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New and revised reference values for trace elements in blood and urine for children – arsenic, lead, cadmium, and mercury

Opinion of the Human Biomonitoring Commission of the German Federal Environmental Agency

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Introduction

Human biomonitoring reference values permit to assess the exposure of individuals or population groups compared to the ubiquitous background exposure. The concept to derive such reference values in environmental medicine has been published by the German Human Biomonitoring Commission [1]. For children, the Commission has derived reference values for the heavy metals lead, cadmium and mercury in blood or urine [3-5] based on the population representative data obtained in the German Environmental Survey of 1990/92, GerES II. Since environmental conditions are changing reference values have to be checked continuously and updated if new information becomes available.

There is a considerable need for updated reference values for children. Unfortunately, environmental field work of the currently run survey for children, GerES IV, which was started in 2003 [6], will not be finished before the second half of 2006. Therefore, the Commission has decided to update the reference values for children based on the results of two studies, "Sentinel Health Departments" in the German Land of Baden-Württemberg of 2002/03 [7] and the pilot study for GerES IV, of 2001/02 [8].

These studies did not cover the whole of Germany and are not representative for the population. However, for the time being they represent the only available data basis for children in Germany that has not been generated by event-related studies, but rather has been obtained for larger study populations selected at random.

Data Basis

The „Sentinel Health Departments in Baden-Württemberg" project is a repeated cross-sectional study started in 1992. Each winter (October to March) school children of the 4th grade age 9-11) from well-defined areas (Mannheim: Neckarstadt-West; Stuttgart: Stuttgart-East/Bad Cannstadt/Untertürckheim; Ortenau county: Kehl; Ravensburg: Aulendorf/Bad Waldsee) are contacted and examined. The methods used (sampling of study population, questionnaire, sampling for analysis, analysis, statistical data treatment) are described in the report "Exposure and effect monitoring 2000/2001" [9].

The German Environmental Surveys (GerESs) are population-representative studies. In the pilot study for GerES IV, the Environmental Survey on Children, children and adolescents aged 0 to 17 years were selected at random within at four study areas (Berlin-Steglitz, Berlin-Friedrichshain, Wesendorf, and Neuruppin). The survey was conducted between March 2001 and March 2002. The methods used (sampling of study population, questionnaire, sampling for analysis, analysis, statistical data treatment) are described in the final report "Pre-test for the Environmental Survey for Children and Adolescents" [8]. For an update of the reference values derived earlier for 6- to 12-year old children, only the results for this age group are taken from the pilot study. As soon as the data from the currently run country-wide Environmental Survey for Children, GerES IV (2003-2006) [6, 10, 11] will become available, it will be possible to present reference values for 3- to 14-year old children.

To analyse As, Cd and Hg in urine, spontaneous urine samples were taken in the „Sentinel Health Departments in Baden-Württemberg" project , whereas morning urine samples were used in the GerES IV pilot study. The comparison of creatinine concentrations in spontaneous urine and morning urine did not show substantial differences. Therefore, it seemed to be acceptable to make use of the results of both methods to determine reference values.

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In both the „Sentinel Health Departments in Baden-Württemberg" project and the GerES IV pilot study elements in blood and urine were determined by atomic absorption spectrometry (AAS). As and Hg concentrations were determined by hydride AAS [8, 9]. Depending on the analyte the 95% confidence intervals of the 95th population percentile were calculated using a parametric procedure assuming a log-normal distribution or a bootstrapping procedure.

In the following the most important results of the reference value setting procedure are summarised. Taking into account the limited sample size the presentation of the results of the GerES IV pilot study are limited to the essential substance-specific parameter of influence that are important for deriving a reference value. As soon as the data of GerES IV (2003/2006) will become available, extensive statistical evaluations will be carried out.

Arsenic in urine

The As concentrations in urine were found to cover the range between 1.5 and 123.5 µg/l (median: 4.6 µg/l) for the 508 children aged 9-11 years studied in Baden-Württemberg (Table 1). There were regional differences: children in Kehl (median: 6.1 µg/l) showed somewhat higher As concentrations in comparison to those from Mannheim (4.9 µg/l), Stuttgart (4.1 µg/l), and Aulendorf/Bad Waldsee (4.4 µg/l). Similarly, Turkish children were found to have somewhat higher AS levels (5.4 µg/l) than German children (4.5 µg/l). Consumption of fish during the 2 preceding days represents the factor influencing the As concentration in urine most strongly (Table 1). No temporal trend in the As concentration in urine could be observed over the last year.

In the GerES IV pilot study As concentrations in urine were between 0.6 and 57.3 µg/l (median: 4.8 µg/l), based on 252 children studied (6-12 years). Both fish consumption during the preceding sampling and frequent fish consumption during the 4 weeks preceding sampling led to higher excretion of As via urine. Compared to the results of GerES II (1990/92) (median: 7.0 µg/l) there seems to be a decrease of As levels in children's urine.

Lead in blood

The lead content of blood was <12.5 to 181 µg/l (median: 20.7 µg/l) for the 430 children studied in Baden-Württemberg (Table 1). Levels in boys were similar to those in girls (20.9/20.5 µg/l). If data are stratified according to living area, nationality, and passive smoking, no influence of these parameters can be detected.

In the GerES IV pilot study the blood lead content of 234 children were fond to be between 7 and 105 µg/l with a median of 24 µg/l (Table 1). Compared to the results of GerES II

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(1990/92) (median 33 µg/l) there is a marked decrease of the mean blood lead content of children.

Table 1:

Arsenic and metals in blood and urine (µg/l) of children

Analyte	Study	Age	N	n<LQ	50thP.	95thP.	GM	CI-GM	CI-95thPP
Arsenic in urine									
	Baden-Württemberg 2002/03								
	Total	9-11 y.	508	0	4.6	19.4	4.5	4.2-4.8	**13.2-16.5***
	No fish consumption during preceding 48 h		428	0	4.4	13.4	4.31	4.0-4.6	
	Fish consumption during preceding 48 h		62	0	7.8	39.6	9.21	7.6-11.2	
	GerES IV Pilot study 2001/02								
	Total	6-12 y.	252	5	4.8	13.9	4.63	4.21-5.10	**12.1-16.8***
	No fish consumption during preceding 48 h		197	5	4.5	11.4	4.09	3.67-4.55	
	Fish consumption during preceding 48 h		46	0	7.0	34.3	7.55	6.21-9.91	
Lead in blood									
	Baden-Württemberg 2002/03								
	Total	9-11 y.	430	42	20.7	37.9	20.3	19.6-21.0	**37.2-41.5***
	GerES IV Pilot study 2001/02								
	Total	6-12 y.	234	2	24	52	24.0	22.6-25.5	**46-55***
Cadmium in blood									
	Baden-Württemberg 2002/03								
	Non-smokers	9-11 y.	430	43	0.25	0.49		0.24-0.26	**0.46-0.51***
	GerES IV Pilot study 2001/02								
	Non-smokers	6-12 y.	231	128	<0.12	0.32	<0.12	/	**0.23-0.38****
Cadmium in urine									
	GerES IV Pilot study 2001/02								
	Non-smokers	6-12 y.	248	74	0.10	0.38	0.087	0.077-0.099	**0.31-0.45****
Mercury in blood									
	GerES IV Pilot study 2001/02								
	Total	6-12 y.	233	73	0.20	1.00	0.25	0.23-0.28	**0.6-1.0****
	Fish consumption up to max. 3 times per month		166	58	0.20	0.8	0.22	0.20-0.25	
	Fish consumption more than 3-mal per month		67	15	0.30	1.56	0.33	0.26-0.40	
Mercury in urine									
	Baden-Württemberg 2002/03								
	Total	9-11 y.	510	330	< 0.2	1.2	0.18	0.17-0.19	**0.40-0.49***
	Without amalgam fillings		406	264	< 0.2	0.55	0.15	0.14-0.16	
	With amalgam fillings		66	0	0.4	3.70	0.46	0.35-0.61	
	GerES IV Pilot study 2001/02								
	Total	6-12 y.	252	46	0.2	0.8	0.17	0.15-0.20	**0.40-0.77****
	Without amalgam fillings		216	41	0.2	0.6	0.15	0.14-0.17	
	With amalgam fillings		33	4	0.4	2.6	0.39	0.26-0.58	

N = number of samples; n < LQ = number of values below LQ; (LQ = Limit of quantification; Values < LQ were set to LQ/2); 50thP., 95thP. = Percentiles of frequency distribution; GM = geometric mean value; CI-GM = Confidence interval of GM, CI-95th PP. = 95%-Confidence interval of 95th Population percentile;
/ = cannot be calculated in a meaningful way
* = parametric procedure
** = bootstrapping procedure

These data demonstrate the generally observed decrease of the internal lead exposure of the population over the last decade. Consequently, the currently existing reference value is lowered.

Cadmium in blood

The cadmium content of blood was between <0.15 and 3.1 µg/l (median: 0.25 µg/l) for the 430 children studied in Baden-Württemberg (Table 1). In adults, the cadmium blood content is mainly determined by the smoking status [4]. Children from smoking homes did not show higher blood Cd content than those from non-smoking homes. No significant change in Cd blood content could be observed over the last 10 years.

In the GerES IV pilot study Cd blood levels were between 0.12 and 1.99 µg/l (median: <0.12 µg/l) for 231 non-smoking children (Table 1). Since no change in Cd blood content of children could be observed over the last 10 years, the currently existing reference value is confirmed.

Cadmium in urine

In the GerES IV pilot study the cadmium contents in urine were between 0.05 and 0.89 µg/l in 248 non-smoking children (median: 0.1 µg/l) (Table 1). Compared to GerES II (1990/92) change in cadmium urine content could not be established with certainty. Consequently, the currently existing reference value is kept. In the “Sentinel Health Departments in Baden-Württemberg” project the cadmium content of urine has not been determined.

Mercury in blood

In the GerES IV pilot study mercury blood levels were between 0.2 and 2.3 µg/l with a median of 0.2 µg/l) for 233 children (Table 1). Compared to the levels observed in GerES II (1990/92) (median: 0.4 µg/l) there is a marked decrease of mercury blood levels even for children. Consequently, the currently existing reference value has been lowered.

Mercury in urine

The mercury concentrations in urine were found to be between <0.2 and 8.2 µg/l (median: <0.2 µg/l) in 510 children studied in Baden-Württemberg (Table 1). The levels increased with increasing number of teeth with amalgam fillings (Table 1). Compared to earlier study years of the “Sentinel Health Departments” programme (1992/93 to 2000/01) there was a decrease in mercury urine levels even for children without teeth with amalgam fillings; today, 65% of the samples exhibit levels below 0.2 µg/l, which is the limit of quantification.

In the GerES IV pilot study mercury urine concentrations were between 0.1 and 8.1 µg/l with a median of 0.2 µg/l, for 252 children studied (Table 1). Amalgam fillings in teeth represent the most important factor influencing the mercury urine content [5]. Compared to the results of GerES II (1990/92) (median: 0.5 µg/l) there is a marked decrease of the mercury content in urine for children [2] as well.

These data show that the internal mercury exposure of children has decreased during the last ten years. Consequently, the currently existing reference value is reduced.

Reference values

The reference value is defined as the 95th percentile of the distribution of concentrations of a specific compound in a body fluid of a reference population [1]. It is estimated based on the 95% confidence interval of the 95th percentile and is given as a rounded figure, if possible.

Based on the 2002/03 part of the "Sentinel Health Departments in Baden-Württemberg" programme [7] and the GerES IV pilot study, and taking into account the resulting 95% confidence intervals of the 95th percentiles (Table 1) the reference values for lead in blood, and mercury in blood and urine of children in Germany are lowered. For arsenic in children's urine reference values are derived for the first time. Since no change in cadmium levels in blood and urine could be detected in comparison to earlier studies, the currently existing reference values are confirmed. As soon as the data of GerES IV (2003/06) will become available, it will be possible to present reference values for 3- to 14-year-old children in Germany.

The following reference values are lowered:

- **Lead in whole blood** from 60 µg/l to **50 µg/l**[1] **for children** (6 to 12 years),
- **Mercury in whole blood**
  from 1.5 µg/l to **1.0 µg/l**[1] **for children** (6 to 12 years) consuming **fish up to three times per month**,
- **Mercury in urine**
  from 1.4 µg/l to **0.7 µg/l**[1,2] **for children** (6 to 12 years) **without** teeth with amalgam fillings.

[1] An analytical uncertainty of ± 20 % has to be taken into account when using the reference values.
[2] Urine samples with creatinine contents <0.3 or >3.0 g/l are excluded.

The following reference value is established for the first time:

- **Arsenic in urine**

  15 µg/l[2] for children (6 to 12 years) **without** fish consumption 2 days before sampling of urine.

The following reference values are confirmed:

- **Cadmium in whole blood**
  0.5 µg/l[1] for **non-smoking children** (6 to 12 years)
- **Cadmium in urine**
  0.5 µg/l[1,2] for **non-smoking children** (6 to 12 years)

The current reference values are given in Table 2.

Table 2:

Reference values for arsenic, lead, cadmium and mercury in blood and/or urine of children

Analyte and sample material	Population group / Age	Reference year[a)]	Reference value [b)]
Arsenic in urine	Children (6 to 12 years) without fish consumption during preceding 48 h before sampling	2001/2003	**15 µg/l**
Lead in whole blood	Children (6 to 12 years)	2001/2003	**50 µg/l**
Cadmium in whole blood	Non-smoking children (6 to 12 years)	2001/2002	**0.5 µg/l**
Cadmium in urine	Non-smoking children (6 to 12 years)	2001/2002	**0.5 µg/l**
Mercury in whole blood	Children (6 to 12 years) Fish consumption up to max. 3 times per month	2001/2002	**1.0 µg/l**
Mercury in urine	Children (6 to 12 years) Without amalgam fillings in teeth	2001/2003	**0.7 µg/l**

[a)] Years in which the study was conducted
[b)] When applying the current reference values an analytical uncertainty of ± 20 % has to be considered.

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[1] An analytical uncertainty of ± 20 % has to be taken into account when using the reference values.
[2] Urine samples with creatinine contents <0.3 or >3.0 g/l are excluded.

When using the reference values given an analytical uncertainty of ± 20 % has to be taken into account as shown in the round robin tests of the occupational and environmental medical and toxicological analyses by the German Society for Occupational and Environmental Medicine (DGAUM). Further information with regard to the analytical determination of element concentrations in blood or urine can be found in the respective monographs [3, 4, 5, 13]. More fundamental information is contained in a position paper on quality assurance in human biomonitoring [14].

It has to be emphasised that reference values are statistically derives values that indicate the upper limit of the current background concentration. They can be used as criteria to classify the values observed in individuals or groups of persons as being "elevated" or "not elevated". The use of reference values to assess a given exposure situation from an environmental medicine or toxicology viewpoint is not possible.

Measures in case of exceeded reference values

If a reference value has been found to be exceeded, the measurements should be repeated for control. In case a reference value for urine is exceeded care should be taken in repeating the measurement that the urine is diluted in a normal way, i.e. that it exhibits a creatinine content between 0.5 and 2.5 g/l. If reliable (checked several times) measurement results show a value above the reference value, they should induce an environmental medicine-based search for sources. Such search should be carried out in a proportionate way. The following sources of the different analytes should be considered:

Arsenic [13]

When checking the arsenic content observed in urine, this should be done at the earliest after 3 days have elapsed without consumption of fish and shellfish. The following sources other than fish and shellfish may be taken into account: local supply of drinking water containing arsenic, mineral water, also for medical treatment, arsenic-containing drugs, or uptake of As-containing dust or soil, e.g. from industrial waste.

Lead [3]

The lead content in blood can be elevated by uptake of lead-containing drinking water (if lines in the building are still made of lead); frequent eating of acid food from dishes with lead-containing glaze or hot drinks from ceramics; but also dropping molten lead into cold water[3], and shooting with lead-containing ammunition, and the uptake of dust or soil contaminated with lead (industrial waste).

Cadmium [4]

The cadmium content of blood can be elevated from the uptake of food, active tobacco smoking or of cadmium-containing dust and soil from industrial waste.

The cadmium content of urine can be elevated from the uptake of food, active tobacco smoking and cadmium-containing dust and soil e.g. from industrial waste.

Mercury [5]

The mercury content of blood[4] can be elevated by frequent consumption of fish and seafood (both crustaceans and molluscs), uptake of mercury vapours in the home due to broken clinical thermometer containing liquid mercury, or mercury-containing drugs.

The mercury content of urine[5] can be elevated when teeth have amalgam fillings, by frequent consumption of fish and seafood (both crustaceans and molluscs), and by the uptake of mercury vapours in the home due to broken clinical thermometer containing liquid mercury, or mercury-containing drugs and bleaching ointments.

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[3] New Year's Eve custom in Germany of telling fortunes by the shapes made by molten lead dropped into cold water.

[4] The determination of Hg in blood permits the evaluation of the internal exposure resulting from organic and inorganic Hg.

[5] The determination of Hg in urine permits the evaluation of the internal exposure resulting from inorganic Hg.

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