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A REGIONAL COMPARISON OF CHILDREN'S BLOOD CADMIUM, LEAD, AND MERCURY IN RURAL, URBAN AND INDUSTRIAL AREAS OF SIX EUROPEAN COUNTRIES, AND CHINA, ECUADOR, AND MOROCCO

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Abstract
Objectives: The authors aimed to evaluate whether blood cadmium (B-Cd), lead (B-Pb) and mercury (B-Hg) in children differ regionally in 9 countries, and to identify factors correlating with exposure. **Material and Methods:** The authors performed a cross-sectional study of children aged 7–14 years, living in 2007–2008 in urban, rural, or potentially polluted ("hot spot") areas (ca. 50 children from each area, in total 1363 children) in 6 European and 3 non-European countries. The authors analyzed Cd, Pb, and total Hg in blood and collected information on potential determinants of exposure through questionnaires. Regional differences in exposure levels were assessed within each country. **Results:** Children living near industrial "hot-spots" had B-Cd 1.6 (95% CI: 1.4–1.9) times higher in the Czech Republic and 2.1 (95% CI:1.6–2.8) times higher in Poland, as compared to urban children in the same countries (geometric means [GM]: 0.13 μg/l and 0.15 μg/l, respectively). Correspondingly, B-Pb in the "hot spot" areas was 1.8 (95% CI: 1.6–2.1) times higher than in urban areas in Slovakia and 2.3 (95% CI: 1.9–2.7) times higher in Poland (urban GM: 19.4 μg/l and 16.3 μg/l, respectively). In China and Morocco, rural children had significantly lower B-Pb than urban ones (urban GM: 64 μg/l and 71 μg/l, respectively), suggesting urban exposure from leaded petrol, water pipes and/or coal-burning. Hg "hot spot" areas in China had B-Hg 3.1 (95% CI: 2.7–3.5) times higher, and Ecuador 1.5 (95% CI: 1.2–1.9) times higher, as compared to urban areas (urban GM: 2.45 μg/l and 3.23 μg/l, respectively). Besides industrial exposure, traffic correlated with B-Cd; male sex, environmental tobacco smoke, and offal consumption with B-Pb; and fish consumption and amalgam fillings with B-Hg. However, these correlations could only marginally explain regional differences. **Conclusions:** These mainly European results indicate that some children experience about doubled exposures to toxic elements just because of where they live. These exposures are unsafe, identifiable, and preventable and therefore call for preventive actions. Int J Occup Med Environ Health. 2023;36(3):349–64

Key words:
biological monitoring, child, mercury, lead, environmental pollutants, cadmium

INTRODUCTION

Cadmium, lead, and mercury are classic toxic elements. Exposure occurs through ingestion and/or inhalation, which, in turn, may depend on where we live [1–5]. For example, urban and rural areas may differ, and local contamination, industrial or other, can potentially affect exposure.

Lead affects the brain, especially its development. Associations between lead and intelligence and/or school performance have been found even at very low exposure levels, reflected by blood-lead concentrations [2,3,5]. For cadmium, recent studies suggest that the brain, the kidney and skeleton is affected [6,7]. No safe level of exposure can be defined for lead, as there is no evidence for a threshold [2] and this may be the case also for cadmium [7], even when considering only non-cancer effects. There is, thus, a clear concern for health effects at the exposures that occur in the general population. For mercury, methylmercury from fish and elemental mercury from dental amalgam are health concerns [8]. There have been concerns that the expansion of heavy metallurgic industry in Eastern Europe during the 1950s and 1960s led to significant, still prevailing, exposure in, e.g., Poland and former Czechoslovakia.

In order to learn more about geographic differences of exposure to these elements, international harmonized human biomonitoring of children's cadmium, lead, and mercury concentrations in blood (B-Cd, B-Pb, and B-Hg, respectively) was made in 2007–2008 in 9 countries within the project Public Health Impact Of Long-Term, Low-Level Mixed Element Exposure In Susceptible Population Strata (PHIME). Six of the countries were European, mainly in Eastern Europe, the other 3 were in China, Ecuador, and Morocco. The authors have previously published international comparisons of results from blood samples from the urban children [9] and from women [10,11], analyzed in 1 single laboratory. These studies showed that the international differences between the studied European countries are modest for cadmium and lead, meaning that the urban children in the studied Eastern European countries did not have much higher exposures than children in Sweden. A later study of cadmium within the European human biomonitoring initiative HBM4EU similarly found no distinct geographic patterns for cadmium in adults' urine in an international comparison of 9 European countries [12], whereas the authors are unaware of any corresponding publications on lead or mercury. While thus European international differences in the general urban population appear to be modest, children may still be additionally exposed from local sources, and it is therefore important not to neglect the issue of regional exposures. Urban and rural areas may differ and it is well-known that living close to an industry or workshop that handles lead, or an industrially contaminated area, can be a major source of lead exposure [5,13]. The authors therefore here further analyze regional variation within countries, including rural children and children from polluted areas, so called "hot spots," in order to learn more about how regional variation within countries affect children's B-Cd, B-Pb, and B-Hg. Concentrations were not compared between countries, only within countries, by reasons described in Material and Methods section.

Thus, the aim of the present study was to describe regional variation in children's B-Cd, B-Pb, and B-Hg between 3 areas in each of the 9 countries where urban children's levels have been previously compared. Also for the European countries, based on questionnaire data, some correlates with exposure, other than geography were described.

MATERIAL AND METHODS

Subjects and study areas

The study was performed in 9 countries: Croatia, the Czech Republic, Poland, Slovakia, Slovenia, Sweden, China, Ecuador, and Morocco, in 2007–2008 (Table 1). In each country, schools were selected in 3 different areas: urban, rural and industrial (potentially polluted "hot spots"). The industrial areas were selected on basis of local environmental researchers' knowledge or suspicion of former or current contamination with heavy metals. Contact was established with the management of each school, and about 50 school children aged 7–11 years (in Morocco up to 14) were recruited. Blood samples and questionnaire data were collected. Data from Morocco have been published separately in a study of renal biomarkers [14] and the urban children are the same as in the previous study [9]. The study was approved by the local ethical committees. Written consent was obtained from a parent of each child and oral consent from the child before sampling.

Table 1. Characteristics of the studied areas and the 1363 children examined 2007–2008, living in urban, rural, or potentially polluted areas in 6 European and 3 non-European countries

Area of sampling	Type of contamination	Participants (girls/boys) [n]	Age [years] (M (range))
Croatia			
urban (Koprivnica)		52 (27/25)	8.7 (8–10)
rural		56 (21/35)	9.0 (7–10)
industrial	petrochemical	42 (21/21)	8.7 (7–10)
Czech Republic			
urban (Prague)		25 (8/17)	8.3 (7–10)
rural		66 (31/35)	9.7 (8–11)
industrial	predominantly Pb/Cd smelter	97 (50/47)	8.9 (7–11)
Poland			
urban (Wroclaw)		35 (10/25)	8.0 (7–8)
rural		39 (22/17)	8.4 (8–9)
industrial	Pb smelter	43 (16/27)	8.5 (8–10)
Slovakia			
urban (Banská Bystrica)		57 (35/22)	8.9 (7–11)
rural		50 (18/32)	8.3 (7–10)
industrial	Hg smelter	50 (31/19)	8.6 (7–10)
Slovenia			
urban (Ljubljana)		45 (26/19)	9.0 (7–11)
rural		65 (31/34)	9.5 (6–11)
industrial	Hg mining	65 (30/35)	9.2 (8–11)
Sweden			
urban (Landskrona)		41 (19/22)	9.1 (8–11)
rural		48 (22/26)	9.1 (8–11)
industrial	Pb smelter	59 (31/28)	9.2 (8–11)
China			
urban (Guiyang)		50 (30/20)	8.2 (7–10)
rural		58 (33/25)	7.3 (7–8)
industrial	Hg mining	42 (15/27)	8.5 (7–10)
Ecuador			
urban (Camilo Ponce Enriquez)		68 (36/32)	7.2 (7–10)
rural		47 (28/19)	7.6 (7–9)
industrial	gold mining	32 (10/22)	7.8 (7–10)
Morocco			
urban (Fez, Sefrou)		39 (18/21)	10.1 (7–14)
rural		68 (38/30)	9.9 (7–14)
industrial	heavy industry (ceramics, metals)	24 (18/6)	8.9 (8–11)

The total number of children examined was 1363 (Table 1). Of the industrial areas/potential "hot spots," 4 were situated around Pb/Cd smelters, 2 were Hg-mining locations, 1 – a gold mining community using Hg for refining of gold, 1 was a petrochemical area and 1 was a heavy industry area (both ceramics and metals). In Morocco, Pb could possibly still be used in petrol, at least to some extent. Therefore, Pb contamination was expected in Morocco's urban areas.

Questionnaire/interview and sampling

Information on individual factors of potential concern for metals exposure was obtained through 3 sources:
- questionnaire to the school,
- questionnaire to the parents,
- interview with/examination of the child.

The questionnaires and interview forms were jointly developed for all countries and were translated into the local languages. Questions were identical, but local additions were allowed as long as they could not be expected to bias answers to the core questions. From the parents' questionnaire, information on their education (basic, middle, high), whether anyone smoked at home (yes/no), source of water and heating, traffic near the home (<1 vs. ≥1 car passing/min), and the child's intake of offal (<1 vs. ≥1 meal/month), fish (<1, 1–2, ≥3 meals/month), and shellfish (<1 vs. ≥1 meal/month) was obtained. Information on number of dental amalgam fillings and the child's attempts to smoke was obtained at the examination.

A nurse took a cubital venous blood sample after cleaning with an ethanol swab. Evacuated plastic tubes with heparin (Greiner Vacuette® 4 ml Lithium Heparin tubes, Greiner-Bio One GmbH, Frickenhausen, Germany) were used. Sampling tubes from one and the same production batch were used in all participating countries. The levels of all 3 metals were <0.03 μg/l at leaching tests of tubes with 4 ml of 2% nitric acid.

Chemical analyses

Analyses of B-Pb, B-Cd and B-Hg were carried out in 5 laboratories (the Czech Republic, Poland, Slovenia, Sweden, and China, which analyzed their own samples; Sweden also analyzed samples from Slovakia, Ecuador and Morocco; Slovenia also from Croatia). In addition, 1 laboratory (Sweden; central laboratory) re-analyzed B-Pb, B-Cd and B-Hg in the urban samples from all countries except those already analyzed in Sweden and those from China where only B-Hg was re-analyzed (because of limited remaining sample volumes), and Slovenia and Croatia where only B-Pb and B-Cd were re-analyzed [9]. Thus, many of the urban samples were analyzed twice. By choosing the Swedish laboratory as central laboratory the number of re-analyses was minimized, as samples from 4 countries had already been analyzed in that laboratory.

Blood cadmium and B-Pb were determined by inductively coupled plasma mass spectrometry (ICP-MS) (samples from Slovenia, Sweden, and China according to the methods modified from Barany et al. [15]) or electrothermal atomic absorption spectrometry (ETAAS, Poland; [16]; and the Czech Republic), B-Hg by ICP-MS (China), cold vapour AAS (Poland; [16]), cold vapour atomic fluorescence spectrometry (Sweden; [17]), or by thermal combustion, amalgamation and atomic absorption spectrometry using Direct Mercury Analyzer (DMA-80) (Slovenia; EPA method 7473), or the single-purpose Atomic Mercury Analyzer AMA 254 (the Czech Republic).

Although each laboratory used its internal quality assurance system (Table 2), involving the use of reference materials, and demonstrated good performance in external proficiency testing schemes, it was decided to organize 4 interlaboratory comparisons. The aim was to demonstrate the level of equivalence between the participating laboratories and to decide whether samples should be analyzed in separate laboratories or centrally. Three intercomparisons used lyophilised samples of human blood from:

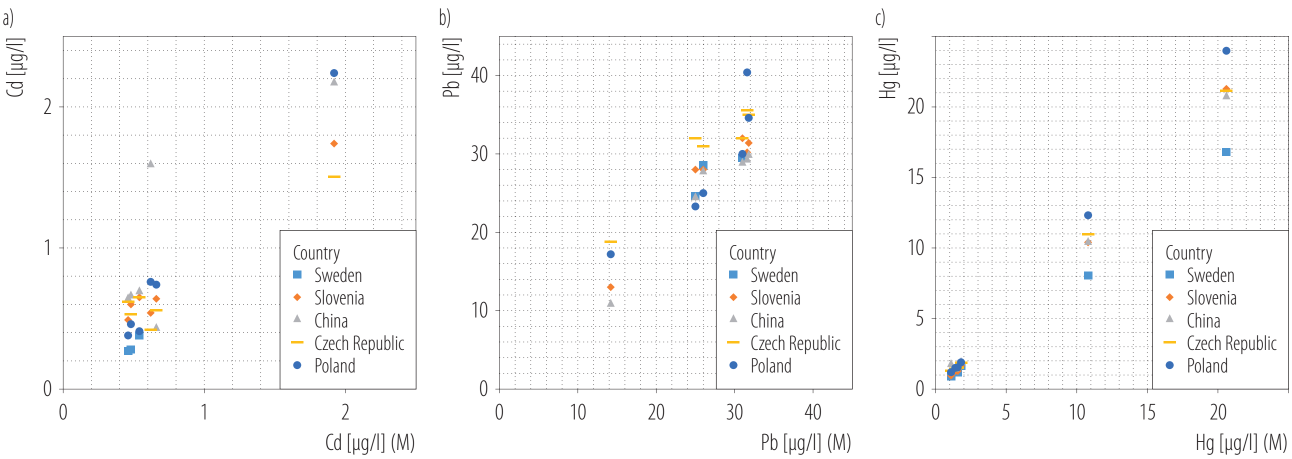
Table 2. Quality control procedures reported from the laboratories participating in the study on children aged 7–14 years, living in 2007–2008 in urban, rural, or potentially polluted areas in 6 European and 3 non-European countries

Country	Reference material	Intercomparisons	Accreditation
Sweden	Seronorm whole blood level 1	Centre de Toxicologie du Quebec, Canada	Swedish Board for Accreditation and Conformity Assessment (SWEDAC) (for mercury)
Slovenia	Seronorm whole blood level 1, NIST 1547, NIST 966, IAEA-086		
Czech Republic	Seronorm whole blood level 1		Czech Accreditation Institute (for trace elements by AAS in biological material)
Poland	Seronorm whole blood level 1	CDC, USA; Instituto Superiore de Sanita, Italy	
China	Seronorm whole blood level 1, 3, Dorm-2, Dolt-3, serum (ClinCheck)		

– non-exposed persons,
– people occupationally exposed to elemental mercury,
– "fish eaters."

In a fourth intercomparison 3 different samples of fresh blood from the general population was used.

Figure 1 shows the results for these 6 samples when analyzed by the 5 laboratories that generated the data. If |Z| ≤ 2 is applied, using a Z-score based on a target relative standard deviation of 25% [18] as a criterion for acceptance, 4 out of the 5 laboratories reported satisfactory results for all samples, and 1 laboratory delivered 2 out of their 18 results outside the satisfactory range. The results of these intercomparisons thus showed results that could be considered as fair but the authors concluded that because samples from different countries were analyzed in different laboratories and systematic differences



On the horizontal axis: the mean result for all laboratory setups (up to 18, including also other laboratories than the here included) participating in the interlaboratory comparison.
On the vertical axis: the mean result for each of the 5 laboratories that carried out the analyses of blood in the present report. Six samples were analyzed, of which 3 were lyophilised (1 was a pooled sample from 12 non-exposed, 1 was from a worker with occupational exposure to inorganic mercury, and 1 was a pooled sample from 3 individuals with high fish consumption), and 3 samples were fresh blood from 3 healthy voluntary donors (data from Snoj Tratnik et al. [19]).

Figure 1. Results of interlaboratory comparisons between the 5 laboratories that carried out the analyses of blood in the present study on children aged 7–14 years, living in 2007–2008 in urban, rural, or potentially polluted areas in 6 European and 3 non-European countries: a) cadmium (Cd), b) lead (Pb), and c) mercury (Hg)

appeared between laboratories, these data could not be used for comparisons of exposure levels between countries [19]. Therefore, a subsample (urban children) from each country was analyzed centrally in 1 laboratory, as described in Hruba et al. [9], where also comparisons between countries are reported. However, systematic differences between laboratories do not affect comparisons within each country. As a consequence, data are not invalidated for studies of regional variation within countries. The present report, which is based on the results from the 5 laboratories, is therefore devoted to comparisons within countries, not between countries.

Statistical analyses

Herein, only regional comparisons of exposure levels within countries were performed, thus, no comparisons were made between countries. The statistical analyses, as a consequence, concern regional differences within countries and exposure correlates other than geography. Assessment of regional differences between urban, rural and industrial areas were based on the ratios between rural and urban, and industrial and urban concentrations. These ratios were calculated based on data from the laboratory that had analyzed all samples from the specific country. First, due to skewed distributions, concentrations were transformed using the natural logarithm. Second, mean differences of log-transformed metal concentrations, corresponding to ratios in data not logarithmically transformed, were calculated and, for each country, estimates of the multiplicative effect of area (that is, the ratios rural/urban and industrial/urban concentrations) were presented. Statistical differences of the differences were evaluated using t-tests.

In order to find out if any geographical differences within the European countries could be ascribed to individual lifestyle factors, rather than differences in the environment, candidate correlates of Cd, Pb and Hg concentrations were evaluated for these countries. The analysis included only the European countries, as these were expected to be fairly homogenous in models of exposure correlates, i.e., interaction between country and correlates should not occur for many of the correlates. The analysis was performed by first evaluating whether the relative difference between areas differed between countries, using log-linear models. As significant interactions between country and area were found for all 3 metals, country- and area-specific means were estimated. Thereafter, the potential association was analyzed between metal concentrations and the following 12 categorical variables, for which specific hypotheses had been formulated [9]: child's sex and age, parental education, smoking at home, type of water source, type of heating source, traffic density, the child's attempt to smoke, number of amalgam fillings, and intake of fish, shellfish, and offal. For those variables that were statistically significant, interactions between the significant influential variable and country, as well as interactions with living area, were also examined. Since a significant interaction between amalgam fillings and country was found, this relationship was studied separately for each country. Otherwise, the final model included country and area, and all other statistically significant correlates. "Statistically significant" denotes $p < 0.05$ (2-sided). Residual distributions were assessed for normality using q-q plots, and homogeneity of variance was assessed visually and using Levene's test. Influential data points were identified using the leverage measure. Stata 10 was used for all statistical analyses.

RESULTS

Cadmium

The variation within countries was substantial for B-Cd but there was no consistent pattern for rural areas, compared to urban ones (Table 3). A major impact of region was observed in Poland, where B-Cd in children for the selected industrial area was approx. double (2.1 times, 95% CI: 1.6–2.8) compared to urban children (geomet-

Table 3. Geometric means of children's blood metal concentrations (lead [Pb], mercury [Hg]) in urban areas of 9 countries and the relative difference comparing urban with rural and industrial areas

Country/Area/Pollution	Blood metal concentration					
	cadmium (Cd)		lead (Pb)		mercury (Hg)	
	central/local lab. [µg/l] (GM)	relative difference[a] point estimate (95% CI)	central/local lab. [µg/l] (GM)	relative difference[a] point estimate (95% CI)	central/local lab. [µg/l] (GM)	relative difference[a] point estimate (95% CI)
Croatia						
urban	0.17/0.26	1.00	17.9/19.4	1.00	n.a./0.44	1.00
rural		1.17 (1.07–1.27)*		1.13 (0.96–1.33)		0.82 (0.66–1.01)
industrial (petrochemical)		1.13 (1.03–1.23)*		1.18 (0.99–1.40)		0.65 (0.51–0.81)*
Czech Republic						
urban	0.13/0.18	1.00	15.5/24.3	1.00	0.21/0.42	1.00
rural		1.20 (1.03–1.42)*		0.62 (0.51–0.77)*		1.01 (0.75–1.37)
industrial (Pb)		1.60 (1.37–1.86)*		0.95 (0.78–1.16)		0.96 (0.72–1.28)
Poland						
urban	0.15/0.20	1.00	16.3/14.2	1.00	0.12/0.31	1.00
rural		1.20 (0.91–1.60)*		1.40 (1.18–1.67)*		0.70 (0.48–0.99)*
industrial (Pb)		2.13 (1.61–2.81)*		2.28 (1.92–2.70)*		0.57 (0.40–0.82)*
Slovakia						
urban	0.14/n.a.	1.00	19.4/n.a.	1.00	0.52/n.a.	1.00
rural		0.87 (0.77–0.99)*		1.12 (0.99–1.26)		0.52 (0.40–0.68)*
industrial (Pb)		0.99 (0.87–1.12)		1.82 (1.61–2.05)*		0.57 (0.44–0.74)*
Slovenia						
urban	0.14/0.27	1.00	13.4/20.2	1.00	n.a./0.94	1.00
rural		1.23 (1.09–1.38)*		1.10 (0.96–1.26)		0.76 (0.63–0.92)*
Industrial (Hg)		0.92 (0.82–1.04)		0.93 (0.81–1.07)		0.97 (0.80–1.17)
Sweden						
urban	0.11/n.a.	1.00	14.0/n.a.	1.00	0.43/n.a.	1.00
rural		0.84 (0.74–0.95)*		0.81 (0.69–0.95)*		1.40 (1.10–1.80)*
industrial (Pb)		1.01 (0.89–1.13)		1.03 (0.88–1.21)		2.09 (1.65–2.65)*
China						
urban	n.a./0.75	1.00	n.a./64.2	1.00	2.45/2.23	1.00
rural		0.95 (0.90–1.01)		0.72 (0.62–0.84)*		1.19 (1.07–1.34)*
industrial (Hg)		0.99 (0.93–1.05)		0.76 (0.64–0.90)*		3.07 (2.71–3.47)*
Ecuador						
urban	0.26/n.a.	1.00	31.7/n.a.	1.00	3.23/n.a.	1.00
rural		1.21 (1.05–1.40)*		1.26 (1.08–1.46)*		0.91 (0.74–1.12)
industrial (Hg)		1.04 (0.88–1.22)		0.95 (0.80–1.12)		1.50 (1.18–1.89)*

Table 3. Geometric means of children's blood metal concentrations (lead [Pb], mercury [Hg]) in urban areas of 9 countries and the relative difference comparing urban with rural and industrial areas – cont.

Country/Area/Pollution	Blood metal concentration					
	cadmium (Cd)		lead (Pb)		mercury (Hg)	
	central/local lab. [μg/l] (GM)	relative difference[a] point estimate (95% CI)	central/local lab. [μg/l] (GM)	relative difference[a] point estimate (95% CI)	central/local lab. [μg/l] (GM)	relative difference[a] point estimate (95% CI)
Morocco						
urban (Pb)	0.21/n.a.	1.00	71.0/n.a.	1.00	0.31/n.a.	1.00
rural		0.98 (0.83–1.15)		0.45 (0.37–0.54)*		0.52 (0.36–0.75)*
industrial (mix)		1.08 (0.88–1.33)		0.66 (0.51–0.84)*		1.25 (0.78–2.02)

GM – geometric mean; n.a. – not analyzed.
[a] Between areas.
* The relative difference vs. the urban area is statistically significant ($p < 0.05$).

ric mean (GM) in central analyses of urban children in Poland: 0.15 μg/l), and in the Czech Republic 60% higher (1.6 times, 95% CI: 1.4–1.9, urban GM: 0.13 μg/l).

The only statistically significant correlation for B-Cd, except region, was traffic density (Table 4). Children who lived close to roads with a traffic density of ≥1 car/min had, on average, 7% higher levels than the others. The effect was consistent over the different European countries, i.e., no interaction with country was observed ($p = 0.2$). The effect did not remain statistically significant when urban children were excluded ($p = 0.15$). Traffic density, when included in the multivariate model, did not change the patterns of differences between urban/rural/industrial areas.

The B-Cd results obtained in the 3 local laboratories were all higher than in the central one, sometimes by a factor of 2 (Table 3).

Lead

A strong impact on the children's B-Pb from environmental contamination was seen in the selected industrial areas in Poland (2.3 times, 95% CI: 1.9–2.7, higher than in urban children, GM 16.3 μg/l) and Slovakia (1.8 times, 95% CI: 1.5–2.1, GM 19.4 μg/l) (Table 3). Within countries, B-Pb was higher in urban than in rural areas in Sweden, the Czech Republic, China, and Morocco, though on quite different levels. On the other hand, rural children had statistically significantly higher B-Pb in both Poland and Ecuador, although the relative differences were small.

Boys had on average higher B-Pb than girls (Table 4). Also, exposure to environmental tobacco smoke correlated with B-Pb; children with such exposure had, on average, 10% higher concentrations. A similar relative increase was seen in children with frequent intake of offal. These factors were all consistent over all the European countries. When they were included in the multivariate model, they did not change the patterns of differences between areas.

For B-Pb, most – though not all – of the local laboratories gave higher results than the central one (Table 3).

Mercury

Children in rural areas could have either lower (Poland, Slovakia, Slovenia and Morocco) or higher (Sweden and China) B-Hg than children in the cities. Likewise, the children from industrial areas could have either lower (Croatia, Slovakia and Poland) or higher (Sweden, China, and Ecuador) B-Hg than the urban children (Table 3).

Table 4. Associations between metal concentrations in blood in children and potential determinants (data from the 6 European countries: Croatia, the Czech Republic, Poland, Slovakia, Slovenia, and Sweden)

Variable	Starting model[a] R^2 [%]	Model with all influential variables included					
		relative change				interaction	
		point estimate	95% CI	p for trend	R^2 [%]	with country p	with area p
Cadmium	57				60		
traffic density				0.014		0.2	0.4
<1 car/min		1.00	ref.				
≥1 car/min		1.07	1.01–1.12				
Lead	33				37		
sex				<0.001		0.8	0.6
girls		1.00	ref.				
boys		1.09	1.04–1.15				
smoking home				0.004		0.4	0.9
no smoker home		1.00	ref.				
a smoker home		1.10	1.03–1.18				
offal intake				0.004		0.9	0.2
≤1 meal/month		1.00	ref.				
>1 meal/month		1.09	1.03–1.16				
Mercury	36				40		
fish intake				<0.001		0.5	0.7
<1 meal/month		1.00	ref.				
1–3 meals/month		1.10	0.99–1.22				
>3 meals/month		1.39	1.24–1.55				
amalgam fillings (Table 5)				<0.001		**0.026**	0.7

R^2 – explained variance, expressed as percentage of the total variance.
[a] Starting model includes country, area, and interaction term between country and area.
Bold is a statistically significant value ($p < 0.05$).

As expected, B-Hg increased with rising intake of fish (Table 4, consistent for the different European countries) and number of amalgam fillings (Table 5, varying effect in different countries). However, these factors, when included in the multivariate model, did not change the patterns of differences between areas.

Two of the 3 countries that had B-Hg determined both locally and in a central laboratory showed considerably higher concentrations than the central laboratory (Table 3).

DISCUSSION

Regional variation

The results show that children in certain contaminated areas, so called "hot spots," in Europe are considerably more exposed to cadmium and/or lead than children living in other areas. The possibility that the exposure at these "hot spots" has decreased since the sampling in 2007–2008 can not be excluded but there is no indications of that.

Table 5. Associations between mercury concentrations in blood and amalgam fillings, and interaction with country (data from 6 European countries) in the study on children aged 7–14 years, living in 2007–2008 in urban, rural, or potentially polluted areas

Amalgam fillings	Mercury concentrations association				
	model with area R^2 [%]	model with area and fish intake[a]			
		relative change		p	R^2 [%]
		point estimate	95% CI		
0–1		1.00	ref.		
≥2					
Croatia	7	1.27	1.04–1.56	**0.019**	14
Czech Republic	0	1.15	0.92–1.45	0.23	5
Poland	6	1.66	0.93–2.96	0.090	8
Slovakia	15	1.78	1.43–2.20	**<0.001**	32
Slovenia	5	1.19	1.02–1.42	**0.038**	8
Sweden	20	–[b]			

R^2 – explained variance, expressed as percentage of the total variance.
[a] Fish intake was an influential variable (Table 4).
[b] No child with ≥2 amalgam fillings.
Bold are statistically significant values ($p < 0.05$).

Contamination of the Eastern European "hot spots" largely stems from old heavy metallurgic industry that expanded largely during the 1950s and 1960s. Examples of children's exposure from such areas have been published before, for example from Poland, where living in the vicinity of a metallurgical slag heap added significantly to the children's lead exposure [13]. However, this industrial expansion does not seem to have produced significant nation-wide exposures, as B-Pb and B-Cd in urban children varied only little between the European countries studied herein [9]. Taken together, this means that exposures due to local contamination is a significant problem in certain areas in Europe. The extent of this problem is unknown.

In China and Ecuador, B-Hg was higher than in the European countries. The industrially contaminated area studied in China is a rather special one, with Hg mines. Evidently, the Hg from this source exposed not only workers, but also children living in the area. In Ecuador, a similar situation was evident for children from the gold-mining area, where large amounts of Hg were used to refine gold, sometimes even indoors at home close to children.

Some relatively small regional differences were noted, for example the somewhat higher B-Pb in rural areas of Ecuador and Poland vs. urban areas. The causes are unknown to the authors. Possibly, differences in pollution control of drinking water (e.g. from private wells), in lifestyle not captured by the questionnaire, or proximity to industrial sources could play roles.

Other correlates of exposure

Blood cadmium was associated with traffic density, confirming previous finding [9]. The cause is obscure, but may be due to Cd in tyres, bioavailability of Cd in freshly generated combustion particles, or residual confounding from socioeconomic factors or different dietary habits. The B-Cd was not associated with other factors such as consumption of offal, fish or shellfish. Consumption of other dietary items such as rice, known to influence B-Cd, was not considered, but it appears unlikely that traffic density was confounded by rice consumption. Therefore, the association between B-Cd and traffic density may well be causal and not caused by confounding. Neither second-hand smoking, nor age was associated with B-Cd. For second-hand smoke, this is in line with other data [20,21].

As to B-Pb, leaded petrol was still relevant in countries with recent (China) or probably prevailing (Morocco) use, where the urban children showed higher levels than the children from other regions. This is suggestive of petrol-Pb exposure or, possibly, Pb in the local water pipes [5]. Alternative explanations in the Chinese city could be combustion of coal [5,22] or industrial emissions [23].

In accordance with a wealth of previous findings, male sex [24] and exposure to environmental tobacco smoke [20] are established determinants for B-Pb. Moreover, there was an association with offal intake. Hence, consumption of, e.g., liver and kidney may contribute to the Pb intake in children, in the same way as has been shown in adults [25]. However, a previously reported by the authors relation to shellfish [9], was not confirmed.

For B-Hg, the relations to fish intake and amalgam fillings were expected, on the basis of earlier observations in adults [26,27] and children [9]. However, it is remarkable that even the rather small intake of fish in these children, as well as their very low number of amalgam fillings, were influential. As regards mercury exposure in Europe, it should be noted that populations in several European countries with coastal regions and larger fish consumption show higher mercury levels than in the countries here represented [28].

Taken together, the observed correlates, other than region, made only a minor contribution (an additional 3–4%) to the explained variance in the statistical model, which probably means that their impact on exposure is small in relation to the dominating factors, i.e., geography, which accounted for 33–57% of the variance.

Design issues

A limitation is that a relatively low number of children from each area was examined. Another limitation is that sampling was carried out only in single schools, and the results cannot give a full picture of the country, or even the specific area. An asset of the present study is the use of common sampling procedures and questionnaires/interviews, but a limitation is that quite simple questionnaires were used. This means that identification of correlates (potential determinants) can only be made in a relatively rough way. Further, soil, air, food or water concentrations of the 3 metals were not investigated.

Blood was used for the analyses. Blood requires invasive sampling but is for lead the recommended matrix. It is also a useful matrix for biomonitoring of cadmium and mercury exposure, although urine is often chosen for assessment of cadmium exposure, especially long-term (several years) exposure in adults. In contrast, B-Cd reflects a combination of long- and short-term exposure. Further, urinary biomonitoring of cadmium involves difficulties as regards adjustment for dilution, urinary flow, and co-elution with other substances, for example proteins [29]. As regards children, very little is known about these effects. Therefore, B-Cd is considered as a good alternative for a comparison of cadmium exposure among children from different regions. A limitation related to the above is that for cadmium it is difficult to compare the present data with studies based on urine samples. It should also be noted that sampling was made in 2007–2008. The authors do believe that the observations of higher exposures in certain polluted areas in Europe are still relevant, as there are no strong indications of general improvements lately as regards "hot spots" exposures.

A somewhat complicated limitation is that the authors did not have full comparability between countries, because different laboratories were used for the analyses of samples from the various countries. It is then hard to make conclusions on differences between countries. Any observations will raise the question: do results reflect variation in actual concentrations or just in laboratory performance? Given the modest variation between countries, an extremely good agreement between laboratories would be required; analyses of the same samples should have to fall within roughly ±20% or even less, considering that variation within ±20% means that the highest acceptable value (1.2×target concentration) will be 1.5 times the lowest acceptable value (0.8×target concentration). This quality control study did not show such low variation. That is the reason why some of the samples were re-analyzed in a single laboratory before an international comparison was made [9]. By the same reason, the authors here refrain from any international comparisons of concentrations and choose not to tabulate each regions concentration in Table 3, as such tabulation might lead readers to make inconclusive comparisons. The table instead shows ratios vs. the urban results. In this way, data from different laboratories can be used for combined analyses. Thus, while direct international comparisons are hindered, conclusions can still be made about regional variation and correlations with exposure other than geography.

It should be noted that difficulties with comparability between laboratories is a common limitation that is hard to overcome. For example, the quality control program applied in the European study of cadmium in urine [12], after taking into account what was technically feasible and realistic in current routine practice, allowed as much as ±50% variation in its interlaboratory comparison ($|Z| \leq 2$, using a Z-score based on a target relative standard deviation of 25%; [18]). This problem of comparability between laboratories is a likely explanation of the fact that there are remarkably few international coherent studies that have presented data on toxic metals that are fully comparable between countries. As regards studies of both B-Pb and B-Cd the authors know of only 3 such studies that include >2 countries [9,10,30] despite significant biomonitoring efforts in, for example, Europe [31].

All European countries' data were modelled together. Then there is a risk that differences in laboratory performance may invalidate analyses, (e.g., factors correlating with blood concentrations) (Table 4). The authors therefore included country in the model, which accounts for most calibration errors. In this way the combined dataset could be used for analysis of factors correlating with exposure.

Health aspects

The B-Cd in the presently studied children is generally low, but because of the long-term accumulation of Cd in the body, this exposure may still lead to risks of kidney and bone effects later in life, in particular in females in contaminated areas [1,7,32]. Possibly, these exposure levels can also affect cognitive development [6].

The B-Pb in the industrial areas in both Poland and Slovakia, and in all Ecuadorian regions, showed geometric means of about 35 μg/l, with a considerable fraction above 50 μg/l, a level nowadays regarded as a cause of an increased risk of slight impairments of cognitive functions [2,3,5]. The levels in China and Morocco were even higher. Recent risk assessments have not ascertained a safe level. In the USA, a "reference level" of 50 μg/l is used to "identify children who have been exposed to lead and who require case management" ([33]; recently suggested to be lowered to 35 μg/l [34]) and European Food Safety Authority [2] and World Health Organization and Food and Agriculture Organization [3] jointly proposed a tolerable intake of lead corresponding to a B-Pb of 12 μg/l.

The B-Hg in the European and Moroccan children was lower than those known for long to cause central nervous and kidney effects in adults [4,26,27]. However, higher levels occur in the areas studied in China and Ecuador. The highest observed B-Hg may cause a risk of damage to the fetal central nervous system, if retained into the fertile period in women, especially if it is in the form of methyl-Hg. High exposure to methyl-Hg is a possibility [35,36] but the present study could not differentiate between inorganic Hg, from e.g. inhalation of elemental mercury, and methyl-Hg from contaminated food.

Recommendations

With the present blood metal concentrations and the knowledge of their toxic effects, there is a need for prevention programs in Europe that decrease human exposure in industrially Cd- and Pb-contaminated areas. Then, the strategy should be to specifically act on "hot spots" exposures, which are unsafe, identifiable, and preventable. Also in the countries outside Europe, measures need to be taken to reduce exposure to all 3 metals among children.

Prevention programs should result in clean-up of areas, and/or alteration of industrial activity. Human biomonitoring of exposure is then a very useful component in the identification and prioritization of areas.

CONCLUSIONS

These mainly European results indicate that some children experience about doubled exposures to toxic elements just because of where they live. These exposures are unsafe, identifiable, and preventable and therefore call for preventive actions.

In addition to previously well-known determinants, traffic density appears to be associated with children's B-Cd, though with a relatively modest effect.

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