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Reference ranges for key biomarkers of chemical exposure within the UK population

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ABSTRACT

Human biomonitoring (HBM) is a widely accepted tool to aid assessment of chemical uptake in risk assessment. However, our understanding of the biological relevance of the results of HBM can be restricted, due in some part to the limited information on background environmental exposures and biomarker concentrations in the general population.

The study described here specifically addresses the question of what constitutes normal background levels in the UK population of a number of biomarkers (the chemical itself or one of its stable metabolites) for a variety of environmental chemicals that are frequently encountered because of their widespread use. The environmental chemicals selected for this study were benzene, chlorinated hydrocarbons, dithiocarbamates, cadmium, mercury, naphthalene, diethylhexyl phthalate, synthetic pyrethroids and xylene.

Volunteers ($n = 436$) were randomly sought by a postal survey based on the UK Electoral Register. Participants were asked to complete a questionnaire and provide a urine sample. The overall response rate was 7.5%, with volunteers being recruited from all areas of the UK including, England, Scotland, Wales and Northern Ireland. Study participants were adults and comprised 45% male and 55% females.

We have conducted a simple, postal-based, cost-effective study and generated similar reference values to very large surveys such as NHANES. This demonstrates that large investigations may not be necessary to get a reasonable idea of environmental exposures, especially in initial 'screening-type' investigations to identify particular exposures of concern or to demonstrate that exposures are reassuring low and that no further survey data needs to be gathered.

Introduction

The general population is exposed to a variety of natural and man-made chemicals present in air, food, water and consumer products, at home and at work. For public health reasons, it is important to determine the extent of exposure to identify the risks and where risk management procedures may be required.

Human biological monitoring (HBM) is a widely acknowledged tool for measurement of chemical exposure. The presence of chemicals and metabolites in body fluids reflects an individual's actual systemic exposure to a chemical agent from all potential routes of exposure (i.e. inhalation, ingestion, and dermal uptake). Biomarkers play an important role in determining exposure to chemicals and have been used widely in epidemiological studies looking at the health effects of exposure to chemicals in both occupational and environmental settings.

Several countries undertake national biomonitoring programmes to characterise exposures to environmental pollutants; to identify trends and susceptible populations; to detect emerging chemical risks and evaluate risk reduction strategies (Angerer et al., 2006). In the US, the Centres for Disease Control and Prevention (CDC) provide biomonitoring data for the large scale National Health and Nutrition Examination Survey (NHANES – CDC, 2009). In Germany, the Commission on Human Biomonitoring is responsible for setting reference values based on studies of the German population and data collected by the German Environmental Surveys (GerES I–III, IV studies children only – GerES, 2002; Schulz et al., 2007, 2011). The UK does not have a national biomonitoring programme and there is a lack of information on background levels of biomarkers in the general UK population (White and Sabbioni (1998) published reference ranges for 13 trace elements).

Reference values (RVs) are statistically derived numbers that indicate the upper margin of background exposure to a given substance in a defined population at a given time (Schulz et al., 2007). Well-established biomarker reference ranges provide a baseline to assess temporal changes in exposure, patterns of use and the effectiveness of exposure reduction interventions. More recently in the UK, the extent to which the general public are exposed to pesticides, fungicides and chemicals found in household and personal care products has become a concern to the

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Table 1
Analytical methods.

Biomarker	Method	CV	LOD	QA
Metals				
Cadmium	Direct nebulisation ICP-MS	5%	1 nM	G-EQUAS
Mercury	Direct nebulisation ICP-MS	5%	1 nM	G-EQUAS
Pesticides				
Pyrethroids (3-PBA, *cis*Cl_2CA, *trans*Cl_2CA, Br_2CA, ClF_3CA)	GC–MS (NCI)	20%	0.5 nM	G-EQUAS
ETU	APCI + LC–MS	18%	0.3 nM	In house
Solvents				
MHA	HPLC-UV	5%	10 μM	G-EQUAS
S-PMA	Enzyme-linked immunoassay	8%	5 nM	G-EQUAS
TCAA	EI-LC–MS-MS	15%	3 nM	G-EQUAS
Others				
DEHP (5-MEHHP, 5-MEOHP)	EI-LC–MS-MS	14%	7 nM	G-EQUAS
Naphthalene (1-naphthol, 2-naphthol)	HPLC-UV	20%	10 nM	In house
Creatinine	Automated alkaline picrate method	2.5%	0.2 mM	RIQAS

RIQAS (www.randox.com); G-EQUAS (www.g-equas.de); CV – inter-assay coefficient of variation LOD – limit of detection; QA – quality assurance scheme.

general public and those involved in public health (Levy et al., 2007; Wolff et al., 2007). Determining the extent of exposure to such chemicals (reference ranges) is important to identify if and when potential health risks from exposure are likely to be of concern (Pirkle et al., 2005). However, there remains a dearth of information on background levels of biomarkers in the UK general population, as the majority of biomarker studies have been conducted to look at high-level, often occupational, exposures and have only examined small control groups for background exposures.

The substances included in this study, for which reference values have been derived, were chosen based on the availability of validated analytical methods for biomarkers in urine and to reflect potential environmental exposure to a range of toxic organic and inorganic substances. The substances are of both anthropogenic and natural origin, and include metals, plasticisers, pesticides and commonly used solvents.

The data presented in this report aims to establish the background levels of a range of biomarkers in urine from the general UK population, some for the first time. This will provide valuable information on the background exposure of the general UK population to a range of common chemicals and act as a baseline for future studies.

Method

Approval for the study was granted by the Central Manchester Local Research Ethics Committee (REC Ref. 05/Q1407/93). The storage and retention of personally identifiable data was carried out in accordance with the Data Protection Act, 1998.

The population studied were volunteers from the UK general adult population who were randomly selected from the UK Electoral Register as described in Levy et al. (2007). Invitations were sent out by post over the course of a year. On completion of a signed consent form, participants were supplied with a study pack and returned, by post, a urine sample and a completed questionnaire relating to demographic details and workplace/lifestyle factors that may have influence on the biomarkers measured. It was calculated that 400 volunteers were required to obtain a representative sample of the UK population and to produce a sufficient number to determine a reliable reference value for the 15 biomarkers (Levy et al., 2007).

Analytical methods

Analysis of the 15 urinary metabolites was performed using a number of analytical procedures as detailed in Table 1. Biomarkers of a range of metals, pesticides and solvents were chosen as well as a common plasticiser and naphthalene. The metabolites of pyrethroid pesticides analysed were 3-phenoxybenzoic acid (3-PBA, generic pyrethroid biomarker), cis and trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylic acid (cis and trans-Cl_2CA, specific biomarker for permethrin and cypermethrin), *cis*-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid (Br_2CA, specific biomarker for deltamethrin) and chlorotrifluorovinylcyclopropanecarboxylic acid (ClF_3CA, specific biomarker for bifenthrin and cyhalothrin). Ethylenethiourea (ETU) was analysed as a generic metabolite of ethylenebisdithiocarbamate fungicides (such as maneb, mancozeb, zineb and nabam). Solvent biomarkers included methylhippuric acid (MHA) for xylene, S-phenylmercapturic acid (SPMA) for benzene and trichloroacetic acid (TCAA) for trichloroethylene. The biomarkers chosen for diethylhexyl phthalate exposure were the secondary metabolites mono(2-ethyl-5-oxohexyl)phthalate (5-MEOHP) and mono(2-ethyl5-hydroxyhexyl) phthalate (5-MEHHP). Creatinine was measured as a possible means of adjusting analyte concentrations for dilution effects.

All assays used in the study were sensitive, robust and reproducible, with coefficients of variation (CV) below 20%. All analyses were carried out by an ISO9001: 2008 accredited laboratory, operating rigorous internal quality control, and participating in External Quality Assurance Schemes where available.

Statistical analysis

Urine samples with creatinine concentrations <0.3 or >3.0 g/L were excluded from statistical analysis (ACGIH, 2010; DFG, 2010; Cocker et al., 2011).

For creatinine and each of the 15 chemical biomarkers, the distribution of raw, creatinine-corrected, Ln-transformed creatinine-corrected and Box-Cox transformed creatinine-corrected data (data not shown but fully available at: http://www.cranfield.ac.uk/health/researchareas/environmenthealth/ieh/page19562.html) were assessed visually and using Q–Q plots (data not shown but fully available at: http://www.cranfield.ac.uk/health/researchareas/environmenthealth/ieh/page19562.html).

Results

Sample population

Over five thousand invitations were issued. Of the 436 individuals (response rate 7.5%) who completed the questionnaire and returned a urine sample, 55% (240) were women and 45% (196) men. Just over half of respondents (59%) were in the mid-age

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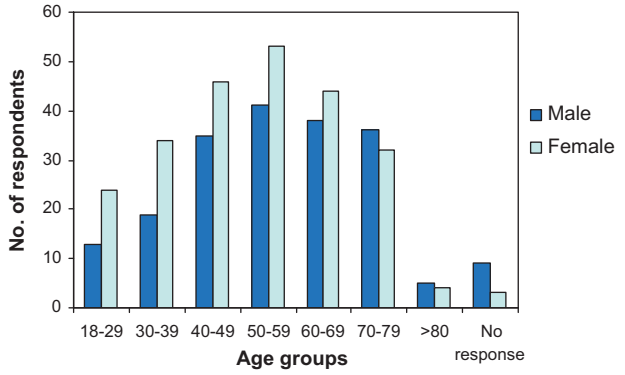

Fig. 1. Age-gender distribution of study participants ($n = 436$).

categories (40–69 years). Although men were less likely to take part in the study, male participants were recruited in all age categories and dominated the oldest age groups (Fig. 1).

A total of 422 (97%) of the participants described their ethnic origin as White, 8 (2%) as Black or Black British, 5 (1%) as Asian or Asian British, and one as other ethnic origin. Participants were recruited from around the UK, with the lowest responses from Northern Ireland and Wales (Fig. 2).

Individuals were most likely to live in suburban areas (57%, $n = 250$), with 31% ($n = 136$) of participants describing where they live as rural, and 12% ($n = 50$) living in a city environment. Twenty-five percent ($n = 109$) of all respondents had an integral garage although only half of this proportion used the garage to store a car.

Biomarkers

A total of 15 biomarkers of chemical exposure, relating to 9 different chemicals or chemical groups were analysed in urine samples from 436 volunteers. Frequency distribution graphs of raw data were clearly skewed to the left for all biomarkers, which can be explained in part by the large number of non-detectable values in many of the biomarker datasets. Table 2 summarises the number of samples analysed and the number of samples that were below the LOD, for each biomarker. Only cadmium, 2-naphthol and the DEHP metabolite 5-MEOHP were detectable in urine from more than 90% of participants, whilst mercury, 3-PBA and 5OH-MEHP were detectable in more than 80% of urine samples. Some other biomarkers (Br_2CA, ClF_3CA, ETU, MHA, TCAA) were detectable in urine from fewer than 50% of the participants.

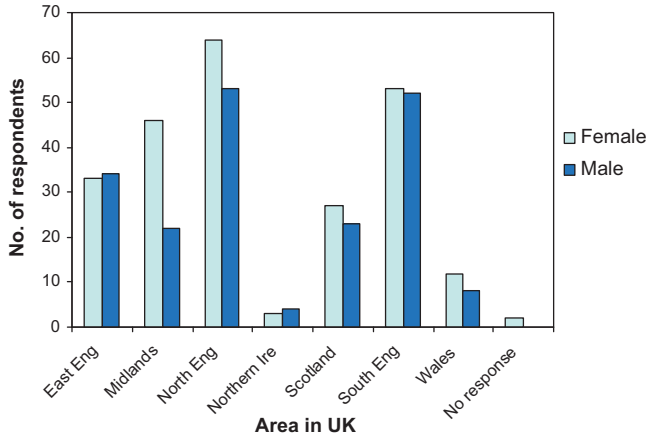

Fig. 2. Distribution of male and female study participants ($n = 436$) by UK region.

Table 2
Summary of the number of samples analysed (N) for each biomarker and the proportion of samples that contained biomarker levels below the LOD.

Biomarker	*N*	*N*[a]	*N*[a] < LOD	% <LOD[a]
Metals				
Cadmium	435	362	9	2
Mercury	435	362	50	14
Pesticides				
Pyrethroids				
3-PBA	405	336	43	13
cisCl_2CA	405	336	156	46
transCl_2CA	404	335	114	34
Br_2CA	405	336	169	50
ClF_3CA	116[b]	92	54	59
ETU	434	361	194	54
Solvents				
MHA	433	360	223	62
S-PMA	426	355	134	38
TCAA	397	330	208	63
Others				
DEHP				
5-MEHHP	402	337	37	11
5-MEOHP	401	337	4	1
Naphthalene				
1-Naphthol	356	298	127	43
2-Naphthol	356	298	1	0.3
Creatinine	436	363	–	–

[a] Within accepted limits for urinary creatinine (between 0.3 and 3.0 g/l).
[b] Sample number low due to technical difficulties with method.

Reference values

The biomarker data from the study of 15 urinary metabolites analysed in this survey of over 400 random, adult volunteers from the UK is presented in Table 3. The analytical methods in this study are sensitive and specific but environmental exposures are low and although the percentage of samples above the limit of detection

Table 3
Reference values of biomarkers in urine of the general adult (>18 years) UK population.

Biomarker	Reference value[a]			
	Creatinine corrected		No correction applied	
	μg/g creatinine	μmol/mol creatinine	μg/l	nmol/l
Metals				
Cadmium	0.9	0.9	0.9	7.9
Mercury	2.8	1.6	3.0	15.0
Pesticides				
Pyrethroids				
3PBA	4.3	2.3	6.1	28.3
cisCl_2CA	0.7	0.4	0.8	3.8
transCl_2CA	1.8	1.0	1.6	7.7
Br_2CA	1.3	0.5	1.6	5.3
Cl_3FCA	1.8	0.8	3.2	10.7
Total Cl_2CA	2.3	1.2	2.5	10.4
ETU	5.2	5.8	4.9	48.0
Solvents				
MHA	94.7[b]	55.4[c]	84.9[d]	440.0[e]
S-PMA	7.0	3.3	9.1	38.0
TCAA	8.7	6.0	8.1	49.6
Others				
DEHP				
5-MEHHP	42.3	15.9	42.9	146.0
5-MEOHP	66.5	25.8	67.2	230.0
Naphthalene				
1-Naphthol	15.2	12.0	15.6	108.0
2-Naphthol	9.6	7.6	11.7	81.0

[a] Derived from 95th percentile value for each biomarker.
[b] mg/g creatinine.
[c] mmol/mol creatinine.
[d] mg/l.
[e] μmol/l.

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Table 4
Comparison with other large national BM surveys.

Biomarker	Reference value (μg/g creatinine)			
	UK (this study)	US NHANES (Year)	Germany (GerES)	Other
Metals				
Cadmium	0.9	1.05 (2007/08) *N* = 1857	0.7 (1998) *N* = 4728	
Mercury	2.8	2.56 (2007/08) *N* = 1861	2.0 (1998) *N* = 4730	
Pesticides				
Pyrethroids				
3PBA	4.3	3.2 (01/02) *N* = 1128		~2 German HBM
cisCl_2CA	0.7	0.9 (01/02) *N* = 1128		~1 (1998) German HBM
transCl_2CA	1.8	2.6 (01/02) *N* = 1123		~2 (1998) German HBM
Br_2CA	1.3	<0.1 (01/02) *N* = 1128		
Cl_3FCA	1.8	NA		
Total Cl_2CA	2.3	NA		
ETU	5.2			4.5–5.0 Colosio et al. (2006) *N* = 95
Solvents				
MHA	94.7[a]			
S-PMA	7.0			
TCAA	8.7			
Others				
DEHP				
5-MEHHP	42.3	164 (07/08) *N* = 1814		~220 (2002) German HBM
5-MEOHP	66.5	87.4 (07/08) *N* = 1814		~150 (2002) German HBM
Naphthalene				
1-Naphthol	15.2	24.2 (03/04) *N* = 1528		
2-Naphthol	9.6	21.8 (03/04) *N* = 1515		

[a] Units are mg/g.

(LOD) is high for some metabolites or substances such as cadmium and mercury, it is far less so for other metabolites analysed such as ETU and MHA. A common approach in these circumstances is to substitute a value of half the LOD but this can affect some of the statistics used to describe the data, especially when the percentage of results below the LOD is significant. We have therefore confined the statistical analysis to a simple derivation of the 95% value, which is not affected and stated the number of results less than the LOD.

Comparison to other surveys

This current study was in part to investigate whether a simple, postal-based cost-effective approach could be used to develop reference values for a large number of environmental chemical substances and the modest number of around 400 random samples was selected based upon a power calculation (Levy et al., 2007). It is thus of particular interest to see how some of the results of the current study compare to those found in larger national surveys for the same substances. This comparison is presented in Table 4 below.

Discussion

This study has successfully recruited sufficient participants using a postal-based method. Overall, the data and the proposed RVs for the UK population are in good agreement with other, much larger, surveys already mentioned (NHANES, GerES). As noted in our pilot study (Levy et al., 2007) and elsewhere (Leira et al., 2005), women and older people were more likely to participate than men and younger people (Fig. 1) however this was not enough to skew the data from that found in more controlled, stratified surveys. The levels of metabolites for naphthalene (1- and 2-Naphthol) and phthalates (5-MEHHP and 5-MEOHP) found in our study are lower than those found in NHANES. Levels of 1- and 2-naphthol in NHANES are similar to those found in smaller studies in Germany (Preuss et al., 2005; Wilhelm et al., 2008) but much lower than those in an earlier study of US adults in 1995 which found 95th percentiles of 43 μg/l and 30 μg/l, respectively from 977 subjects (Hill et al., 1995). Environmental exposure to naphthalene may come from cigarette smoke, incomplete combustion of fuels and some pesticides such as carbaryl although carbaryl is no longer registered for use in Europe. Similar differences are seen for the

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metabolites of DEHP with the German HBM values for 2002 being greater than the later NHANES, perhaps reflecting substitution of DEHP with other phthalates. The lower levels found in our study for both naphthalene and phthalates may simply reflect different environmental exposures and changes in exposure over time. The strengths and weaknesses of using this postal methodology for establishing background data for large numbers of environmental chemicals on a cost-effective basis using either urine or blood as the matrix need careful consideration. Firstly, we have used a random method of volunteer selection and this has produced a particular distribution from the population of UK adults. If one wishes to have an equal or stratified (e.g. NHANES studies) number of volunteers in each age group, then it would be necessary to send out far more invitation letters until the required number was reached. Other or additional methods of volunteer selection would be required to recruit children. The approach we have used of random selection does make the assumption that exposure to the substance of concern is generally normally distributed in the population (in the air, water, soil, etc.) which of course may not be the case and it may be that targeted sampling by geographical location, particular diet or some other factor that may impinge upon exposure.

As noted in the methodology, we initially undertook a power calculation to determine the number of samples required to provide a reasonable estimate of exposure in the population and to provide sufficient data from which to give reference values. Our estimate of some 400 samples seems to have provided reasonably reliable results and, reassuringly, the RVs shown in Table 4 are remarkably similar to the far larger US and German population surveys. One potential problem in any study or survey of low-level environmental exposure is how one deals statistically with those results below the LOD. For some substances there may be a high proportion of results below the LOD but the same problem can occur with larger surveys as well as the one reported here. We have avoided this potential problem by simply calculating the 95% percentile and stating the number of samples below the LOD.

With any study there may be issues of variations in exposure. This study collected samples over a year and so reflects any seasonal variations in exposure, for example to pesticides. Shorter-term variation in exposure (e.g. intermittent exposures, short half-lives and sample collection times) are also included in the results of this study.

The concentration of biomarkers in urine may vary between individuals due to differences in systemic exposure and metabolism, but also to the hydration state of the individual and volume of urine produced. This variation is most commonly compensated for by expressing the concentration of biomarker as a ratio to the concentration of urinary creatinine. Urine samples with a creatinine concentration of less than 0.3 g/l or greater than 3.0 g/l were flagged as 'Low' or 'High' creatinine, respectively and excluded from the statistical analysis, according to the WHO guidelines for calculating reference limits (Schulz et al., 2007). The validity of carrying out creatinine adjustment is dependent on whether the biomarker is excreted in the same way as creatinine, and for many biomarkers this is not known. As a consequence there is little consensus in published studies whether to report creatinine-corrected values for many of the biomarkers measured here. In this study we present both creatinine-corrected and uncorrected values.

Conclusion

We have conducted a simple, postal-based cost-effective study but generated similar reference values to very large surveys such as NHANES. This demonstrates that large investigations may not be necessary to get a very reasonable idea of environmental exposures, especially in an initial 'screening-type' investigations to identify particular exposures of concern or to demonstrate that exposures are reassuring low and that no further survey data needs to be gathered.

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References

ACGIH, 2010. TLVs and BEIs based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices: ACGIH Cincinnati Ohio, USA. ISBN 978-1-607260-28-8.

Angerer, J., Bird, M.G., Burke, T.A., Doerrer, N.G., Needham, L., Robinson, S.H., Sheldon, L., Zenic, H., 2006. Strategic biomonitoring initiatives: moving the science forward. Toxicol. Sci. 93 (1), 3–10.

CDC, 2009. National Report on Human Exposure to Environmental Chemicals. http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf (last accessed 18.08.11).

Cocker, J., Mason, H.J., Warren, N.D., Cotton, R.J., 2011. Creatinine adjustment of biological monitoring results. Occup. Med. 61 (5), 349–353.

Colosio, C., Visentin, S., Birindelli, S., Campo, L., Fustinoni, S., Mariani, F., Tiramani, M., Tommasini, M., Brambilla, G., Maroni, M., 2006. Reference values for ethylenethiourea in urine in Northern Italy: results of a pilot study. Toxicol. Lett. 162 (2–3), 153–157.

DFG, 2010. Deutsche Forschungsgemeinschaft List of MAK and BAT values 2010. Commission of the Investigation of Health Hazards of Chemical Compounds in the work area Report No. 46. Wiley-VCH Verlag GmbH Weinheim, ISBN 978-30527-32815-4.

GerES, 2002. German Environmental Survey 1998, Vol. III: Human Biomonitoring. Pollutants in Blood and Urine of the German Population. http://www.umweltdaten.de/publikationen/fpdf-l/2104.pdf (last accessed 18.08.11).

Hill, R.H., Head, S.L., Baker, S., Gregg, M., Shealy, D.B., Bailey, S.L., Williams, C.C., Sampson, E.J., Needham, L.L., 1995. Pesticide residues in urine of adults living in the United States: reference range concentrations. Environ. Res. 71, 99–108.

Leira, H.L., Bratt, U., Slåstad, S., 2005. Notified cases of occupational asthma in Norway: exposure and consequences for health and income. Am. J. Ind. Med. 48 (5), 359–364.

Levy, L.S., Jones, K., Cocker, J., Assem, F.L., Capleton, A.C., 2007. Background levels of key biomarkers of chemical exposure within the UK general population – Pilot study. Int. J. Hyg. Environ. Health 210 (3–4), 387–391.

Pirkle, J.L., Osterloh, J., Needham, L.L., Sampson, E.J., 2005. National exposure measurements for decisions to protect public health from environmental exposures. Int. J. Hyg. Environ. Health 208 (1–2), 1–5.

Preuss, R., Drexler, H., Bottcher, M., Wilhelm, M., Bruning, T., Angerer, J., 2005. Current external and internal exposure to naphthalene of workers occupationally exposed to polycyclic aromatic hydrocarbons in different industries. Int. Arch. Occup. Environ. Health 78, 355–362.

Schulz, C., Angerer, J., Ewers, U., Kolossa-Gehring, M., 2007. The German human biomonitoring commission. Int. J. Hyg. Environ. Health 210 (3–4), 372–382.

Schulz, C., Wilhelm, M., Heudorf, U., Kolossa-Gehring, M., 2011. Human Biomonitoring Commission of the German Federal Enviroment Agency. Update of the Reference and HBM values derived by the German Human Biomonitoring Commission. Int. J. Hyg. Environ. Health 215 (1), 26–35.

Wilhelm, M., Hardt, J., Christine, S., Angerer, J., 2008. New reference value and the background exposure for the PAH metabolites 1-hydroxypyrene and 1- and 2-naphthol in urine of the general population in Germany: basis for validation of human biomonitoring data in environmental medicine. Int. J. Hyg. Environ. Health 211, 447–453.

White, M.A., Sabbioni, E., 1998. Trace element reference values in tissues from inhabitants of the European Union. X. A study of 13 elements in blood and urine of a United Kingdom population. Sci. Total Environ. 216 (3), 253–270.

Wolff, M.S., Teitelbaum, S.L., Windham, G., Pinney, S.M., Britton, J.A., Chelimo, C., et al., 2007. Pilot study of urinary biomarkers of phytoestrogens, phthalates, and phenols in girls. Environ. Health Perspect 115, 116–121.

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