the use of cadmium-containing sewage sludge as a fertilizer in agriculture is regulated.

Lead pipes for drinking water distribution can be a significant source to lead exposure, as well as lead-soldered cans, but should not constitute a problem in Sweden since lead pipes are very rare and most tins on the Swedish market are not lead-soldered. Lead in wine is also considered to be an important contributor to the daily intake for heavy wine-consumers. The wine consumption per capita and year, estimated from the volume sold, in the general population of Sweden is about 12 litres and in the Stockholm area about 22 litres (1987). Sweden does not produce wine but imports it from other countries.

YOKOHAMA

The survey was carried out in Yokohama, Japan's second largest city after Tokyo. Yokohama is located at 35.5° north-latitude and 139.5° east-longitude on the coast of Tokyo Bay. The total population of Yokohama is about 3.1 million. Population per family was 2.89 persons, and population density per km^2, 7,282 persons. Yokohama assumed the aspect of a "dormitory community" for people commuting to neighbouring Tokyo for work. The area is about 430 km^2 and the one-fourth is farmland, mountains and forests. The remaining areas are residential, commercial and industrial.

The climate in Yokohama is temperate, although it varies with the seasons. It is warm in spring and autumn, hot and humid in summer and is mostly fine in winter, with hardly any snowfall. The annual mean temperature in 1987 was 15.8° C. The mean

temperature reached 26.8°C in August, the hottest month of the year. The lowest monthly mean was 5.6°C in January. The annual precipitation in 1987 amounted to 1,259 mm and the annual mean humidity 68 percent. The period from mid-June to mid-July is the rainy season. In August and September Yokohama is visited occasionally by rainstorms caused by typhoons. The annual mean wind velocity in 1987 was 3.7 metres per second. Usually, north winds prevail in winter and southwest or southwest-by-south winds in the other seasons.

According to the Origin-Destination Survey (1985), passenger cars are 10.70 million x km/day and trucks, 7.42 million x km/day. There are about 0.91 million cars in the city, corresponding to 3 cars per 10 inhabitants. In addition, there is a well developed public transportation system with buses, subways and railways for commercial transport.

Yokohama is situated in the largest littoral industrial belt of Japan and is a major industrial centre. Industry in Yokohama represents one of the principle industrial structures of the country, consisting as it does of a wide spectrum of industries such as oil refining, transport equipment, foodstuffs, appliances and general machinery.

To check the air pollution situation the city operates 16 full-time monitoring stations and eight automobile exhaust monitoring stations. The latter, also maintained on a full-time basis, are located along main roads. Fuel consumption levels and pollutant concentrations at 40 large industrial factories are measured automatically. Monitoring data are centrally recorded by telemeters at the Air Pollution Surveillance Center. Guidelines have been established to control emission levels of sulfur oxides and nitrogen oxides. At present, sulfur dioxide emissions are kept at the level of the municipal environmental standard - 0.04 ppm per day on the average. However, the volume of nitrogen dioxides, which forms oxidants and causes photochemical or white smog, remains at a considerably high level. In Japan the addition of lead to petrol has been banned since 1975 and the discharge of cadmium into the environment has been strictly prohibited by the Basic Law for Environmental Pollution Control. As for water pollution, toxic substances such as cyanide and cadmium are no longer detected in the industrial waste liquids, thanks to the regulatory and supervisory measures taken by the municipality and other authorities.

ZAGREB

The HEAL pilot phase study has been carried out in Zagreb, the capital of the Republic of Croatia. It is situated at 15°59' eastern longitude and 45°49' northern latitude, between the south-west slopes of the 1035 m high Mt Medvednica and the Vukomeric hills, on both banks of the Sava river, 122-160 m above sea level.

Zagreb has a moderate continental climate. Measured over a thirty-year period the average monthly temperature has been 21.3°C in July and 0.5°C in January. The average annual precipitation is 903 mm. There are on the average 146 rainy, 28 snowy and 59 clear days and 1800 hours of sunshine per year.

Greater Zagreb covers an area of 1709 km^2, of which 859 km^2 is agricultural land and 594 km^2 is covered by woods. It has a population of over 900,000, about 70% of whom live in the urbanized area (139 km^2). Population density varies from 45,000 inhabitants per km^2 in the inner city to a two digit number in suburban parts.

Out of 410,000 employed persons 35% are in industry and crafts, 11.5% in construction, 6.5% in transport, 15.5% in trade and tourism, 20.5% in education, science, health care and administration and 0.6% in agriculture.

About 70% of the employed do not live in the community in which they work and they have to commute to the workplace. Most people travel by tram, the rest by bus or private car. In 1986 there were about 216,000 motor vehicles, 90% of which are privately owned. Of the total 175,000 are personal cars, 1,154 buses, 23,000 trucks and special vehicles and 2400 motorcycles. There are 247 tramcars and 473 city buses transporting daily on the average 630,000 and 380,000 passengers respectively. In rush hours the traffic density in narrow streets in the city centre may reach more than 10,000 cars per hour. The lead content of petrol is 0.6 g/l. Lead-free petrol is available (but is used mostly by foreign tourists).

Zagreb inhabitants consume mostly (in descending order) milk and dairy products, vegetables, bread and cereals, fruit and meat. As far as alcoholic drinks are concerned, they prefer wine (average consumption 17.5 l/year by a household member).

The main sources of lead are food and beverages, followed by car exhausts and cigarette smoking. The latter is a major source of cadmium. High lead intake may exceptionally occur by drinking home made brandy distilled from soldered copper kettles or through the use of lead glazed pottery for storing food. Water coming from public water supplies contains on the average 1.3 ug Pb/l and that from individual wells from 4 to 11 ug Pb/l. The concentration of lead in Zagreb air varies on the average from 10 ug/m^3 at the busy crossings to 0.5 ug/m^3 in the general atmosphere.

The lead content of cigarettes varies depending on the quality class from 1.1 to 2.1 ug/cigarette and that of smoke condensate from 0.10 to 0.15 ug/cigarette. The cadmium content of the same brands of cigarettes varies much less: from 2.5 to 2.6 ug/cigarette and that of smoke condensate from 0.22 to 0.27 ug/cigarette (Ivičic´ et al, 1985). However, the exposure to cadmium through smoking can result on average in a 5-6 fold increase in the blood cadmium levels of the adult general population in Zagreb (Telišman et al, 1986).

References

Ivičic´, N., Tomic´, L. and Simeon, V. (1985) Cadmium and lead in cigarettes and in smoke condensate. Arh. hig. rada toksikol., 36: 157-164.

Telišman S, Azaric´ J and Prpic´-Majic´ D (1986) Cadmium in blood as an indicator of integrated exposure to cadmium in the urban population. Bull Environ Contam

ANNEX B. GUIDELINES FOR SAMPLING PROCEDURES FOR BLOOD, FAECES, AIRBORNE PARTICLES AND DUPLICATE DIETS

UNEP/WHO Global Environment Monitoring Programme

HUMAN EXPOSURE ASSESSMENT LOCATION

HEAL PROJECT

CADMIUM AND LEAD

EXPOSURE MONITORING

GUIDELINES FOR

SAMPLING PROCEDURES

AND

SAMPLE HANDLING AND STORAGE

Technical Coordinating Centre
for Metals
Stockholm - Sweden

January, 1988
HEAL TCC Sweden

BLOOD SAMPLING

The concentrations of cadmium and lead in blood are normally very low. Therefore it is extremely important that contamination of the samples be avoided. The following recommendations concern mainly measures to be taken in order to avoid such contamination.

Laboratories and personnel

Tobacco smoke often contains cadmium in amounts that may seriously contaminate the blood samples. Therefore, it is an absolute requirement that the sampling, treatment and analysis of blood samples are carried out in a room where smoking is prohibited. All personnel handling the blood samples should be non-smokers. If this is not possible, smoking personnel should wear a clean laboratory coat and cover their hair during sampling and handling of blood samples.

Protective gloves of Pb/Cd-free material should always be used when handling blood samples.

See separate recommendations "Handling of potentially contagious human biological material.

Procedures and equipment

According to the Pb/Cd protocol blood sampling should be carried out on the morning after the last day of the test period. If possible, blood should also be taken on the morning of the first day of the test period.

It is recommended to collect the blood samples not earlier than 2 hours after breakfast.

Before the blood sample is taken, the skin should be carefully washed and then cleaned with disposable napkins containing metal-free disinfectant (70% ethanol or isopropyl alcohol is recommended).

All equipment that will come in contact with the blood should be acid-washed before use (not evacuated blood collection tubes!)

Sampling of venous blood (10 ml) should be carried out using the Venoject system with evacuated blood collection tubes, containing about 140 IU of sodium heparin. A detailed sampling instruction for the Venoject system is enclosed. The Venoject tubes will be provided by the TCC after checking the metal content (a few tubes in each batch).

After the blood has been drawn, the Venoject tubes should be inverted several times in order to mix the blood with the anticoagulant.

Label each blood tube with the date of sampling and the name or code number of the person sampled.

Keep the Venoject blood tubes at +4°C. It is recommended to transfer (by pouring) the blood (turn the tube several times before transfer!) as soon as possible to 2-3 smaller, acid washed polyethylene tubes (provided by TCC). Label the tubes properly and store them deep-frozen until analysis. One of the tubes may be kept for later reanalysis and/or analysis of other compounds.

When the blood is to be taken out from the Venoject tube, open the rubber cap carefully to avoid splashing. Avoid inhaling the aerosol that sometimes may be formed.

HANDLING OF POTENTIALLY CONTAGIOUS HUMAN BIOLOGICAL MATERIAL

When handling biological samples of human origin it is important to prevent transfer of contagious material, e.g. viruses such as Hepatitis B and HIV.

Hands

- Always use protective gloves when handling samples of human blood, urine or tissues which have not been previously sterilized.

- Note that the gloves will become contagious. Change gloves as often as possible.

-Do not use gloves when taking notes, working at a type-writer or computer, making telephone calls, etc. Never take the gloves outside of the laboratory.

-Wash your hands and/or disinfect them after handling samples of human material.

-Do not wear rings, watches or bracelets when working.

Protective clothes

-Always wear a long-sleeved laboratory coat when working in the laboratory.

-These protective clothes should not be worn outside of the laboratory.

Laboratory techniques

-Safety goggles and inhalation mask should be used in case of risk for splashing or formation of aerosols. Safety shields may also be useful.

-Centrifuges should have a splash protector.

-Mixing, sonication, etc. should be carried out in a protection box.

Cleaning and disinfection

-Always keep laboratory benches clean.

-In case of contamination, clean with a suitable disinfectant, e.g. 5% chloramine. (mind your hands!)

-Wash benches and centrifuges daily with a suitable disinfectant, e.g. 5% chloramine, followed by water and a suitable cleaning fluid.

-Non-disposable equipment should be disinfected by heat or with a suitable disinfectant, e.g. chloramine.

Sampling

- Always use protective gloves.

-In cases of blood sampling using evacuated blood collection tubes, follow the instructions carefully. Always use the tube holder.

-Label record sheets, test tubes and containers "Contagious material" if the samples are suspected to be contagious.

Accidents

- Rinse immediately in plenty of water.

- Report the incident immediately to the work supervisor and safety officer.

- Write a report of the incident.

- Report the incident to the appropriate authority and arrange any sampling to be made. During unusual hours contact the on-duty doctor at the infections clinic.

These recommendations are based on the report "Protection against blood infection" released by the Swedish Occupational Health Board (ASF 1986:23) and have been recommended by the Department of Hygiene at the Karolinska Hospital, Stockholm.

FAECES SAMPLING

All faeces corresponding to the food consumed during the first 4 days of the food and air sampling period are to be collected (see section 3.3.5 in the Pb/Cd protocol).

Faeces should be collected directly into specially designed plastic bags (one bag for each collection), which should be placed in the toilet seat. Plastic bags will be provided by the TCC.

The subjects collecting the faeces should wash their hands before handling the plastic bags in order to avoid contamination.

Urination in the plastic bags should be avoided, e.g. by urinating before the plastic bag is placed in the toilet seat and/or by absorbing smaller volumes of urine onto a disposable napkin or sanitary towel during defecation. Paper, cigarettes etc. must not be thrown into the plastic bag.

After the defecation the bags should be carefully sealed and immediately put in a plastic container with a tightly fitting lid.

Label each sample with the date of sampling and name or code number of the subject. Store in a cool place until transportation to the institute where storage in a freezer is recommended. Upon arrival at the institute the total weight of each plastic bag with its content should be determined before storage.

Subjects suffering from severe diarrhoea should not be included in the study.

For sample treatment and analysis see Pb/Cd protocol section 5.4.

SAMPLING OF DUPLICATE DIET

General instructions are given in section 3.3.3 of the Pb/Cd protocol. Analytical procedures are given in section 5.2 of the Pb/Cd protocol. Note that the weight of the duplicate diet samples should be recorded before homogenization.

For food record questionnaires to be completed by the subjects see appendix 3a in Pb/Cd protocol.

For food record follow-up questionnaires to be completed by the project investigator together with each subject see appendix 3b in the Pb/Cd protocol.

Instructions for collection of duplicate diets

Everything you eat during the test period should be duplicated and collected. Use two (or more) appropriately labelled buckets for each 24-hour sampling period, starting at midnight.

When you sit down for a meal you put an extra plate and glass on the table. Each food item you serve yourself, you duplicate on the second plate. When you have eaten the serving you empty the second plate into the bucket. If you leave anything uneaten on your plate, remove the same amount from the second plate before emptying the plate into the bucket. Proceed likewise if you have a second helping.

Do not forget to fill in the food record during or immediately after the meal.

Drinking water should first be collected in a jug or other vessel. Two equal volumes of the water should then be consumed and collected, respectively.

Meals eaten at restaurants or similar places outside home are duplicated by ordering another portion for the bucket. Do not forget beverages!

Remember that snacks as well as candies should be duplicated and recorded. If you consume anything that you cannot put into the bucket, e.g. medicine, please inform the investigator.

At the end of each sampling period the buckets must be put into a refrigerator or other cool place or preferably in a freezer, if available.

BON APPETITE AND GOOD LUCK WITH THE SAMPLING.

AIR SAMPLING

General information about air sampling procedures is given in section 3.3.2 of the Pb/Cd protocol.

Total suspended particulates (TSP) in the inhaled air during the whole 7-day test period are to be collected. This means that the air collection pump must operate, with a constant flow, during the whole test period and that 24-hour sampling periods are recommended. Extra filters should always be at hand in case of clogging.

The concentrations of lead and especially cadmium in air are normally very low. Therefore, it is extremely important that contamination of the samples be avoided. The following recommendations concern mainly measures to be taken in order to avoid such contamination and to obtain a representative sample.

Laboratories and personnel

Tobacco smoke often contains cadmium in amounts that may seriously contaminate the air filters. Therefore, it is an absolute requirement that treatment and analysis of air samples are carried out in a room where smoking is prohibited. It is recommended that personnel handling the air samples be non-smokers. If this is not possible, personnel using tobacco should be extremely cautious while handling the samples. A clean laboratory coat and a hair cover should be worn during handling of air samples.

Procedures and equipment

All tools that will come in contact with the filters should be acid-washed before use.

According to the Pb/Cd protocol a low-volume personal air sampler with a flow rate of about 2 litres/minute should be used. Normally the batteries for this type of equipment last for about 8 hours only. In order to enable 24 hour sampling using one and the same equipment, it is recommended to use an AC-adapter that can recharge the battery during operation and within about 7-8 hours, e.g. when the participant is asleep. During the day the adapter should be used as much as possible e.g. while sitting in the office.

Particles are to be collected on 37 mm white plain filters (Millipore HAWP 03700, provided by the TCC) with a pore size of 0.45 um. All filters are from one and the same batch and found to contain very little cadmium and lead. The white HEAL filter (take away the blue protective paper!) is placed on the filter holder. Filter support (absorbent pad) necessary for some holders is provided by the TCC. After a 24-hour sampling period the filter should be placed in a plastic petri dish (provided by the TCC).

The filter holder should be located as close to the breathing zone as possible. Connect the filter holder to the pump with about 1 m of latex tubing. Since the battery voltage output and thereby the flow rate of the sampler is temperature dependent it is recommended to keep the pumps at as constant temperature as possible.

The participating institute should calibrate and check the equipment before delivery to participating subjects as follows.

Recharge the sampler battery fully (about 14 hours) and adjust the flow rate to 2 litres/minute using a rotameter, with the filter connected. Recharge again. Check the battery operation time without the adapter. Recharge again during 7-8 hours operation with the filter connected. Check the battery operation time again. Compare with the previous battery operation time in order to get an idea about how long adapter time is required for 24 hours operation.

It is important that the participating subjects are clearly informed about procedures for handling the air sampling equipment and the risk for contamination and sampling errors. The institutes should train each participating subject according to the equipment manual and the experience of the institute.

PERSONAL AIR MONITORING DEVICES

TCC has reviewed technical data for various personal air monitoring devices available in Sweden. The following criteria were considered:

Battery operation time
Flow rate and stability
Size, weight and noise level
Price, service
Built-in flow meter, low battery shutdown device which turns off the pump automatically at low voltage.

T 13350 Casella (UK) personal sampling pump AFC 123:

TCC considered this model the best choice due to low noise level, operation possible during 8-16 hours on battery, small size (118x74x44 mm) and low weight (460 g). Flow rate at 2 l/min is kept within ±5%. A low battery shutdown device is built-in. Hence it is easy to discover when the AC adapter needs to be connected to recharge the battery.

GSA 2000 (West Germany)

+ Sampling time display, low noise, ±5% flow rate control
- Separate battery unit needed for 8 hours operation gives total weight of 500 g

MSA model G (USA)

+ Built-in flow meter
- Negative in tests, weight 760 g

SKC Airchek VII (USA)

+ Built-in flow meter and low battery shutdown device
- High noise level

Du Pont P2500B (USA)

+ Low noise level, flow rate control±5%
- Expensive, weight 737 g

Gilian HFS-113 AC DK (USA)

+ Built-in timer and flow meter
- Weight 936 g

Reference of interest:

L.A. Wallace and W.R. Ott "Personal Monitors: A State of the Art Survey", Journal of the Air Pollution Control Association 1982, 32, 601-610.

ANNEX C. ANALYTICAL PROCEDURES

BRAZIL:

Lead and cadmium in blood. After haemolyzing 3 ml blood with Triton X-100 a direct APDC/MIBK extraction was performed. The organic phase was analysed by flame AAS utilizing a Varian AA-175 instrument (single beam and no background correction system) without a recorder. Only lead was measured since the detection limit for cadmium with this method is about 20 ug Cd/l blood.

Air filters and dust were wet digested during 2 hours at 120°C and the final 10% HNO_3 solutions were analysed by flame AAS utilizing a Varian AA-1475 instrument (double beam and no background correction system) without a recorder.

CHINA:

All utensils used were acid-washed with 30% HNO_3 and rinsed several times with deionized water and air dried before use. All standards used were prepared from stock standards containing 1000 mg/l, which were prepared from 99.999% pure $Pb(NO_3)_2$ and spectro pure cadmium metal.

Lead and cadmium in blood. Samples collected in screw cap tubes were thawed and mixed. 0.3 ml blood was added to a 1.5 ml Eppendorf centrifuge tube containing 0.4 ml pure water (distilled with a silica sub-boiling distillation equipment). Then, 0.1 ml 4.8 N HNO_3 was added and mixed at once to prevent large clot formation, vortexed for 15 seconds and centrifuged at 12000 rpm for 5 minutes. The supernatant was analyzed for lead and cadmium using GFAAS (Perkin-Elmer 3030) with a deuterium background correction and peak height evaluation. Calibration solutions were prepared by addition of known amounts of lead and cadmium to bovine blood. A 20 ul sample was used for lead and cadmium determination.

Lead and cadmium in air filters. Air filters were put into 10 ml graduated test tubes and 2 ml acid mixture (HNO_3:$HC10_4$ = 3:1) was added. The tubes were heated in an electrical heating block at 220 °C until white fumes appeared and the residue acid was minimum. The volume was made up to 5 ml with deionized water in the same test tubes. Lead and cadmium were determined with GFAAS (Perkin-Elmer 3030) with a deuterium background correction and peak height evaluation. Calibration solutions were prepared by the addition of known amounts of lead and cadmium to graduated test tubes and treated as the samples. Lead and cadmium in blank filters were determined as the samples, and the values of lead and cadmium in blank filters were deducted from the sample reading before the results were calculated.

Lead and cadmium in duplicate diets. Samples, which were homogenized in a food blender and stored at -20°C, were thawed and re-mixed with a plastic spoon. The samples were weighed into 100 ml beaker, mostly in triplicate. 10 ml high purity grade HNO_3 (Beijing Chemical Works) and 1 ml guaranteed reagent grade $HClO_4$ (Tianjin Chemical Works) were added. The beaker was covered with a watch glass and kept overnight. The beaker was heated on an electrical plate until white fumes appeared and the

solution became colourless. A few ml of pure water (as indicated above) was added and heated again to drive off the excess acid. Then, the content was transferred and washed into a 10 ml graduated test tube and pure water was added to 5 ml final volume for lead determination.

Lead and cadmium were determined by GFAAS in Varian SpectrAA 30/40 with a deuterium background correction system. The matrix was modified by adding an equal volume 2% $(NH_4)_2HPO_4$ solution. Blanks were taken through the whole procedure. The mean lead and cadmium levels of these blanks were then deducted from the sample readings before the results were calculated.

Lead and cadmium in faeces. The frozen samples were thawed and mixed by squeezing each bag by hand from the outside. A hole was then cut and duplicate 5 g subsamples were weighed into petri dishes for the determination of water content by drying at 105°C in an oven until constant weight was obtained. At the same time, another duplicate 5 g subsample was weighed into 50 ml beaker for the determination of lead and cadmium. To each beaker, 10 ml high purity grade HNO_3 and 1 ml guaranteed reagent grade $HClO_4$ were added. The beakers were covered with watch glasses and kept overnight. Then, digestion was performed on an electrical plate until white fumes appeared and the solution became colourless. A few ml pure water were added and the solution was heated again to drive off the excess acid. The residue was transferred together with washing solutions into a 10 ml graduated test tube and made up to 10 ml final volume. Lead and cadmium were determined by GFAAS in Varian SpectrAA 30/40 with deuterium background correction. Matrix was modified by $(NH_4)_2HPO_4$. Blanks were taken through the whole procedure. The mean lead and cadmium levels of those blanks were then deducted from the sample readings before the results were calculated.

For evaluation of the homogeneity of the subsamples, the percentage difference of determined values of lead and cadmium between duplicates were calculated as follows:
$D = 100 \times (M-A)/A$,
where D is the percentage difference
M is the maximum value
A is the average value of the duplicate

The average, SD, range and 95% percentile of the percentage difference for lead are 5.54, 3.22, 0.3-11.4 and 10.3, respectively, and for cadmium are 4.65, 3.71, 0-15.0 and 11.8, respectively.

INDIA:

Lead and cadmium in blood were determined using a modified Delves' cup technique (microsample technique utilizing flame): 10 ul of whole blood was taken into previously conditioned sample cups, and dried in an oven at 110-115°C. Both the metals were analysed in a Perkin-Elmer (PE) AAS instrument, model 373, equipped with deuterium (D_2) background correction (BC) system and recorder 056. Calibration solutions were prepared by adding known amounts of lead and cadmium solutions to IQC samples.

Lead and cadmium in air filters were determined using wet digestion (nitric acid, sulphuric acid, perchloric acid, all of Analar grade, and distilled water, 10:1:1:8,) on a hotplate at low temperature. The final clear solution was aspirated into a PE 373 AAS equipped with D_2 BC, recorder 056 and printer PRS 10 using the regular flame. Values for blank filters were subtracted.

Lead and cadmium in dust were determined using dry ashing. Samples were kept in an oven at +85°C for 8 hours. Known amounts of samples were then transferred to a glazed porcelain crucible and dry ashed at 450°C in a calibrated muffle furnace. The ash was dissolved in 1 M HNO_3 and analysed using flame - AAS.

JAPAN:

All utensils used were acid-washed with 3% HNO_3 and rinsed several times with deionized water and dried before use. The borosilicate glass test tubes (75 x 20 mm) for digestion of duplicate food samples were heated at 200° C with 5 ml of HNO_3 and 0.5 ml of $HClO_4$ in an aluminum block on a hotplate (Thermolyne Co., U.S.A) until the acidic solution dried up. The test tube was rinsed with deionized and distilled water. All standards used were prepared from stock standard solution (Wako Chemical Industries Co., Japan) containing 1000 mg/l of the metals in the form of $Pb(NO_3)_2$ and $CdCl_2$.

Lead and cadmium in blood were determined according to the method described below. The method has been routinely used for many years.

A sample of 0.5 ml blood is digested with 4-5 ml of mixed solution of HNO_3 and $HClO_4$ (10:1) and the solution was evaporated to almost dryness at 150-350°C in an aluminum block on a hotplate. The residue was dissolved in 0.5 M HNO_3 and made up to 2 ml with 0. 5 M HNO_3. The solution was analyzed for lead and cadmium using a Nippon Jarrel Ash graphite furnace atomic absorption spectrophotometer (GFAAS, model 8200+FLA 10) equipped with deuterium (D_2) BC system and peak height evaluation, and a Rikadenki Co. (model B-281 L) recorder. Calibration solutions were prepared from bovine blood spiked with known amounts of lead and cadmium.

Air filters and dust were digested with 5 ml concentrated HNO_3 and 0.1 ml concentrated $HClO_4$ at 150°C on a hotplate for 2.5-3.5 hours in glass beakers (Pyrex) covered with watch glasses. The digested solution was evaporated to almost dryness and the residue was dissolved with 0.5 M HNO_3. The beaker and the cover glass were washed several times with 0.5 M HNO_3. The solution was combined with the washing solutions and made up to a final volume of 10 ml. Blanks were run in the same way. The solutions were analysed by GFAAS using the same method as described for metals in blood samples except for preparing calibration solutions.

Lead and cadmium in duplicate diets. The sample was thawed and homogenized in a food blender with a stainless steel knife. Using Teflon coated spoon, 0.5 g samples were weighed into the test tube, and digested gently and gradually with 4 ml of HNO_3 at 140°C in an aluminum block on a hotplate. When the HNO_3 solution had almost dried up, 2 ml of HNO_3 and 0.3 ml of $HClO_4$ were added to the tube. The tube was heated from 140 to 200°C. When the acidic solution had dried up completely, the residue was cooled and

0.5 ml of 0.5 M HNO_3 was added to the tube. Three portions of the solution were spiked with internal standard solution of zero concentration, another three portions were spiked with internal standard solution of low concentration, and the other three portions were spiked with internal standard solution of high concentration. A total of nine portions were assayed for lead and cadmium by the internal standard method using GFAAS using the same method as described for the metals in blood except for preparing calibration solutions.

Lead and cadmium in faeces. After squeezing well, 2-10 g were sampled from 3 points per sample, and dried at 105°C until a constant weight was reached. The loss on drying was determined. Samples of 1-2 g were taken for analysis, from the same site as the samples for loss on drying, and digested with 5-6 ml of a mixture of HNO_3 and $HClO_4$ (10:1) at 150-350°C on a hotplate for 4 hours. The residue was dissolved in 0.5 M HNO_3 and made up to 3 ml and the metals were determined simultaneously with the analysis of QC samples by external standard method. A working curve was made from QC samples which were spiked with standard solutions. Determination was made on a Hitachi Z-800 Zeeman type atomic absorption analyser by flame method and peak height determination method.

SWEDEN:

All utensils used were washed with 10% HNO_3 and rinsed several times with deionized water and dried before use. All standards used were prepared from stock standards (BDH, U.K.) containing 1000 mg/l of the metal in the nitrate form.

Lead and cadmium in blood were determined according to the method described by Stoeppler et al (1978) and Stoeppler and Brandt (1980), with certain modifications (Elinder et al, 1983; WHO, 1983). The method has been used routinely for many years. A sample of 0.3 ml blood was deproteinized by the addition of 0.5 ml 0.8 M nitric acid. The supernatant was analyzed for lead and cadmium using graphite furnace atomic absorption spectrophotometry (GFAAS) with background correction (BC) and peak area evaluation. Calibration solutions were prepared by the addition of known amounts of lead and cadmium to cow blood.

Both metals were first analyzed using a Perkin-Elmer (PE) AAS instrument, model 373, equipped with deuterium (D_2) BC system, GFAAS system, HGA 500, autosampling system, AS-40, two channel recorder (model 056) and an Epson Hx20 computer with a printing device. Standard graphite tubes and pure argon gas were used for both analyses. Since the concentrations of cadmium in most of the monitoring samples were below the detection limit (0.3 ug Cd/l), all blood samples were reanalyzed using the PE model 5000 Zeeman AAS instrument, which has powerful optics and an advanced Zeeman BC system, HGA-500, AS-40, recorder 056, the PE computer model 7500 and PR-210 printer. The analysis was performed using l'Vov's platform in a pyrolytical graphite tube, pure argon gas and peak area evaluation.

After thawing and mixing, an aliquot of blood was deproteinized in an Eppendorf tube. After storage overnight (+4°C), mixing and centrifugation, the supernatant from each tube was transferred to a sampling cup. Injections (20 ul) into the HGA-500 were performed in duplicate.

Air filters and dust were wet digested with 2 ml concentrated HNO_3:$HClO_4$ 1:1 at 100°C (water bath) during 20 minutes in glass beakers (Duran). The warm residue was transferred by a Pasteur pipette into a glass tube and the beaker was rinsed several times with deionized water. All rinsing solutions were pooled in the glass tube to give a final volume of 10 ml. Calibration solutions were prepared by the addition of known amounts of lead and cadmium to a beaker (containing a filter for the filter analysis). The solutions were evaporated almost to dryness. The standards were then treated as described above for the samples. Blanks were prepared in the same way, but deionized water was added instead of standards. The solutions were analysed by flame AAS (FAAS) using a PE 5000, D_2 BC, the integration mode and the recorder 056. This flame AAS method has been used for many years (Adamsson, 1979). Due to the very low concentration in the monitoring samples, all samples were reanalyzed using GFAAS. From each solution, 0.5 ml was transferred to the autosampling cup and 0.5 ml deionized water was added in order to reduce the acid concentration. The same advanced instrumentation as for cadmium in blood (re-analysis) was used.

Lead and cadmium in duplicate diets. The buckets containing the samples were thawed and their contents homogenized in a food blender provided with a titanium knife. Duplicate aliquot samples were then weighed into platinum crucibles and, after drying, ashed at 450°C in a time/temperature programmable furnace (Carbolite food ashing furnace). When the ashes were free from visible carbon particles the ash was dissolved in 20 ml 0.1M HNO_3. The method has been described in detail earlier (Jorhem et al, 1984).

Lead and cadmium were determined by GFAAS in a Perkin-Elmer 3030/HGA-500 with a deuterium background correction system, AS-40 autosampler and printer PR-100.

Empty platinum crucibles were taken through the ashing procedure and volume of the final solutions was made up to 20 ml with 0.1M HNO_3. The mean lead and cadmium levels of these blanks were then deducted from the sample readings before the results were calculated.

Lead and cadmium in faeces. The frozen sample was thawed and transferred to a glass petri dish and dried at 105°C in an oven to constant weight. Subsamples were then homogenized by grinding in liquid nitrogen using a ring mill (Shatterbox, Model 8500, Spex Ind.). Ice cubes of deionized water were ground in the ring mill in between each sample in order to control the efficiency of the procedure for cleaning the grinding dish. All homogenized subsamples were pooled and spread out on a glass petri dish and freeze-dried (Edwards Modulyo EF4). Duplicates of 2.4 g dried sample (corresponding to about 10 g wet weight) were transferred to 40 ml glazed porcelain crucibles and the sample was re-dried overnight in an oven at 105°C. The samples were dry-ashed at 470°C overnight in a time/temperature programmable muffle furnace (Carbolite, model Food-ashing), after which the ash was dissolved in 15 ml 1M HNO_3. The solutions were transferred to glass tubes and stored in a refrigerator (+4°C) prior to the analysis. Empty crucibles were used as blanks and were, like the samples, placed randomly in the furnace.

FAAS was used for the analysis and the same equipment as described for the analysis of air filters and dust was used. Standards were made in 1M HNO_3. The method has been used for many years (Kjellström et al, 1978; Bruaux and Svartengren, 1985).

USA:

Lead and cadmium in blood were determined by GFAAS after deproteinization with 0.8 M HNO_3. The deuterium background compensation system (D_2-BC) and peak area evaluation facilities of the instrument were used. Calibration solutions were prepared from blood spiked with known amounts of lead and cadmium.

Air filters and dust were wet digested and final solutions in 8% HNO_3 were obtained. GFAAS was used for the determination via D_2-BC, peak area evaluation and the platform technique.

Lead and cadmium in duplicate diets. The samples were dry ashed at 450° for 12 hours and the ash was then dissolved in 1 ml concentrated HNO_3 and diluted to 25 ml with deionized water. GFAAS using the D_2-BC system of the Perkin Elmer 5000 instrument was used for the determination.

Lead and cadmium in faeces. The samples were dry ashed and final solutions in 4% HNO_3 were obtained. GFAAS was used for the determination, using the instrumentation mentioned above for air filters and dust.

YUGOSLAVIA:

Lead and cadmium in blood were determined according to the method described by Stoeppler et al (1978) and Stoeppler and Brandt (1980) with certain modifications (Telišman, 1985). The method has been routinely used for 7 years and controlled by means of participation in the U.K. External Quality Assessment Scheme for blood lead and cadmium. For the daily internal quality control, the reference blood samples of the Commission of the European Communities have been applied (Community Bureau of Reference - BCR Nos. 194, 195 and 196). All the labware used was acid-washed in 10% HNO_3, as well as soaked in 3% $Na_2CaEDTA$ solution for 24 h. All standards were prepared from the stock standards containing 1000 mg/l of the metal in the nitrate form (BDH, U.K.), and concentrated nitrate acid "Aristar" was used (BDH, U.K.). Both metals were analysed using the Perkin-Elmer AAS instrument, model 403, equipped with a deuterium background correction system, graphite furnace system HGA 72, autosampler AS-1, and recorder model 056. Standard graphite tubes and pure argon gas were used. The background correction and the peak height evaluation was used for both metals.

All the analyses were performed at least in duplicate. An aliquot of 200 ul blood was deproteinized by the addition of 600 ul 1 M HNO_3, thoroughly mixed, and 50 ul of 0.02 M HNO_3 was added. After repeated mixing for 30 min and centrifugation, the supernatant was transferred into an autosampler cup, sealed with Parafilm and stored overnight at 4°C. After allowing to reach room temperature (1 h), the supernatant was analysed for lead and cadmium by injecting 20 ul into the graphite tube (performed in triplicate). For very low concentrations of lead and cadmium in blood, the method of preconcentration was also applied (2x 20 ul or 3x 20 ul injection of supernatant into the graphite tube, each following the pyrolysis step of the previous aliquot). Three blank samples were prepared and analysed for lead and cadmium (instead of 200 ul blood, 200 ul of deionized water was added). The calibration solutions were prepared daily by the addition of known amounts

of lead and cadmium to the bovine blood IQC D (200 ul of the blood IQC D, plus 600 ul 1 M HNO_3, plus 50 ul of the Pb and Cd standards prepared in 0.02 M HNO_3). However, when applying the method of preconcentration, the spiked blood standards for calibration, the blanks and all the internal quality control samples were analysed the same way as the unknown samples.

It should be mentioned that the calibration lines for blood lead, when prepared by the use of a human blood (four different blood samples, containing 52-90 ug Pb/l blood, not ultrasonicated and not centrifuged, each containing 1.5 mg K_2EDTA/ml blood) systematically showed 11-17% lower slopes as compared to the calibration lines prepared by the use of the cow blood IQC D, and thus yielding correspondingly higher results of blood lead. However, these results could not meet the criteria of acceptability as defined in the actual quality control programme.

Air filters were wet digested with 2 ml concentrated HNO_3 in glass beakers and heated on a hotplate at about 70°C, almost to dryness. To the residual solution 200 ul of concentrated HNO_3 was added and the mixture was transferred to a glass tube with small portions of warm redistilled water. The final solutions were about 0.3 M HNO_3, adjusted to 10 ml. Calibration standards were prepared by adding small volumes of cadmium and lead standards (BDH) on filter in the same identical glass beakers, dried and treated as described above for the samples. A few blank filters were treated in the same way. The solutions were analysed for lead and cadmium by flame AAS using a Pye Unicam instrument Model SP9 equipped with Slotted Tube Atom Trap (STAT-system), with deuterium background correction and in integration - concentration mode.

Lead and cadmium in duplicate diets. After sampling, each duplicate diet was weighed and homogenized in a homogenizer (Braun-Iskra, Multipractic Plus) normally used for domestic food mixing, provided with stainless steel blender. One litre of homogenate was stored in a plastic container and kept at -20°C prior to analysis. After thawing of the samples 10 g of homogenate was weighed into quartz glass crucibles, dried at 105°C to constant weight and ashed overnight on 450°C in a muffle furnace ("Gallenkamp"). The method used to obtain a white ash, free of all organic particles has been described earlier (Blanuša and Breski, 1981). The ash was dissolved in concentrated HNO_3, and adjusted to 10 g with redistilled water. The final solution was 0.6 M HNO_3. A few blank samples were prepared by adding 10 ml of redistilled water mixed in the homogenizer and processed on the same way as food samples. Cadmium was analysed by flame AAS on a Pye Unicam SP9 instrument with deuterium background correction and in the integration - concentration mode. Lead was analysed by the electrothermal atomisation method on a Perkin Elmer 4000 AAS instrument with deuterium background correction, HGA 400, autosampler AS-40, printer GP 100 and recorder 56.

Lead and cadmium in faeces. After collection the total wet weight of each faecal sample was recorded. All samples were kept frozen at -20°C until the analysis. Duplicates of each thawed sample were weighed into a glazed porcelain crucible (about 5 g) and dried at 105°C to constant weight. Ashing, dissolving and adjusting of samples was carried out in the same way as for duplicate diets. Cadmium and lead were analysed by flame AAS on a Pye Unicam SP9 instrument with deuterium background correction and in the integration - concentration mode.

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ANNEX D. REFERENCE ANALYSES

One problem with the HEAL QC samples was to obtain the reference values. There is no absolute method for the determination of lead and cadmium. Even experienced laboratories using sophisticated analytical techniques may produce erroneous results (Lind et al, 1988). Reference analyses of the HEAL QC samples have been performed at:
1) Karolinska Institutet, Institute of Environmental Medicine and Department of Environmental Hygiene, Stockholm, Sweden
2) National Food Administration, Uppsala, Sweden
3) Swedish Environmental Research Institute, Stockholm, Sweden
4) Institute for Chemistry, KFA, Jülich, FRG
5) Institute of Hygiene and Epidemiology, Brussels, Belgium
6) CEC Joint Research Centre, ISPRA, Italy
7) Agricultural Research Centre, Jokioinen, Finland
8) Technical Research Centre of Finland, Espoo, Finland
9) Ministry of Agriculture, Fisheries and Food, Norwich, U.K.

The results of some of the reference analyses are given in tables 1-8. The reference laboratories are referred to with the numbers given above. The abbreviations for the analytical techniques are given below.

FAAS: flame atomic absorption spectrophotometry
GFAAS: graphite furnace atomic absorption spectrophotometry
DPASV: differential pulse anodic stripping voltammetry
IDMS: isotope dilution mass spectrophotometry
RNAA: radiochemical neutron activation analysis
ICP-MS: inductively coupled plasma mass spectrophotometry

The reference values for lead and cadmium in blood QC samples are based on the spiked amounts of lead and cadmium and the original concentrations in the cow blood used. Reference analyses were carried out to validate the spiking and the estimated concentrations in the original blood. Tables 1 and 2 show the results of some reference analyses of lead and cadmium in blood QC samples.

Table 1. *Lead in blood QC samples, ug Pb/l.*

Lab No	Tech-nique	Sample No 28	16	2	20	18
1	GFAAS	28	56	78	121	283
4	DPASV	25		74	118	
6	IDMS		60		122	288
Reference value		28	53	74	116	283

Table 2. *Cadmium in blood QC samples, ug Cd/l.*

Lab No	Tech-nique	Sample No 28	32	20	34	18
1	GFAAS	0.3	0.8	0.9	2.3	4.3
3	RNAA			1.1	2.8	4.4
4	DPASV	0.3	0.9	1.1	2.7	
6	IDMS			1.4		4.4
Reference value		0.3	0.8	1.0	2.5	4.4

The QC membrane filters were spiked with lead and cadmium solutions. Since the concentrations of these metals in the unspiked filters were extremely low the spiked amounts of lead and cadmium were used as the reference values. Some reference analyses were performed to validate the spiked levels.

For the dust QC samples the tentative reference values, based on the determinations made at the Institute of Environmental Medicine (IEM), were used. In order to check the accuracy of the method used, reference dust from NBS (SRM 1648) was analyzed together with the manufactured QC samples. Tables 3 and 4 show the results of a few reference analyses, carried out at a later stage of the training phase.

Table 3. *Lead in dust QC samples, ug Pb/g dry weight.*

Lab No	Tech-nique	Sample No BL1	SA	UB1
1	FAAS	44; 44	57	79; 88
4	FAAS	54	62; 63	91
4	GFAAS	53	61; 61	86
4	DPASV	49	64; 66	94
Reference value		44	57	83

Table 4. *Cadmium in dust QC samples, ug Cd/g dry weight.*

Lab No	Tech-nique	Sample No UB1	SA	BL1
1	FAAS	3.0	4.0	5.6
3	RNAA	3.6; 5.2	4.4; 4.9	6.3; 6.4
4	FAAS	3.3	4.0; 4.9	5.6
4	GFAAS	3.8	5.2; 5.2	6.7
4	DPASV	3.8	5.4; 4.6	6.4
Reference value		3.0	4.0	5.6

For lead and cadmium in faeces QC samples tentative reference values, based on IEM's determinations, were used until results of further reference analyses were carried out at a few reference laboratories (tables 5 and 6). The results of the reference analyses agreed fairly well with the tentative reference values.

Table 5. *Lead in faeces QC samples, ug Pb/g dry weight.*

Lab No	Tech-nique	Sample No C	P1	P2	P3	P4
1	FAAS	0.4	1.1	2.3	4.2	13.6
2	GFAAS	0.34	0.94	2.4	6	14.5
4	DPASV	0.34	1.08	2.1	4.08	11.3
5	GFAAS	1.1	1.5	1.9	4.6	14
Reference value		0.4	1.0	2.3	3.9	12.5

Table 6. *Cadmium in faeces QC samples, ug Cd/g dry weight.*

Lab No	Tech-nique	Sample No P4	P2	M1	M4	M2
1	FAAS	0.42	0.55	1.54	2.84	6.1
2	FAAS	0.38	0.51	1.4	2.7	5.2
2	GFAAS	0.43	0.58	1.7	3.3	6
3	RNAA	0.35	0.46	1.53	2.92	5.83
4	DPASV	0.41	0.58	1.59	2.92	7.02
5	GFAAS	0.44	0.49	1.4	2.6	4.8
Reference value		0.37	0.55	1.54	2.84	6.13

For lead and cadmium in diet QC samples the reference values were based on the mean of the results from seven reference laboratories (tables 7 and 8).

Table 7. *Lead in diet QC samples, ug Pb/kg dry weight.*

Lab No	Tech-nique	Sample No A	B	C	D	E	F
1	GFAAS	33	47	97	203	270	523
2	GFAAS	25	32	89	189	239	398
3	GFAAS	65	65	135	230	345	490
4	DPASV	28	46	102	250	272	416
7	GFAAS	29	47	122	260	322	457
8	GFAAS	15	15	110	210	250	420
9	ICP-MS	52	73	170	241	309	495
Reference value		35	46	117	226	287	457

Table 8. Cadmium in diet QC samples, ug Cd/kg dry weight.

Lab No	Tech-nique	Sample No A	B	C	D	E	F
1	GFAAS	30	87	223	497	573	960
2	GFAAS	27	95	212	512	573	965
3	GFAAS	29	115	270	510	595	1100
4	DPASV	28	90	200	490	576	880
7	GFAAS	32	97	209	379	482	803
8	GFAAS	21	78	190	440	490	860
9	ICP-MS	30	113	197	451	561	798
Reference value		28	96	214	468	550	909

References

Lind B, Vahter M, Rahnster B and Björs U (1988) Quality control samples for the determination of lead and cadmium in blood, faeces, air filters and dust. Fresenius Z Anal Chem 332: 741-743.

ANNEX E. RESULTS OF QC-ANALYSES, TRAINING PHASE

The results from the training phase, QC rounds 1-4, are presented in figures 1-9. Each diagram shows the regression lines based on the values reported from the participating laboratories for each QC round. The acceptance intervals for the regression lines (for explanation see 2.5.2.2) are indicated by the dotted lines.

Lead and cadmium in blood

Figure 1 shows the results for lead in blood. Five of seven regression lines were accepted according to the criteria $y = x \pm (0.05x + 10)$ in the first QC round. However, one of the five used a method which gave a high residual deviation. By QC 3 all four participating institutions produced acceptable results. The institutes that produced the results far outside the acceptance intervals in QC 1 and 2 did not participate in QC 3 and 4. In QC 4 one QC result was slightly outside the acceptance interval.

There was no common or prevailing type of error. There were about as many regression lines with function values lower than the reference values at the evaluation points as those with higher values. Furthermore, there were about as many regression lines with a slope < 1.0 as there were with a slope > 1.0. The average error of the method for all the accepted QC results was 5.2 ug/l.

For cadmium in blood (figure 2), only three of six laboratories had accepted QC 1 results according to the criteria $y = x \pm (0.05x + 0.2)$. In QC 4 only one of four regression lines was rejected, and this rejected line was not very far outside the acceptance interval. The average error of the method for all the accepted QC results was 0.14 ug/l.

Lead and cadmium in air filters

The results for lead in spiked air filters (figure 3) indicate that the quality of the analytical performance varies more than for lead in blood. In QC 1 four of eight regression lines (from seven countries) were accepted according to the criteria, $y = x \pm (0.1x + 1)$, while in QC 2 only one of four regression lines was accepted. The institute that produced the results far outside the acceptance interval in QC 1 did not participate in the other QC runs. The average error of the method for all the accepted QC results was 0.9.

The analytical performance for cadmium in air filters is shown in figure 4. In QC 1 four of six regression lines were accepted according to the criteria $y = x \pm (0.1x + 10)$. In QC 3 two of four regression lines were accepted. The average error of the method for all the accepted QC results was 5.9.

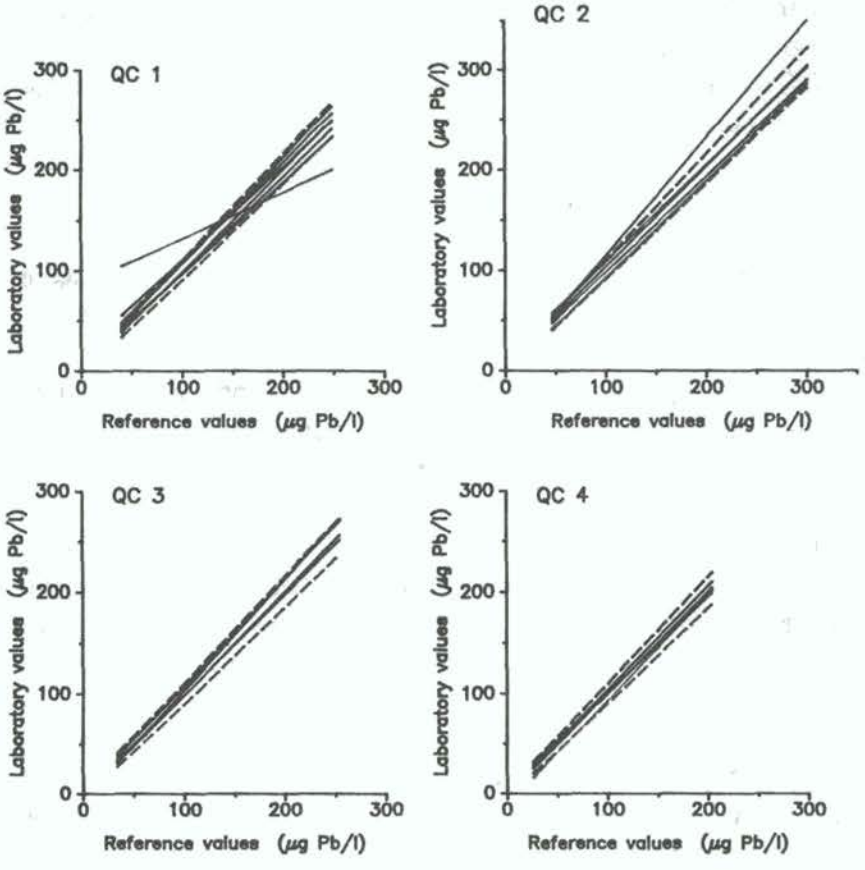

Figure 1. Results on lead in blood, QC 1-4. MAD criteria: $y=x\pm(0.05x+10)$. The acceptance interval is indicated by broken lines.

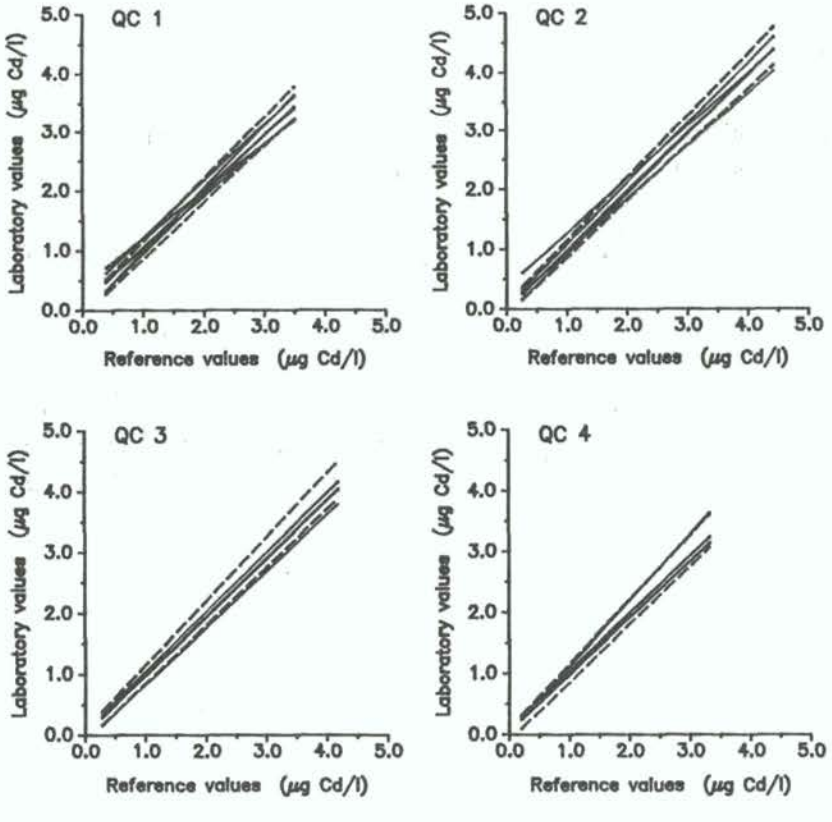

Figure 2. Results on cadmium in blood, QC 1-4. MAD criteria: $y=x\pm(0.05x+0.2)$. Acceptance interval indicated by broken lines.

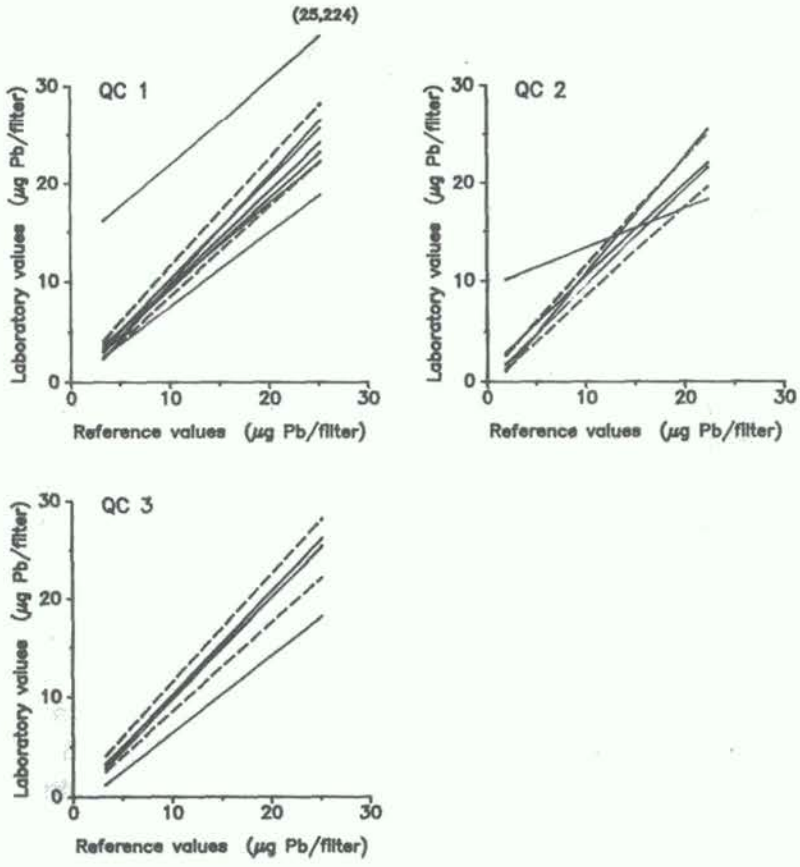

Figure 3. Results on lead in air filters, QC 1-3. MAD criteria: $y=x\pm(0.1x+1)$. Acceptance interval indicated by broken lines.

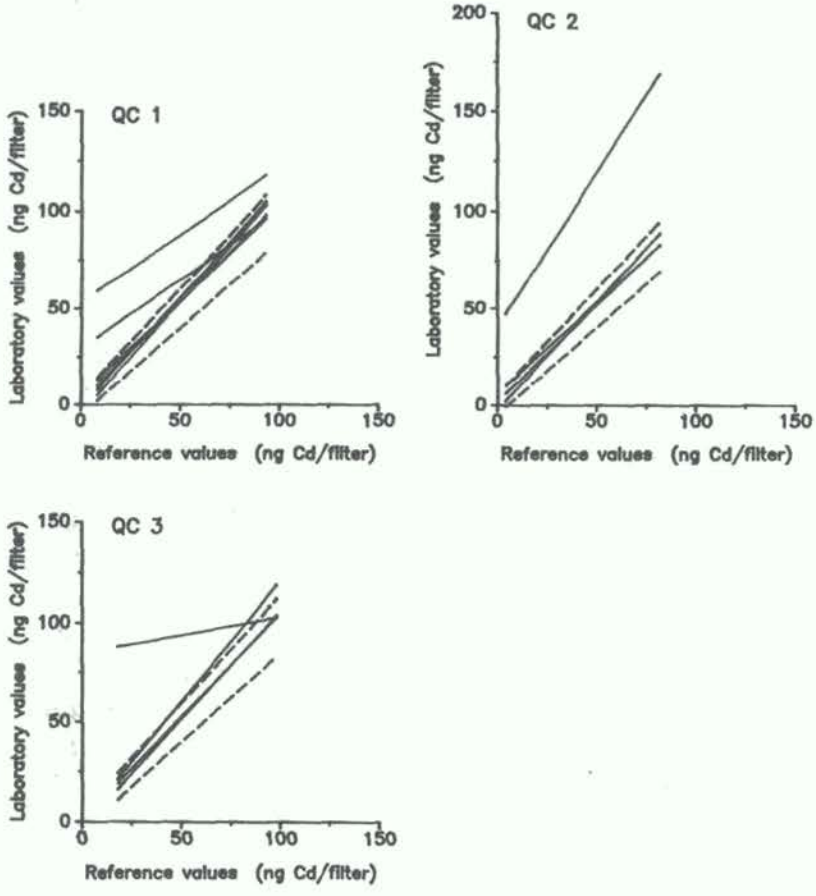

Figure 4. Results on cadmium in air filters, QC 1-3. MAD criteria: $y=x\pm(0.1x+10)$. Acceptance interval indicated by broken lines.

Lead and cadmium in dust

Dust was used as QC samples in order to check that the digestion system used could dissolve the particles collected on the monitoring filters. The first QC round consisted of one QC sample only (NBS SRM 1648, urban particulate matter) the reference value of which was 6 550 ug Pb/g, dry weight.

The reported values (9 laboratories from 7 countries) ranged from 996 to 6 710 ug Pb/g, dry weight (mean value 5 501 ug Pb/g). Seven of the laboratories presented data within 10% of the certificated value. In QC round 2 one of three regression lines for lead in dust (figure 5) was accepted according to the criteria $y = x \pm (0.1x + 5)$. After QC 2 the laboratories were recommended to use the small sample size (< 0.1 g), expected to be collected on the filters during the monitoring, and to use the same analytical methods as for the QC filters. This introduced several problems. The QC results indicate difficulties in dissolving particles in dust. In QC 3 two of three regression lines were slightly outside the acceptance interval. The average error of the method for the two accepted QC results was 6.3.

The reference value for cadmium in the first QC sample was 75 ug Cd/g, dry weight. The reported values ranged from 49 to 74 ug Cd/g (mean value 64 ug Cd/g). Only four of the nine laboratories presented data within 10% of the certified value. In QC 3 only one of three regression lines for cadmium in dust (figure 5) was accepted according to the criteria $y = x \pm 0.1x + 1$). The average error of the method for the two accepted QC results was 0.30.

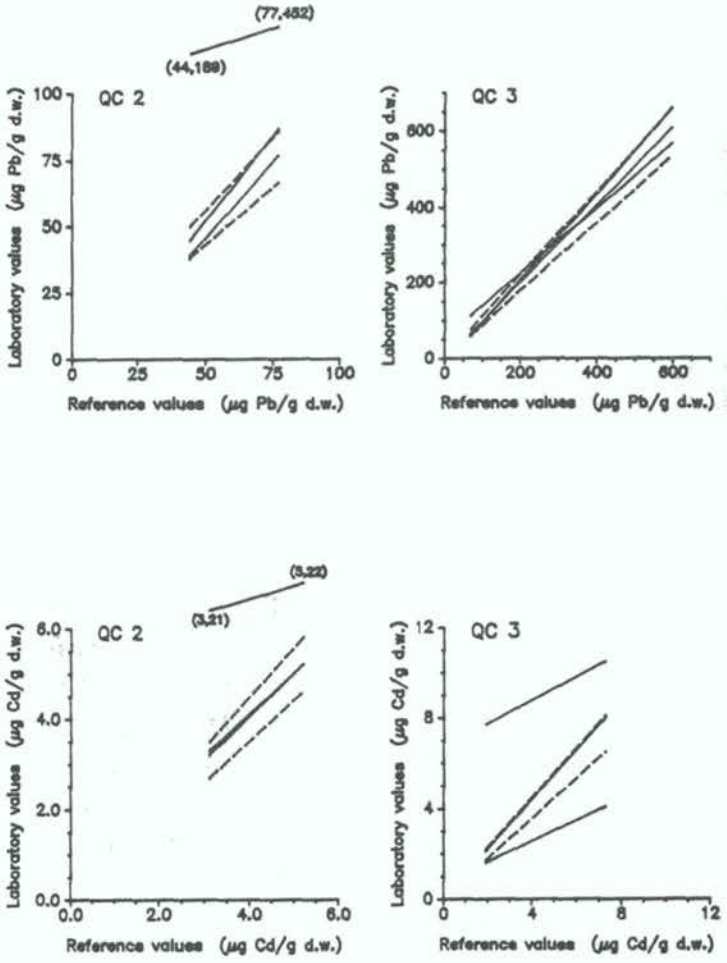

Figure 5. Results on lead and cadmium in dust, QC 2-3. MAD criteria: $y=x\pm(0.1x+5)$ for lead and $y=x\pm(0.1x+0.2)$ for cadmium. Acceptance interval indicated by broken lines.

Lead and cadmium in diets

The limited number of EQC-samples (totally 6) for the diet study made it necessary to limit the number of samples to 3-4 in each QC-round. Since the acceptance intervals are dependent on the number of QC-samples included in each round, the use of 3 or 4 QC-samples makes the acceptance interval so narrow that the results from virtually all participating laboratories would not be accepted according to this criterion. Therefore, the regression lines falling within the MAD-interval were considered satisfactory.

For lead in diets (figure 6) three of the five laboratories produced results for QC 1 that were accepted according to the criteria: $y=x\pm(0.1x+25)$. Three of four laboratories produced accepted results for QC 3. (USA participated in QC 1, but not in QC 3).

For cadmium in diets (figure 7), accepted results were produced by three of five laboratories for QC 1 according to the acceptance criteria: $y=x\pm(0.1x+25)$. Three of four laboratories produced accepted results for QC 3. Both random and systematic errors were detected during the training phase.

The random errors of the method, based on the results of the reference laboratories, were 16 ug/kg for lead and 20 ug/kg for cadmium. Although this is somewhat higher than the estimated error, it was decided not to make any changes in the MAD-criteria during the pilot phase of the project. The average errors of the method for the accepted QC results were 16 for both lead and cadmium.

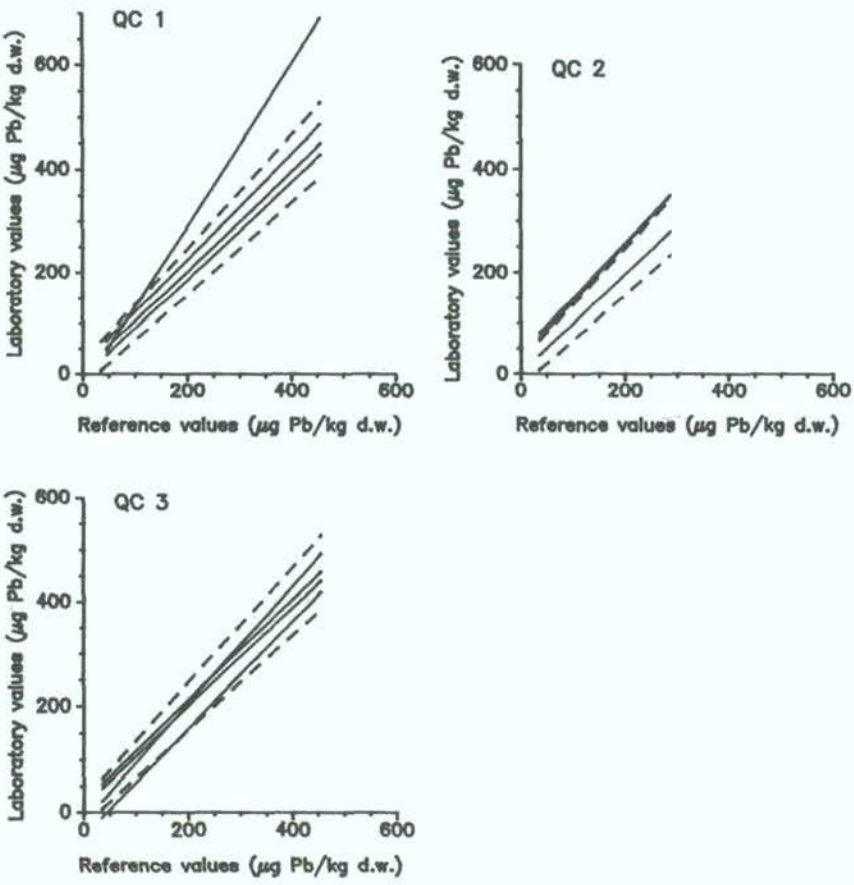

Figure 6. Results on lead in diets, QC 1-3. MAD criteria: $y=x\pm(0.1x+25)$. MAD interval indicated by broken lines.

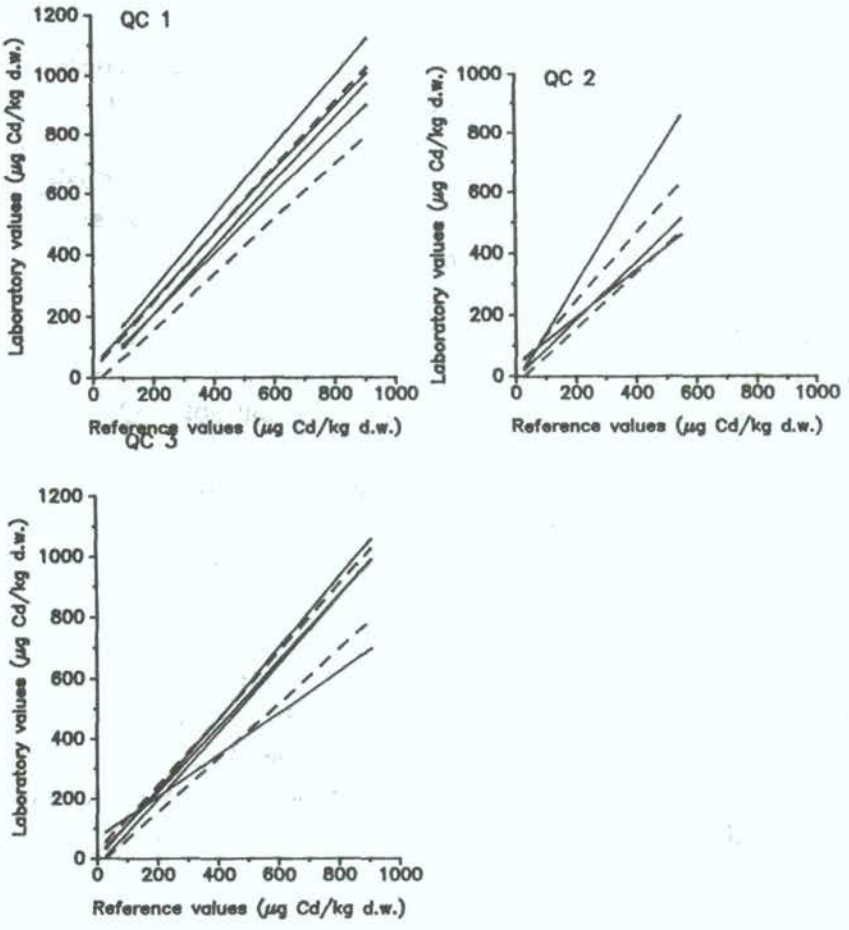

Figure 7. Results on cadmium in diets, QC 1-3. MAD criteria: $y=x\pm(0.1x+25)$. MAD interval indicated by broken lines.

Lead and cadmium in faeces

Figure 8 shows the results for lead in faeces. In QC 1 two of four regression lines were accepted according to the criteria $y = x \pm (0.1x + 1)$. In QC round 3 one of three regression lines was rejected, but it was not very far outside the acceptance line. The average error of the method for the accepted QC results was 0.30.

Figure 9 shows the QC results for cadmium in faeces. In QC 1 three of four regression lines were accepted according to the criteria $y = x \pm (0.1x + 0.5)$. In QC 3 two of three regression lines were accepted. The average error of the method for the accepted QC results was 0.10.

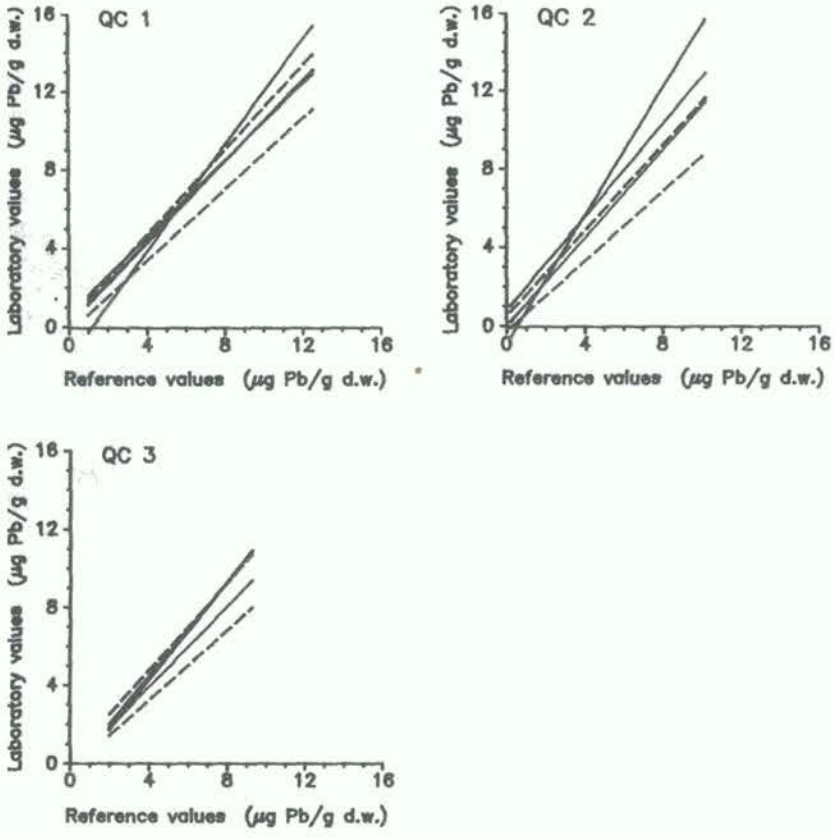

Figure 8. Results on lead in faeces, QC 1-3. MAD criteria: $y = x \pm (0.1x + 1)$. Acceptance interval indicated by broken lines.

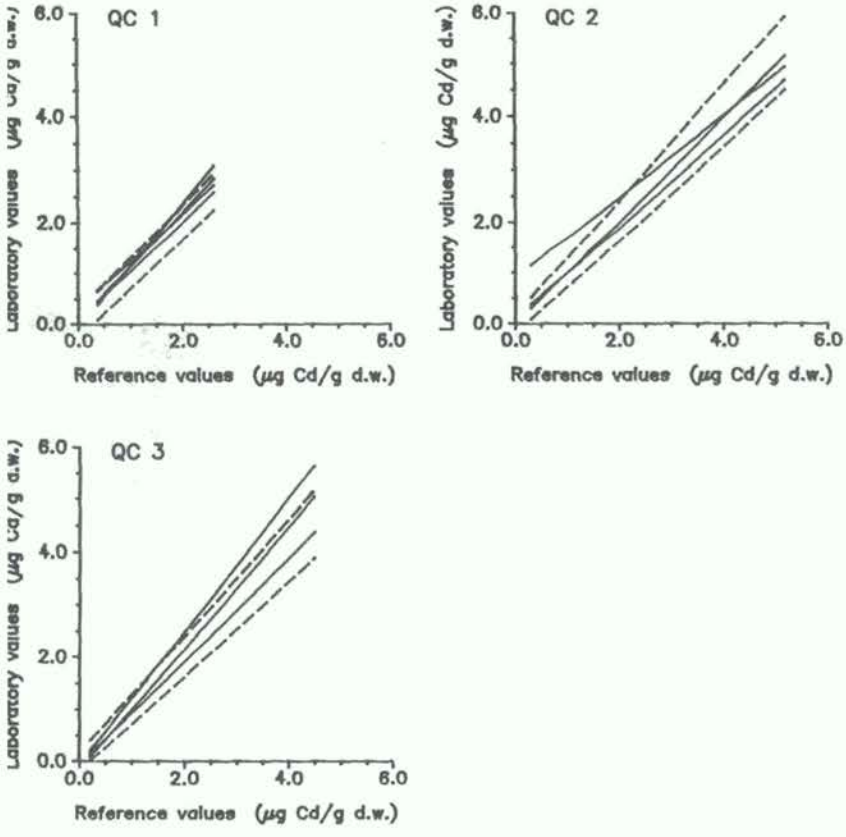

Figure 9. Results on cadmium in faeces, QC 1-3. MAD criteria: $y = x \pm (0.1x + 0.5)$. Acceptance interval indicated by broken lines.