International Journal of Hygiene and Environmental Health 216 (2013) 170–174

Contents lists available at SciVerse ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

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

R. Bevan[a,*], K. Jones[b], J. Cocker[b], F.L. Assem[a], L.S. Levy[a]

[a] Institute of Environment and Health, Cranfield University, Cranfield, Bedfordshire MK43 0AL, UK
[b] Health and Safety Laboratory, Harpur Hill, Buxton, Derbyshire, UK

ARTICLE INFO

Article history:
Received 1 December 2011
Received in revised form 3 March 2012
Accepted 8 March 2012

Keywords:
Human biomonitoring
Urine
Environmental exposure
Postal survey
UK population
Reference range

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

* Corresponding author. Tel.: +44 1234758279; fax: +44 12347578517.
E-mail address: r.bevan@cranfield.ac.uk (R. Bevan).

1438-4639/$ – see front matter © 2012 Elsevier GmbH. All rights reserved.
doi:10.1016/j.ijheh.2012.03.005

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