

# Intestinal Absorption of Dietary Cadmium in Women Depends on Body Iron Stores and Fiber Intake

Marika Berglund, Agneta Åkesson, Barbro Nermell, and Marie Vahter

Institute of Environmental Medicine, Karolinska Institutet, S-171 77 Stockholm, Sweden

Measurements of intake and uptake of cadmium in relation to diet composition were carried out in 57 nonsmoking women, 20–50 years of age. A vegetarian/high-fiber diet and a mixed-diet group were constructed based on results from a food frequency questionnaire. Duplicate diets and the corresponding feces were collected during 4 consecutive days in parallel with dietary recording of type and amount of food ingested for determination of the dietary intake of cadmium and various nutrients. Blood and 24-hr urine samples were collected for determination of cadmium, hemoglobin, ferritin, and zinc. There were no differences in the intake of nutrients between the mixed-diet and the high-fiber diet groups, except for a significantly higher intake of fiber ( $p < 0.001$ ) and cadmium ( $p < 0.002$ ) in the high-fiber group. Fecal cadmium corresponded to 98% in the mixed-diet group and 100% in the high-fiber diet group. No differences in blood cadmium (BCd) or urinary cadmium (UCd) between groups could be detected. There was a tendency toward higher BCd and UCd concentrations with increasing fiber intake; however, the concentrations were not statistically significant at the 5% level, indicating an inhibitory effect of fiber on the gastrointestinal absorption of cadmium. Sixty-seven percent of the women had serum ferritin  $< 30 \mu\text{g/l}$ , indicating reduced body iron stores, which were highly associated with higher BCd (irrespective of fiber intake). BCd was mainly correlated with UCd, serum ferritin, age, and fiber intake. UCd and serum ferritin explained almost 60% of the variation in BCd. UCd was mainly correlated with age, fiber intake, cadmium intake, and serum ferritin, besides BCd. Age and fiber intake explained 22% of the variation in UCd. The results of the present study indicate that BCd mainly reflects body burden at long-term, low-level cadmium exposure. *Key words:* bioavailability, cadmium exposure, dietary exposure, duplicate diets, fiber intake, iron, vegetarianism. *Environ Health Perspect* 102:1058–1066 (1994).

Cadmium poses a threat to human health mainly because of its extremely long biological half-time, 10–40 years in the liver and kidneys (1). The cadmium concentration in the kidneys increases steadily with age (2). At a critical concentration of cadmium in kidney cortex, damage of the proximal renal tubular cells occurs, resulting in increased urinary excretion of low molecular weight proteins, which may be used as biomarkers of cadmium-induced kidney damage (3–5). Recent studies on

the effects of environmental exposure to cadmium in the general population in Belgium indicate that the critical concentration of cadmium in the kidney cortex is about 50 mg/kg (4), which is considerably lower than previous estimates and not much higher than that found in the general population (6). Therefore, it is important to identify significant sources of cadmium exposure and factors influencing the uptake.

The diet is the main source of cadmium exposure (>99% on average) in the general nonsmoking population of Sweden (7). Most foods contain relatively low concentrations of cadmium, but high concentrations may be found in certain mushrooms, liver, and kidney; cadmium is accumulated in liver and kidney, and shellfish, especially the hepatopancreas (5,8,9). Cereals, especially the unrefined wheat products, rice, and vegetables, often have elevated cadmium concentrations compared to dairy products, meat, and fish. Thus, it seems likely that people eating a lot of unrefined cereals and vegetables have an elevated intake of cadmium. The addition of cadmium to soil via air pollution, fertilizers, and sewage sludge has caused a steady increase of cadmium in Swedish wheat during the last decades (10–12). The ongoing acidification of soil (due to acid rain and application of fertilizers) may increase the solubility of soil cadmium and thereby the bioavailability to plants.

The average gastrointestinal (GI) absorption of cadmium (about 5% in adults) varies considerably between individuals (5,13,14). Experimental animal studies indicate that the GI absorption of cadmium may be greatly influenced by diet composition and nutritional factors, e.g., dietary content of fiber components, and low dietary intake of zinc, calcium, and iron (13,15–20), but the mechanisms involved have not been elucidated. The whole-body retention after a single dose of radiolabeled cadmium mixed with rolled oats and milk was shown to be inversely correlated with serum ferritin concentrations in 22 humans, indicating an increased absorption of cadmium at low body iron stores (19). On the other hand, serum ferritin was not correlated with cadmium concentrations in urine or blood in a study of the general population in Belgium (21). Little is known about the influence of diet composition and nutri-

tional status on metal absorption in human subjects.

This paper describes the uptake and body burden of cadmium in relation to the dietary intake of cadmium, the dietary composition, and the nutritional status. Cadmium concentrations in blood, urine, and feces were compared to dietary cadmium intake in women consuming a mixed or a high-fiber diet.

## Materials and Methods

**Study group.** Nonsmoking women, 20–50 years of age, not occupationally exposed to cadmium, were recruited via the local radio and press in two towns in the western part of Sweden. Women were chosen as subjects because they have higher cadmium concentrations in blood and higher body burdens of cadmium than men (2,4,22). Furthermore, low iron stores, which have been associated with increased GI absorption of cadmium, are more common among premenopausal women (23). Because cigarette smoking may significantly increase body burden (kidney concentration), and blood cadmium concentration as much as five times (22), only women who had been nonsmokers for at least 5 years were eligible for the study. None of the women were pregnant or lactating at the time of the study.

A first selection of women was made via telephone interviews, using a questionnaire on personal characteristics such as age, weight, height, former smoking habits, general dietary habits, medication, and possible GI disorders. Women with a body mass index (BMI) between 20 and 30 kg/m<sup>2</sup> [normal to slightly overweight (24)], and no GI disorders or any other illness requiring medication were identified as study participants.

**Dietary survey/food-frequency questionnaire.** For evaluation of the usual dietary habits, the selected women were asked to complete a self-administered food-frequency questionnaire (FFQ) with questions concerning food choice, food consumption frequencies, meal patterns, and the use of dietary supplements. Based

Address correspondence to M. Berglund, Institute of Environmental Medicine, Karolinska Institutet, PO Box 210, S-171 77 Stockholm, Sweden.

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on this information, the women were categorized into two groups: a high-fiber group ( $N = 23$ ) and women on a mixed diet ( $N = 34$ ). Women with no meat consumption or a high consumption frequency of vegetables and unrefined cereal products constituted the high-fiber group. The mixed-diet group included women who did not report high consumption frequencies of fiber products or high consumption of shellfish, which are known to contain relatively high concentrations of cadmium (8). A major part of the FFQ used in the present study has been validated by comparison with a dietary history interview (25).

**Sample collection and food records.** The women were invited to information meetings before the study began, and detailed sampling instructions were given. The importance of careful sampling and not changing dietary habits during the study period was emphasized.

We collected duplicate diets to determine the dietary intake of cadmium. Duplicate portions of all foods and beverages, including drinking water, consumed during 4 consecutive days were collected in acid-washed plastic containers as two to three samples per day and kept cool at  $-4^{\circ}\text{C}$  until sample preparation and analysis. To cover both the interseasonal and intraweekly variations in food consumption, samples were collected during four study periods between December 1991 and October 1992. During each study period, half of the subjects started sampling on a Sunday and the other half on a Wednesday.

Combined weighed and estimated dietary records were completed in parallel with the duplicate diet collection to enable calculation of intakes of various food components (e.g., energy/caloric intake, fiber, and certain minerals). Most women used an electronic balance to weigh all food items consumed. A nutritionist visited the homes of the women daily to provide guidance about sampling and documentation, interview them about their previous 24-hr dietary record, and help identify any food forgotten. The dietary records were coded by the nutritionist and converted to amounts of various food groups and nutrients by a computer program at the National Food Administration in Uppsala. The program contains 1600 food items, products, and meals, and 49 nutrients. All data entered into the computer were checked by the nutritionist.

Consumption frequencies of various food groups, calculated based on the FFQ and the four days dietary records, were compared to test how the current intake of various food groups differed from the usual intake. The food frequencies in the FFQ were transformed to points with one point

representing the consumption of an item once a month (26). The maximum sum was arbitrarily set to 40 (corresponding to consumption of an item more than once a day), except for dairy products that are consumed several times a day, for which the maximum sum was set to 112. The dietary intakes recorded over 4 days were converted to food-frequency points and extrapolated to 28 days.

All feces corresponding to the diet ingested during the duplicate diet collection period were collected to estimate the absorbed amount of cadmium and to validate duplicate diet cadmium. Only a few percent of ingested cadmium is absorbed in the GI tract. Feces were collected in plastic bags that were placed in the toilet. The plastic bags were sealed and put into plastic containers with a tight lid. The samples were stored deep frozen ( $-20^{\circ}\text{C}$ ) until sample preparation and analysis. A colored marker (0.6-1 g carmine red) was ingested to identify start and end of the collection period.

Blood ( $2 \times 10$  ml) was drawn from the brachial vein using Venoject evacuated blood-collecting tubes (VT-100, Terumo Corp., Tokyo). One tube contained heparin as an anticoagulant (whole blood), and one did not contain heparin (serum). Whole blood was analyzed for cadmium [blood cadmium, BCd; ongoing exposure (27)] and hemoglobin (Hb); serum was analyzed for ferritin [SFer; index of body iron stores (28)] and Zn (SZn).

A 24-hr urine sample was collected in acid-washed plastic containers to determine cadmium excretion (UCd) and body burden (27,29). The women were asked to record the time of the start (after the first morning urine) and end (including the next morning urine) of the urine collection on the plastic containers and to report any lost specimens.

**Analytical procedures.** Duplicate diets were thoroughly homogenized in a food blender. Subsamples were weighed in duplicate into platinum crucibles, dried at  $105^{\circ}\text{C}$ , and ashed at  $450^{\circ}\text{C}$  (Carbolite, Food Ashing, Sheffield, UK). The ash was dissolved in 15 ml of 1 M nitric acid (8). Cadmium was determined by flame atomic absorption spectrophotometry (detection limit  $0.001\text{--}0.002 \mu\text{g Cd/g}$ ). Samples with cadmium concentrations below or close to the detection limit were reanalyzed by graphite furnace AAS (detection limit  $0.0001 \mu\text{g Cd/g}$ ), using L'vov's platform, method of standard addition technique (Perkin Elmer model 5000 Zeeman with HGA-500). The frozen feces samples were thawed, dried at  $105^{\circ}\text{C}$ , homogenized by liquid nitrogen grinding (Shatterbox, model 8500, Spex Industries, Metuchen, New Jersey), and freeze-dried (Edwards

Modulyo EF4). Duplicate subsamples (2.4 g, corresponding to about 10 g of wet weight) were dry ashed at  $470^{\circ}\text{C}$  and dissolved in 15 ml of 1 M  $\text{HNO}_3$ . Cadmium was determined by flame-AAS with deuterium background correction (30,31).

Cadmium in blood was determined by graphite furnace AAS with background correction, using L'vov's platform in a pyrolytical graphite tube and peak area evaluation (Perkin Elmer model 5000 Zeeman with HGA-500), following deproteinization by addition of 0.5 ml 0.8 M nitric acid ( $\text{HNO}_3$ ), according to Stoeppler and Brandt (32) and Elinder et al. (33). Hemoglobin in blood was analyzed colorimetrically by a Photometer AI 204 (Analysinstrument, Stockholm) using a standard solution of cyanmethemoglobin (BDH clinical reagents, BDH Laboratory Supplies. Zinc in serum was determined spectrophotometrically, using a colorimetric zinc assay (Wako Chemicals, Neuss, Germany), and ferritin in serum was determined using an immunoassay (IMX Ferritin Assay, IMX System, Abbott, Stockholm), at Medilab AB, Stockholm. Urine samples were controlled for glucose, proteins (albumin) and pH using N-Combur-Test (Boehringer-Mannheim, Mannheim, Germany) before determination of creatinine (34) and density (Goldberg refractometer), since variations in the former parameters may influence the determination of the latter. The concentration of UCd (duplicate samples) was determined by graphite furnace AAS (method of standard addition) after acidification (35).

**Quality control and validation procedures.** All the materials used for sample collection, preparation, and storage were acid washed with 10%  $\text{HNO}_3$ , rinsed several times with deionized water, and tested for possible cadmium contamination before the study began. Cadmium concentration was below detection limits (mean of blanks + 3 SD of mean of blanks). Quality control samples of bovine blood spiked with cadmium (36), simulated human diets (37), and freeze-dried human feces (36) were analyzed together with the monitoring samples. Evaluation of analytical performance was based on linear regression analysis of laboratory results versus reference values (22,38) and recommended by UNEP/WHO (39) and Friberg (40). For comparison, the spiked blood quality control samples were also analyzed at a reference laboratory (Department of Occupational and Environmental Medicine, University of Lund, Sweden). Standard reference materials used included bovine liver (with diet samples), urine for cadmium, and serum for ferritin and zinc. Duplicate analyses ( $N = 2$ ) of Hb were car-

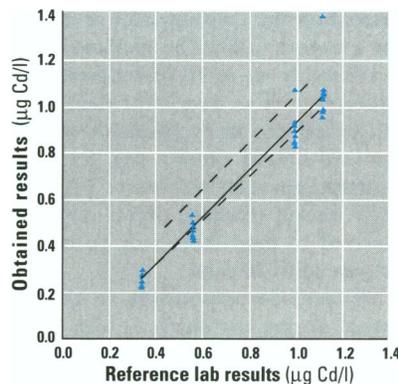
ried out at a reference laboratory (The Clinical Chemistry Laboratory, Karolinska Hospital, Stockholm). The study was approved by the Ethics Committee of Karolinska Institutet, Stockholm.

## Results

**Quality control.** Food records and sampling were complete for the entire study period by all women. Daily contact with the study nutritionist encouraged the women to cooperate and complete the sampling and enabled a certain control of sampling efficiency. No significant seasonal variations in food consumption could be detected. Because reliable 24-hr urine samples are difficult to obtain, UCd  $\mu\text{g}/24$  hr was correlated to UCd  $\mu\text{g}/\text{l}$  (adjusted to a density of 1.012) and UCd  $\mu\text{g Cd}/\text{g creatinine}$ . The correlation coefficient was 0.94 ( $y = 1.57x - 0.76$ ) and 0.90 ( $y = 1.01x - 0.35$ ), respectively, indicating that the 24-hr urine samples were fairly complete (on a group level). Five of the women repeated their 24-hr urine sampling due to self-reported incomplete sampling. No influence on BCd or UCd could be detected for women who reported cessation of smoking more than 5 years ago ( $N = 20$ ,  $p > 0.1$  Mann-Whitney nonmatched test).

The results of the analytical quality control were satisfactory. Results of analyses of blood quality control samples (spiked bovine blood), evaluated by linear regression of obtained analytical results versus reference values, are shown in Figure 1. With the regression line inside the interval indicated by broken lines in Figure 1, it is ascertained with 90% power that the true regression line does not fall outside the maximum deviation interval defined by  $\pm(0.05x + 2\sigma)$ , where  $\sigma$  ( $0.035 \mu\text{g Cd}/\text{l}$ ) is the error of the method estimated based on several previous analyses at several different occasions. The empirical residual deviation (error of the method) was  $0.08 \mu\text{g Cd}/\text{l}$ . The interlaboratory comparison of cadmium in blood quality control samples (Fig. 2) showed good agreement of the analytical results between the two laboratories.

Sets of 6 diet quality control samples were analyzed with each analytical run of duplicate diet samples, for a total of 12 runs (72 quality control samples total). The obtained values (mean  $\pm$  SD) and the reference values of the six different diet quality control samples are given in Table 1. The regression equation for the obtained values versus the reference values was  $y = 1.01x + 2.48$  ( $\mu\text{g Cd}/\text{kg dry weight}$ ),  $R^2 = 0.999$ . The maximum deviation interval (90% power) was  $\pm(0.05x + 4.0)$ , the empirical residual deviation was  $9.4 \mu\text{g Cd}/\text{kg dry weight}$ . Feces quality control samples, 8 different concentrations, a total of 23 quality control samples, were ana-



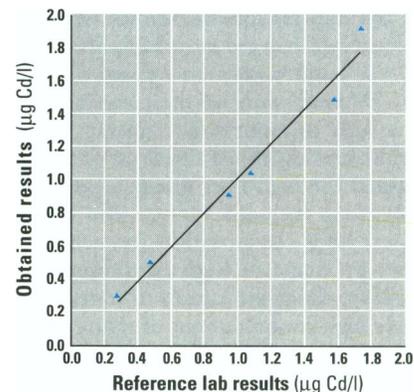
**Figure 1.** Results of the analyses of external quality control blood samples (obtained values) versus the reference values, evaluated by linear regression analysis. The broken lines indicate the acceptance interval for the regression line ( $y = -0.10 + 1.07x$ ;  $R^2 = 0.95$ ). With a statistical power of 90%, it can be estimated that the true regression line for blood cadmium does not fall outside the interval  $y = x \pm (0.05x + 0.07)$ .

lyzed together with the feces samples collected. The regression equation for the obtained values versus the reference values was  $y = 0.92x + 0.07$  ( $\mu\text{g Cd}/\text{g dry weight}$ ),  $R^2 = 0.996$ . The maximum deviation interval (90% power) was  $\pm(0.04x + 0.08)$ , the empirical residual deviation was  $0.04 \mu\text{g Cd}/\text{g dry weight}$ .

Results of analyses of standard reference materials for cadmium in bovine liver (NIST, Washington, DC) and urine (Seronorm, Nycomed Co., Oslo, and NIST), SFer (IMX Ferritin Controls, Abbott Scandinavia AB, Stockholm), and zinc in bovine serum (Nycomed Co.), are presented in Table 2. Duplicate analyses of Hb ( $N = 2$ ) showed values of 127 versus 128, and 145 versus 142 g/l.

**Personal characteristics and dietary survey.** Personal characteristics of the women included in the study (age, weight, height, and body mass index) are given in Table 3. There were no significant differences between the two dietary groups ( $p > 0.07$ , Mann-Whitney nonmatched test).

The mean food frequency points (consumption frequencies) for various food groups, calculated based on the FFQ (usual



**Figure 2.** Linear regression analysis of the analytical results in the interlaboratory comparison of blood cadmium quality control samples ( $y = 0.04 + 1.04x$ ;  $R^2 = 0.98$ ): our results (obtained results) versus those obtained at the Department of Occupational and Environmental Medicine, University of Lund (reference laboratory results).

intake) and the dietary records (current intake), were compared. Overall, there was good agreement between usual and current intake, both in the mixed-diet group and in the high-fiber group, with the exception of biscuits ( $p < 0.001$  in both groups, Mann-Whitney nonmatched test), sweets ( $p < 0.004$  in the mixed-diet group and  $p < 0.026$  in the high-fiber group), and vegetables ( $p < 0.022$  in the high-fiber group) being reported as consumed more seldom than they actually were during the study period (Fig. 3). The results indicate that dietary records reflected the usual dietary intakes of the main food groups well.

**Table 1.** Results of analysis of diet quality control samples<sup>a</sup>

Reference value ( $\mu\text{g}/\text{kg dw}$ )	Obtained values ( $\mu\text{g}/\text{kg dw}$ )
28	29 $\pm$ 4.4
96	98 $\pm$ 5.9
214	212 $\pm$ 13
468	486 $\pm$ 18
550	572 $\pm$ 13
909	915 $\pm$ 13

dw, dry weight.

<sup>a</sup>The obtained values are the means  $\pm$  SD of 12 analytical runs.

**Table 2.** Results of analysis of reference material

Reference samples (source)	Reference value	Obtained value
Cd in bovine liver (NIST)	0.27 $\pm$ 0.04 $\mu\text{g}/\text{g}$	0.27 $\pm$ 0.004 $\mu\text{g}/\text{g}$
Cd in urine (Nycomed)	6.2 $\mu\text{g}/\text{l}$	5.6 $\pm$ 0.4 $\mu\text{g}/\text{l}$
Cd in freeze-dried human urine, low and elevated (NIST)	0.4 $\mu\text{g}/\text{l}$ 88 $\pm$ 3 $\mu\text{g}/\text{l}$	0.5 $\pm$ 0.2 $\mu\text{g}/\text{l}$ 78 $\pm$ 8 $\mu\text{g}/\text{l}$
Zn in serum (Nycomed)	14–16 $\mu\text{mol}/\text{l}$	14.7/15.0 $\mu\text{mol}/\text{l}$ <sup>a</sup>
Ferritin in serum (Abbott)	20 $\mu\text{g}/\text{l}$ 150 $\mu\text{g}/\text{l}$ 400 $\mu\text{g}/\text{l}$	19/21 $\mu\text{g}/\text{l}$ <sup>a</sup> 153/154 $\mu\text{g}/\text{l}$ <sup>a</sup> 423/432 $\mu\text{g}/\text{l}$ <sup>a</sup>

<sup>a</sup> $N = 2$  of each concentration.

Figure 3 also shows that the main differences in mean consumption frequencies between the two diet groups concerned the consumption of meat ( $p < 0.001$ ), fish ( $p < 0.003$ ) and milk/yogurt products ( $p < 0.042$ , Mann-Whitney nonmatched test), all being reported consumed more often by the mixed-diet group, which support the group characterization based on the FFQ.

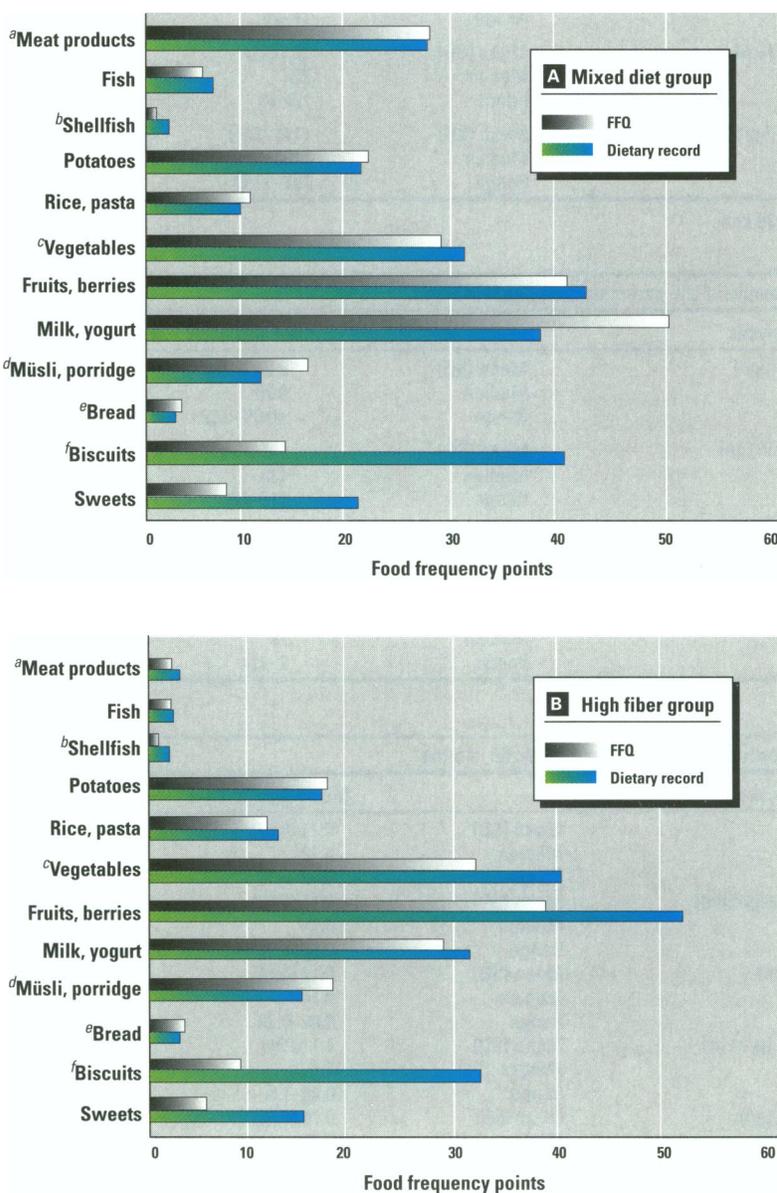
Intakes of energy, protein, dietary fibers, and minerals, calculated from the dietary records, are given in Table 4. The only statistically significant difference between the two dietary groups was a higher intake of fiber in the high-fiber group than in the mixed-diet group ( $p < 0.001$ , Mann-Whitney nonmatched test). The intake of energy (MJ) and protein (E%) constituted 90% and 110%, respectively, of the Swedish recommendations. The intakes of fiber, iron, zinc, and calcium were in agreement with the recommendations. Thus, it may be assumed that the women were eating a relatively balanced diet. Some of the women reported intake of supplementary iron in the FFQ (6 out of 23 women in the high fiber group, and 10 out of 34 women in the mixed-diet group). However, according to the dietary records, only three women in the high-fiber group and no woman in the mixed-diet group supplemented their diet with iron during the study period. Reported intake of supplementary iron, according to the FFQ, was not associated with higher SFer concentrations. The three women who supplemented their diet with iron, according to the dietary records, had SFer concentrations of 8, 13, and 13  $\mu\text{g/l}$ .

#### Duplicate diet, feces, blood, and urine.

Daily intake of cadmium via food, calculated based on analyses of 24-hr duplicate diets, and cadmium concentrations in the corresponding feces are given in Table 5. The concentration of cadmium in all feces collected as a percentage of the dietary intake of cadmium were on average 98% and 100%, respectively, in the mixed-diet and the high-fiber diet group. In spite of a significantly higher intake of cadmium in the high-fiber group ( $p = 0.0016$ , Mann-Whitney nonmatched test), no difference in BCd could be detected between the dietary groups. Nevertheless, there was a tendency of higher concentrations of BCd (and lower SFer) in the high-fiber group, although they were not statistically significant on the 5% level. The results of the blood and urine analyses are presented in Tables 6 and 7. The concentrations of Hb, SZn, and urine creatinine (g/24 hr) were within normal ranges (41), but SFer concentrations were low in both groups, despite an iron intake corresponding to the Swedish nutritional recommendations.

**Table 3.** Personal characteristics of the women in the study

		Mixed diet (N = 34)	High fiber (N = 23)
Age (years)	Mean (SD)	37 (7.4)	36 (8.4)
	Median	38	38
	Range	20–50	20–50
Weight (kg)	Mean (SD)	63 (8.2)	61 (7.3)
	Median	61	61
	Range	52–82	46–77
Height (cm)	Mean (SD)	166 (6.2)	167 (7.7)
	Median	166	167
	Range	151–184	152–187
Body mass index (kg/m <sup>2</sup> )	Mean (SD)	23 (2.8)	22 (2.1)
	Median	22	22
	Range	20–30	19–27



**Figure 3.** The intake of some of the more characteristic food groups shown for (A) mixed-diet group and (B) high-fiber group. Food frequency points (for explanation see text) based on food frequency questionnaires (FFQ) and 4-day dietary records (extrapolated to 4-week intake). <sup>a</sup>Meat products: includes meat, fowl, sausages, offal, and blood products; <sup>b</sup>shellfish: includes shrimps, crab, lobster, mussels and oysters; <sup>c</sup>vegetables: includes vegetables and root vegetables; <sup>d</sup>whole-grain products; <sup>e</sup>bread: slices of bread per day; <sup>f</sup>biscuits: includes buns and cookies.

**Table 4.** Daily intake of energy (E), dietary fibers, iron, zinc, and calcium in relation to type of diet calculated from 4-day dietary records<sup>a</sup>

		Mixed diet (N = 34)	High fiber (N = 23)
Energy (MJ)	Mean (SD)	7.68 (1.50)	7.77 (1.82)
	Median	7.65	7.49
	Range	4.52–10.17	4.96–13.71
Protein (E%)	Mean (SD)	15 (1.9)	13 (2.5)
	Median	14	13
	Range	12–20	8–18
Dietary fiber (g)	Mean (SD)	19 (5.8)	30 (7.2)
	Median	18	30
	Range	8.5–33	19–43
Dietary fiber (g/MJ)	Mean (SD)	2.5 (0.6)	4.0 (1.3)
	Median	2.4	3.7
	Range	1.5–4.1	2.2–6.5
Iron (mg/10 MJ)	Mean (SD)	18 (3.4)	19 (4.8)
	Median	17	18
	Range	12–28	11–34
Zinc (mg/10 MJ)	Mean (SD)	12 (2.2)	12 (2.1)
	Median	12	11
	Range	7.9–17	7.8–16
Calcium (mg/10 MJ)	Mean (SD)	1170 (249)	1330 (347)
	Median	1190	1280
	Range	757–1750	657–2040

<sup>a</sup>1 MJ = 239 kcal.**Table 6.** Results of the parameters analyzed in blood

Blood analyses		Mixed diet (N = 34)	High fiber (N = 23)
Blood Cd (µg/l)	Mean (SD)	0.24 (0.13)	0.32 (0.23)
	Median	0.23	0.25
	Range	≤0.09–0.68	≤0.09–0.96
Hemoglobin (g/l)	Mean (SD)	135 (8.8)	133 (7.9)
	Median	133	132
	Range	119–154	114–147
Serum zinc (µmol/l)	Mean (SD)	16 (2.4)	15 (1.9)
	Median	16	15
	Range	10–24	10–17
Serum ferritin (µg/l)	Mean (SD)	31 (30)	26 (26)
	Median	18	13
	Range	3–124	3–83

**Table 7.** Results of the parameters analyzed in urine

Urine analyses		Mixed diet (N = 34)	High fiber (N = 23)
Cd (µg/l) <sup>a</sup>	Mean (SD)	0.11 (0.07)	0.13 (0.10)
	Median	0.10	0.09
	Range	0.02–0.32	≤0.02–0.41
Cd (µg/g creatinine)	Mean (SD)	0.17 (0.09)	0.20 (0.16)
	Median	0.15	0.14
	Range	0.02–0.36	≤0.05–0.58
Cd (µg/24 hr)	Mean (SD)	0.17 (0.11)	0.19 (0.18)
	Median	0.14	0.13
	Range	0.02–0.28	≤0.02–0.75
Creatinine (g/24 hr)	Mean (SD)	1.1 (0.23)	0.93 (0.27)
	Median	1.1	0.87
	Range	0.48–1.5	0.46–1.4
Creatinine (g/l)	Mean (SD)	0.78 (0.34)	0.59 (0.34)
	Median	0.70	0.54
	Range	0.14–1.6	0.17–1.6
Density (g/ml)	Mean (SD)	1.014 (0.005)	1.010 (0.004)
	Median	1.013	1.010
	Range	1.004–1.026	1.004–1.021
24-hr urine volume (l)	Mean (SD)	1.6 (0.71)	1.9 (0.96)
	Median	1.5	1.8
	Range	0.61–4.2	0.59–4.1

<sup>a</sup>Adjusted to a density of 1.012 g/ml.**Table 5.** Daily intake of cadmium via food and cadmium concentrations in the corresponding feces

		Mixed diet (N = 34)	High fiber (N = 23)
Dietary Cd (µg/day)	Mean (SD)	11 (4.2)	16 (7.1)
	Median	10	13
	Range	5.7–26	5.5–38
Dietary Cd (µg/10 MJ)	Mean (SD)	15 (5.6)	21 (8.6)
	Median	14	17
	Range	7.8–38	6.6–45
Cd in feces (µg/day)	Mean (SD)	11 (4.5)	16 (7.5)
	Median	10	14
	Range	4.8–26	4.4–38

The low SFer concentrations indicate reduced body iron stores (SFer < 30 µg/l) in 67% of the women, and depleted iron stores (SFer < 15 µg/l) in 44% of the women. The only parameters analyzed in blood and urine that were statistically significantly different (Mann-Whitney non-matched test) between the two dietary groups were urine density (g/ml,  $p = 0.008$ ) and urine creatinine (g/l,  $p = 0.011$ ), both being lower in the high-fiber group. This might be explained by a higher intake of water and other beverages (supported by a tendency of larger urine volumes in the high-fiber group), and a lower intake of meat products in the high-fiber group.

#### Factors influencing cadmium uptake.

To identify relevant predictors of BCd and UCd, bivariate regression analyses of BCd and UCd versus daily dietary intake of cadmium, energy intake, SFer, SZn, fiber intake, iron, zinc, and calcium intake, age, and body mass index were performed, following logarithmic transformation of cadmium in duplicate diets, blood and urine, and of ferritin in serum, to approach normal distribution (Table 8). The strongest correlations with log BCd were obtained with log UCd, log SFer, age, and fiber intake, and to a lesser extent with intake of energy and of cadmium. The SFer concentrations were negatively associated with BCd (Fig. 4), while the fiber intake was positively associated with BCd (Fig. 5). For log UCd, the strongest correlation was obtained with age, besides BCd, and weaker correlations were obtained with fiber intake and SFer. Both log BCd and UCd were negatively associated with SFer and positively associated with fiber intake (g/day and g/MJ), energy intake, and age. Log BCd and UCd were highly correlated ( $R = 0.67$ ).

To determine the relative influence of various independent variables (predictors) on BCd and UCd, the variables in Table 8 with a  $p$ -value  $\leq 0.1$  were entered into a stepwise multiple regression model, one for BCd (log UCd, log SFer, fiber intake, age, energy intake), and one for UCd (log SFer,

fiber intake, age). There were two significant variables (UCd and SFer,  $p < 0.001$ ) for BCd ( $R^2 = 0.59$ ):  $\log \text{BCd} = 1.65 + 0.51 \times \text{UCd} - 0.23 \times \text{SFer}$  (SE of the regression coefficients were 0.079 and 0.055 for UCd and SFer, respectively). If log UCd was excluded from the BCd model, stepwise multiple regression analysis resulted in three significant variables (SFer, age and fiber intake,  $p < 0.05$ ) for BCd ( $R^2 = 0.42$ ):  $\log \text{BCd} = 2.14 - 0.23 \times \text{SFer} + 0.0093 \times \text{age} + 0.0074 \times \text{fiber intake}$  (SE were 0.068, 0.0036 and 0.0033, respectively, for the three regression coefficients). Essentially the same result was obtained when fiber intake was replaced by cadmium intake ( $R^2 = 0.43$ ):  $\log \text{BCd} = 2.14 - 0.25 \times \text{SFer} + 0.011 \times \text{age} + 0.011 \times \text{Cd intake}$  (SE were 0.06, 0.0035 and 0.0044, respectively for the three regression coefficients). For UCd, there were two significant variables (age and fiber intake,  $p < 0.05$ ;  $R^2 = 0.22$ ):  $\log \text{UCd} = 1.32 + 0.012 \times \text{age} + 0.0088 \times \text{fiber intake}$  (SE were 0.0045 and 0.0043, respectively). If BCd is included in the model, it is the only significant variable ( $R^2 = 0.44$ ,  $p < 0.001$ ).

Since SFer and fiber intake were inversely correlated with BCd, the relative influence of SFer and fiber intake on BCd was evaluated by dividing the women into groups in relation to low and high concentrations of SFer (depleted and repleted body iron stores), and low and high intakes of fiber (g/MJ) according to Table 9. The median BCd concentration was significantly higher at a low SFer (<20  $\mu\text{g/l}$ ) than at a high SFer (>30  $\mu\text{g/l}$ ), irrespective of fiber intake. Both BCd and UCd concentrations were higher at the high fiber intake, irrespective of SFer concentration, however, not statistically significant at the 5% level (Table 9). As expected, the daily dietary intake of cadmium was higher at the high fiber level than at the low fiber level (Table 9).

## Discussion

We previously reported a median dietary intake of cadmium (7-day duplicate diets) in 15 nonsmoking women of 8  $\mu\text{g Cd/day}$  (11  $\mu\text{g Cd/10 MJ}$ ), with a range of 2–56  $\mu\text{g Cd/day}$  in a total of 105 daily duplicate diets (7,42). This was similar to the earlier estimated cadmium intake based on analyses of seven prepared typical Swedish daily diets of 10  $\mu\text{g Cd/day}$  or 8.4  $\mu\text{g Cd/10 MJ}$  (43). In the present study, however, the median cadmium intake was 11  $\mu\text{g/day}$  (17  $\mu\text{g/10 MJ}$ ), with a range of 7–77  $\mu\text{g Cd/day}$  in a total of 228 daily duplicate diets, and higher in the high-fiber group than in the mixed-diet group. This may indicate an increased intake of cadmium in the Swedish population over time, possibly due to increased mobilization of cadmium, for example, caused by the ongoing envi-

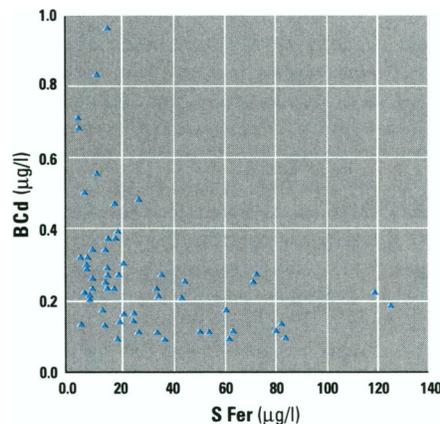
ronmental acidification. However, the concentrations of cadmium in blood and urine found in the present study were similar to

those found in previous national studies (7,22,44,45). If there is a true trend of increasing cadmium exposure over time

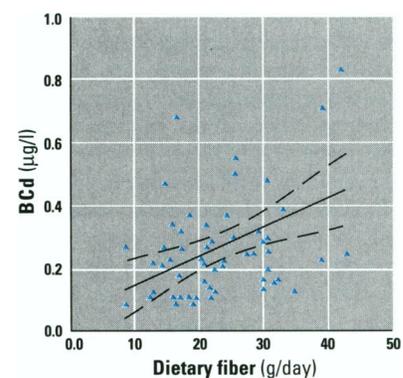
**Table 8.** Bivariate linear regression analyses of log blood cadmium (BCd) and log urinary cadmium (UCd) versus various independent variables

Variable	log BCd (ng/l)		log UCd (ng/l) <sup>a</sup>	
	R <sup>2</sup>	p	R <sup>2</sup>	p
Log intake of Cd ( $\mu\text{g/day}$ )	0.034	0.172	0.039	0.143
Intake of energy (kJ/day)	0.047	0.104	0.025	0.241
Log serum ferritin	0.273	<0.001	0.055	0.079
Serum Zn	0.008	0.513	0.028	0.210
Daily intake of fiber (g/MJ)	0.072	0.044	0.047	0.105
Intake of fiber (g/day)	0.160	0.002	0.105	0.014
Daily intake of Fe (mg/10 MJ)	0.009	0.494	0.001	0.792
Daily intake of Zn (mg/10 MJ)	0.006	0.342	0.001	0.842
Daily intake of Ca (mg/10 MJ)	0.000	0.451	0.010	0.451
Age (years)	0.199	<0.001	0.155	0.002
Body mass index (kg/m <sup>2</sup> )	0.030	0.196	0.009	0.487
log UCd	0.444	<0.001		

<sup>a</sup>Adjusted to a density of 1.012 g/ml.



**Figure 4.** Blood cadmium (BCd) concentrations versus serum ferritin (S Fer) concentrations of all the women included in the study ( $N = 57$ ).



**Figure 5.** Result of linear regression analysis of blood cadmium (BCd) concentrations versus fiber intake (g/day) of all the women included in the study ( $y = 0.058 + 0.009x$ ;  $R^2 = 0.18$ ;  $N = 57$ ). Broken lines indicate the 95% confidence interval.

**Table 9.** Median levels of BCd and UCd at low and high SFer and low and high dietary intake of fiber<sup>a</sup>

S Fer ( $\mu\text{g/l}$ )		Daily intake of fiber (g/MJ)		p-value <sup>b</sup>
		<2.6 ( $\mu\text{g/l}$ )	>2.6	
<20	BCd ( $\mu\text{g/l}$ )	0.27	0.31	0.247
	UCd ( $\mu\text{g/l}$ )	0.10	0.14	0.077
	S Fer ( $\mu\text{g/l}$ )	14	8	0.042
	Fiber (g/MJ)	2.3	3.9	0.000
	Cd intake ( $\mu\text{g/day}$ )	10	12	0.023
	N	14	18	
>30 and <85	BCd	0.11	0.22	0.075
	UCd	0.07	0.09	0.136
	S Fer	53	52	0.810
	Fiber	2.2	3.3	<0.001
	Cd intake ( $\mu\text{g/day}$ )	10	13	0.043
	N	9	8	
p-value	BCd ( $\mu\text{g/l}$ )	0.003	0.012	
	UCd ( $\mu\text{g/l}$ )	0.078	0.141	
	S Fer ( $\mu\text{g/l}$ )	<0.001	<0.001	
	Fiber (g/mJ)	0.450	0.578	
	Cd intake ( $\mu\text{g/day}$ )	0.801	0.317	

Abbreviations: BCd, blood cadmium; UCd, urinary cadmium; SFer, serum ferritin.

<sup>a</sup>Urinary cadmium adjusted to a density of 1.012 g/ml.

<sup>b</sup>Statistical differences between groups were tested using Mann-Whitney nonmatched test.

during the last decade, it may eventually increase kidney concentrations in the general population. Thus, there is a need to continue to monitor the dietary cadmium exposure in Sweden, in addition to biological monitoring of cadmium exposure. The concentrations in blood and urine, as well as the dietary intake of cadmium, are still notably lower than those reported from most other countries (5,9). Whether these differences are real or due to analytical errors is not known because many studies have not reported analytical quality control data. Due to the very low concentrations in blood and urine in nonsmoking, nonoccupationally exposed individuals, the risk for contamination of the samples during sampling and analysis is very high. Therefore, it is crucial to report quality control data for the study results.

Prospective dietary surveys, such as duplicate diet collection and dietary recording, influence dietary habits (46). A 13% reduction in energy intake, evenly distributed over the whole diet, has been attributed to duplicate diet collection (47). The energy intake of the women included in this study (7.8 MJ/day) was about 90% of the Swedish recommendation, which is 8.5 MJ/day (48). In our earlier study of 15 Swedish women, 27–46 years of age, including 7 days of duplicate diet collection, the average energy intake was 7.8 MJ/day (42). In a dietary survey (simplified 7 days dietary record), carried out among a representative sample of the Swedish population, the average energy intake among women 19–44 years of age was 7.7 MJ/day (49). In the present study, the intakes of calcium and protein corresponded to the nutritional recommendations (i.e., no influence on cadmium absorption of calcium and protein intake could be expected). Thus, there were no indications that the dietary habits of the selected women were extreme in any way or that dietary habits had changed considerably during the sampling period.

However, it should be emphasized that dietary intake of various nutrients calculated based on 4-day dietary records may not adequately reflect the usual intake, especially of nutrients for which day-to-day variations in intake are large (50). On the other hand, there was a good agreement in consumption frequencies (how often a certain food is eaten) between the two dietary survey methods used (FFQ and dietary records), except for vegetables, biscuits, and sweets. In the FFQ, the maximum consumption frequency, corresponding to consumption of an item more than once a day, was arbitrarily set to 40 points. For food items consumed several times a day, the frequencies calculated from the dietary records tended to be somewhat higher than

those calculated from the FFQ. However, if a maximum sum of 40 was used for sums above 28 in the dietary records (consumption of an item more than once a day), the difference in food frequency points between methods for consumption of vegetables disappeared. This indicates that the difference between methods in vegetable consumption was mainly due to methodological problems. The underreporting of consumption of biscuits and sweets compared to the actual consumption during the study period did not disappear following the same recalculation procedure. This is supported by earlier findings that there is often an underreporting of sucrose-containing foods and foods that are typically eaten on impulse (50,51). Thus, it may be assumed that the dietary intake during the 4 days did not deviate substantially from the usual intake.

The cadmium content in the feces collected corresponded well with the cadmium content in duplicate diets, showing that feces may be used as indicator media instead of duplicate diets for assessment of dietary intake of cadmium. Feces collection is cheaper than duplicate diet collection, and no food has to be wasted. Further, there is no obvious risk for decreased food intake during collection, which could give rise to underestimations of the usual dietary cadmium intake. The reluctance to use feces as biological media is mainly associated with concerns about the willingness of people to submit stool specimens. In the present study, no objections to stool specimen sampling were voiced. It is not possible to estimate the absorbed amount of the cadmium ingested during duplicate diet collection, using carmine red as a marker. Comparisons of cadmium input and output on an individual level indicate that carmine has a shorter GI transit time than cadmium, which could possibly be trapped within the epithelial cells of the intestine and eventually excreted via feces with the desquamating cells (14,18).

In the present study, 44% of the women had SFer <15 µg/l, indicating depleted bone marrow iron stores as defined by Milman et al. (52), and 67% had reduced iron stores (SFer <30 µg/l; 52). Two of the women (3%) displayed iron deficiency anemia (SFer <15 µg/l; Hb <121 g/l (53)). When body iron stores are reduced, the iron-transfer system in the small intestine is induced, leading to increased absorption of iron. In the present study, there was a significant negative correlation between BCd and SFer ( $R^2 = 0.27$ ), and SFer was one of the most important determinants for BCd. No woman with SFer above 30 µg/l (indicating adequate iron stores) had a BCd above 0.27 µg/l, whereas women with SFer below

20 µg/l had BCd up to 0.96 µg/l (Fig. 4). It seems likely that cadmium competes with Fe<sup>2+</sup> for a common binding site in the iron-transfer system in the intestinal mucosa at low body iron stores (19). At repleted iron stores, cadmium is probably absorbed via other mechanisms (54).

The specific influence of dietary fiber on the absorption of cadmium (and iron) is difficult to evaluate because fiber intake and SFer concentrations were inversely correlated with BCd. Based on experimental animal studies, showing that fiber inhibits GI absorption of cadmium (and iron), possibly due to formation of insoluble complexes with phytates in the intestine (15,55,56), it would be expected that a diet rich in unrefined cereal grains would prevent high absorption of dietary cadmium. In the present study, the high-fiber diets contained significantly more cadmium than the low-fiber diets, which is in agreement with the location of cadmium mainly in the bran fraction. Fiber intake was highly correlated with cadmium intake ( $R = 0.57$ ), indicating that most of the cadmium in the diets originated from the fiber. There was a tendency toward higher BCd and UCd with increasing fiber intake, irrespective of SFer concentrations, but the trend was not statistically significant on the 5% level.

It has generally been accepted that BCd cadmium concentrations mainly reflect ongoing exposure, whereas UCd mainly reflects the body burden of cadmium, especially at relatively low exposure levels (5,27). However, it should be noted that the metabolic model established for cadmium (13) is mainly based on high-dose animal and human exposure situations, which may not be valid at long-term, low-level exposure. The present study shows that at exposure levels giving rise to a median blood concentration of 0.23 µg Cd/l (range: ≤0.09–0.96), BCd was highly correlated with UCd ( $R = 0.67$ ), i.e., the body burden of cadmium, and UCd was the main determining factor for BCd. In fact, there was no correlation between BCd and daily dietary intake of cadmium. Thus, BCd is not a useful indicator of ongoing exposure at the low exposure levels found in the present study. Both BCd and UCd were significantly and positively correlated with age, which has previously been shown for UCd (2,44).

The median urinary cadmium excretion in the present study was 0.13 µg/24 hr, with a 90th percentile of 0.37 µg/24 hr. It has been suggested, based on investigation of cadmium exposure and signs of kidney damage in the general population in Belgium, that at urinary excretion of cadmium below 2 µg/24 hr, the risk of occurrence of renal effects remains low (4).

In the Belgian population, almost 11% of the subjects excreted more than 2 µg Cd/24 hr, corresponding to a renal cortex concentration of about 50 µg Cd/kg wet weight. It was estimated that in nonsmokers, this concentration is reached after 50 years of daily oral intake of about 1 µg/kg body weight (60 µg/day for a 60-kg person) at a GI absorption rate of 5%. With the increased GI absorption of cadmium in people with low body iron stores, the critical kidney concentration would be reached at even lower daily intakes of cadmium. Thus, the daily intake of cadmium in the present study, median 11 µg/day and 90th percentile 21 µg/day, does not offer a large safety margin for people with low body iron stores, such as premenopausal women, who may be considered a group at risk for cadmium-related health effects. It is important to investigate to what extent the increased cadmium absorption and related effects (kidney damage, osteoporosis, osteomalacia) can be diminished if iron status among women is improved.

In conclusion, there was a tendency of higher BCd and UCd, although it is not statistically significant on the 5% level, with increasing intake of fiber when standardized for SFer concentration. This indicates that the inhibitory effect of the fiber on the GI absorption of cadmium to a large extent, but not completely, compensated for the higher cadmium intake via fibers. A low SFer concentration (<20 µg/l) resulted in significantly higher BCd, irrespective of fiber intake, indicating an increased absorption of cadmium at reduced body iron stores. The dietary cadmium intake was seemingly higher in the present study than in previous Swedish studies, indicating a trend of increasing dietary exposure. Consequently, a great number of premenopausal women risk high body burdens of cadmium. BCd was to a large extent predicted by UCd, besides SFer, indicating that BCd concentrations mainly reflect body burden at long-term, low-level cadmium exposure in a nonoccupationally exposed, nonsmoking population.

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## Biopersistence of Respirable Synthetic Fibres and Minerals

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Volume 102, Supplement 5, contains the proceedings of the Workshop on the Biopersistence of Respirable Synthetic Fibres and Minerals, held September 7–9, 1992, in Lyon, France. Because of the adverse health effects of asbestos and its substitutes, the main objective of the meeting was to find how to define the ideal biopersistence for fibers, so that the market can be restricted to natural and synthetic fibers with known and controlled physico-chemical parameters. Sponsors of the workshop were the International Agency for Research on Cancer; the Institut National de la Santé et de la Recherche Médicale, France; and the Centre National de la Recherche Scientifique, France.

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