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EUROPEAN ENVIRONMENT AND HEALTH PROCESS

Human biomonitoring:

facts and figures

Abstract

This report summarizes the available human biomonitoring (HBM) data in the WHO European Region with a focus on children's exposures. It is intended to support the evaluation of the status of Parma Declaration commitments under the Regional Priority Goal 4, "Preventing disease arising from chemical, biological and physical environments" and the commitment to "…develop a consistent and rational approach to human biomonitoring as a complementary tool to assist evidence-based public health and environmental measures…". The report provides background information on the principles and applications of HBM, summarizes results of recently conducted international and national surveys and research projects, provides summaries of temporal trends and spatial patterns for specific pollutants, and outlines major accomplishments, data gaps and priority environmental health issues based on the analyses of HBM data.

Keywords
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Contents

List of tables

List of figures

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Abbreviations

1-OH-P	1-hydroxypyrene
2cx-MMHP	mono-[2-(carboxymethyl)hexyl]phthalate
5cx-MEPP	mono(2-ethyl-5-carboxypentyl)phthalate
α-HCH	alpha-hexachlorocyclohexane
ADHD	attention deficit hyperactivity disorder
ADI	acceptable daily intake
ADME	absorption, metabolism, distribution and elimination
ALARP	as low as is reasonably practicable
ALSPAC	Avon Longitudinal Study of Parents and Children
ApoE4	apolipoprotein E-e4
As	arsenic
As (III)	arsenious acid (arsenite)
As (V)	arsenic acid (arsenate)
ATSDR	Agency for Toxic Substances and Diseases Registry
β-HCH	beta-hexachlorocyclohexane
BBzP	butyl benzyl phthalate
BE	biomonitoring equivalents
BFR	brominated flame retardants
BMUB	Bundesministerium für Umwelt, Naturschutz, Bau und Reaktorsicherheit (German: Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety)
BPA	bisphenol A
CAL REL	California Acute Reference Exposure Level
CAPI	computer-assisted personalized interviews
Cd	cadmium
CDC	Centers for Disease Control and Prevention
CIOMS	Council for International Organizations of Medical Sciences
COO	carboxylate
COPHES	Consortium to Perform Human biomonitoring survey on a European Scale
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
CROME	Cross-Mediterranean Environment and Health Network
CRP	C-reactive protein
CVAAS	cold vapour atomic absorption spectrometry
CYP1A1	cytochrome P450, family 1, subfamily A, polypeptide 1
CYP2E1	cytochrome P450, family 2, subfamily E, polypeptide 1

CZ-HBM	Czech Republic, the Human Biomonitoring Project
DAP	dialkyl phosphate
DDD	dichlorodiphenyldichloroethane
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
DEHP	di(2-ethylhexyl) phthalate
DEMOCOPHES	DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale
DEP	diethyl phthalate
DETP	diethyl thiophosphate
DiBP	di-iso-butyl phthalate
DiDP	di-iso-decyl phthalate
DiNP	di-iso-nonyl phthalate
DMA	dimethylarsinic acid
DMDTP	dimethyl dithiophosphate
DMP	dimethyl phthalate
DMTP	dimethylthiophosphate
DNA	deoxyribonucleic acid
DnBP	di-n-butyl phthalate
DNEL	derived no-effect level
DPHP	di(2-propylheptyl) phthalate
DPP	dipentyl phthalate
EC	European Commission
ECA	Norway's Environment and Childhood Asthma study
ECEH	WHO European Centre for Environment and Health
ECF	exposure conversion factors
EDC	endocrine disrupting chemical
EFSA	European Food Safety Authority
ELFE	Etude Longitudinale Française depuis l'Enfance (French: French Longitudinal Study of Children)
ELISA	enzyme-linked immunosorbent assay
EMR	electromagnetic radiation
ENNS	Étude nationale nutrition santé (French: National Nutrition and Health Survey)
EPA	Environmental Protection Agency, United States of America
EQAS	external quality assessment scheme
ERK	extracellular signal-regulated kinase
ESB	Environmental Specimen Bank of Germany
ESL	effects screening levels
ETS	environmental tobacco smoke
EU	European Union
EXHES	Exposure and Health Examination Survey

F	female
FAO	Food and Agriculture Organization of the United Nations
FLEHS	Flemish Environment and Health Study
FSU	former Soviet Union
γ-HCH	gamma-hexachlorocyclohexane
GC-MS	gas chromatography-mass spectrometry
GC-HRMS	gas chromatography-high resolution mass spectrometry
GDP	gross domestic product
GEMS/Food	Global Environment Monitoring System—Food Contamination Monitoring and Assessment Programme
GerES	German Environmental Survey
GM	geometric mean
GRO-alpha	growth related oncogene-alpha
Hb	hemoglobin
HBM	human biomonitoring
Hg	mercury
IARC	International Agency for Research on Cancer
ICH	International Conference on Harmonisation
ICI	interlaboratory comparison investigations
ICP-MS	inductively-coupled plasma mass spectrometry
IL-1β	interleukin-1 beta
INMA	Infancia y Medio Ambiente (Spanish:project on children and environment of the Spanish Environment and Childhood Research Network)
InVS	Institut de Veille Sanitaire (French: Institute for Public Health Surveillance)
IPCS	International Programme on Chemical Safety
IUPAC	International Union of Pure and Applied Chemistry
JECFA	Joint FAO/ WHO Expert Committee on Food Additives
LC/MS	liquid chromatography–mass spectrometry
LC-TOF-MS	Liquid chromatography time-of-flight mass spectrometry
LH	luteinizing hormone
LLE	liquid-liquid extraction
LOAEL	lowest-observed-adverse-effect level
LOD	limit of detection
LOQ	limit of quantitation
LPME	liquid-phase microextraction
M	male
MAE	microwave-assisted extraction
MBP	monobutyl phthalate
MBzP	monobenzyl phthalate
MCP-1	monocyte chemoattractant protein-1

MED	median
MEHHP	mono-(2-ethyl-5-hydroxyhexyl)phthalate
MEHP	mono-(2-ethylhexyl) phthalate
MEOHP	mono-(2-ethyl-5-oxohexyl) phthalate
MEP/mEP	mono-ethyl phthalate
MMA	monomethylarsonic acid
MoBa	Norwegian Mother & Child Cohort Study
MRL	minimal risk level
mRNA	messenger ribonucleic acid
NCHS	National Center for Health Statistics, United States of America
NHANES	National Health and Nutrition Examination Survey, United States of America
NRC	National Research Council, United States of America
OPP	organophosphorus or organophosphate pesticide
PAH	polycyclic aromatic hydrocarbons/polyaromatic hydrocarbons
P90	90th percentile
P95	95th percentile
Pb	lead
PBBs	polybrominated biphenyls
PBBK	physiology based biokinetic (model)
PBDEs	polybrominated diphenyl ethers
BDE 99	2,2',4,4',5-pentabromodiphenyl ether
PBPK	physiology based pharmacokinetic (model)
PBTD	physiology based toxicodynamic (model)
PBTK	physiology based toxicokinetic (model)
PC	polycarbonate
PCBs	polychlorinated biphenils
PCDDs	polychlorinated dibenzodioxins
PCDFs	polychlorinated dibenzofurans
PCOS	polycystic ovary syndrome
PCR	polymerase chain reaction
PELAGIE	Perturbateurs Endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance (French: Endocrine Disruptors: Longitudinal Study on Disorders of Pregnancy, Infertility and Children)
PFC	perfluorinated compound
PFOA	perfluorooctanoic acid/perfluorooctanoate
PFOS	perfluorooctanesulfonic acid/perfluorooctane sulfonate
PIVUS	Sweden Prospective Investigation of the Vasculature in Uppsala Seniors
PK	pharmacokinetics
PLE	pressurized liquid extraction
POP	persistent organic pollutant

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROBE	PROgramma per il Biomonitoraggio dell'Esposizione della popolazione generale (Italian Programme for biomonitoring the general population exposure)
PVC	polyvinyl chloride
QA	quality assurance
QC	quality control
ΣDDT	sum of DDT and its daughter chemicals
ReV	reference value
RfC	reference concentration
RfD	reference dose
ROS	reactive oxygen species
RPG	Regional Prioritiy Goal
RV95	reference HBM value based on the 95th percentile of the biomarker values in the reference (unexposed) population
SAICM	Strategic Approach to International Chemical Management
SBSE	stir-bar sorptive extraction
SCF	European Commission Scientific Committee on Food
SES	socioeconomic status
SFE	supercritical fluid extraction
SOP	standard operating procedures
SPE	solid-phase extraction
S-PMA	S-phenylmercapturic acid
SPME	solid-phase microextraction
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCEQ	Texas Commission on Environmental Quality
TCPy	3,5,6-trichloro-2-pyridinol
TDI	tolerable daily intake
TEF	toxic equivalency factors
TEQ	toxic equivalency quantity
TMAO	trimethylarsine oxide
TNF-alpha	tumour necrosis factor-alpha
TRA	toxicologically relevant arsenic
UBA	Umweltbundesamt (German: Federal Environment Agency)
UNEP	United Nations Environment Programme
USE	ultrasonic extraction
UV	ultraviolet
VOC	volatile organic compounds
y.o.	years old

Executive summary

This report summarizes human biomonitoring (HBM) data in the WHO European Region. The report includes a brief overview of the types of biomarkers, HBM studies and approaches to the interpretation of HBM data, and it presents background information on major environmental pollutants. Assessments of spatial patterns and temporal trends in human exposure are based on national surveys or monitoring programmes conducted during the past 15 years.

Information on metals covers the most important metals and metalloids: mercury (organic and inorganic forms), cadmium, lead and arsenic. The persistent organic pollutants (POPs) section covers dioxins, polychlorinated biphenils (PCBs), polybrominated biphenyl ethers (PBDEs) and organochlorine pesticides, while the non-persistent organic pollutants characterized in this report include non-persistent pesticides and herbicides, bisphenol A (BPA), parabens, phthalates, volatile organic compounds (VOCs) and polyaromatic hydrocarbons (PAHs).

The available data show that exposures to toxic metals remain a serious public health problem. Substantial numbers of European residents have levels of cadmium and lead in excess of national guidance values, such as the HBM-I and HBM-II levels established by the German HBM Commission. In countries with high levels of fish consumption, prenatal exposures to the developmental neurotoxicant, methyl mercury, also frequently exceed levels that are considered safe. The implementation of the global legal instrument on mercury, the Minamata Convention, is expected to alleviate economic losses caused by mercury-induced neurological deficits. Experience from previously conducted international projects shall be utilized to develop a harmonized HBM methodology for assessing temporal trends in exposures and evaluating the effectiveness of the Minamata Convention.

While exposures to most POPs have declined dramatically in most countries following the adoption of the Stockholm Convention on POPs (UNEP, 2011), the levels of dioxins in human milk still exceed the level that can be considered safe for infants. There is a large country-to-country variability in levels of dichlorodiphenyltrichloroethane (DDT) and its metabolites in human milk, with the highest levels observed in low income countries. The most recent available results of the WHO/United Nations Environment Programme (UNEP) Human Milk survey show that exposures to DDT are abnormally high in Tajikistan. At the same time, there are no comparable data on neighbouring countries in central Asia with potentially similar exposure patterns.

While the levels of many phthalates have declined in high income countries following the adoption of national and international regulations aimed at preventing exposures, there is a strong inverse association between national gross domestic product (GDP) per capita and phthalate exposure in the European Union, with the highest levels observed in some new EU Member States with relatively low GDP per capita. The lack of HBM data on phthalates in countries in the eastern part of the Region, with even lower GDP per capita, is an issue of concern.

There is a gap in the HBM data in the eastern part of the European Region where few systematic national surveys have been conducted. The main available source of information on exposures to POPs in some newly independent states is the WHO/UNEP Human Milk survey.

No publicly available data were found for several Member States during a search of major on-line databases. Closing this gap in knowledge in the eastern part of the Region will remain a major challenge requiring the development of standardized approaches suitable for countries with limited resources, as well as efforts aimed at building capacity and promoting international cooperation.

The application of standardized approaches to surveillance will ensure international comparability of HBM data and enhance support to policy actions and targeted interventions through identifying populations with elevated exposure levels and enabling follow-up monitoring to evaluate intervention effectiveness.

1. Introduction

Exposure to environmental pollutants occurs through different routes, such as inhalation, ingestion, and dermal absorption. The amount of pollutant uptake is often termed as the "absorbed dose." Thus, the body burden of a specific pollutant is determined by factors, such as the pollutant's concentration in a specific environmental medium, its physical and chemical properties, and timing of exposure, as well as individual factors, such as uptake, metabolism and excretion rates. Human biomonitoring (HBM) takes into account all these factors by measuring the concentrations of a chemical or its metabolites in human matrices. In contrast, for environmental pollutants with multiple exposure pathways, comprehensive exposure assessment based on environmental data requires quantitation of pollutant levels in multiple media and data on individual behavioural patterns affecting exposure, such as the consumption of contaminated foods.

HBM can be defined as "the method for assessing human exposure to chemicals or their effects by measuring these chemicals, their metabolites or reaction products in human specimens" (CDC, 2005). Biomonitoring involves measurements of biomarkers in bodily fluids, such as blood, urine, saliva, breast milk, sweat, and other specimens, such as faeces, hair, teeth, and nails.

Biomonitoring data directly reflect the total body burden or biological effect resulting from all routes of exposure, and interindividual variability in exposure levels, metabolism and excretion rates. Such data are often the most relevant metric for health impact assessment, especially for bioaccumulating or persistent chemicals that are stored in the body for a long period of time, such as persistent organic pollutants (POPs), lead and cadmium. For chemicals that are excreted rapidly, cross-sectional biomonitoring data reflect recent exposure, while characterization of long-term exposure patterns at the individual level requires repetitive sampling.

For a given chemical, HBM can identify spatial and time trends, lifestyle contributing factors, and specific at-risk groups. HBM is an important tool to support environment and health policy-making because it can provide useful quantitative information regarding the actual exposure of a population to environmental pollutants including emerging ones, as well as data regarding the resulting health effects and/or population susceptibility to these xenobiotic compounds. HBM allows direct and more precise assessment of the distribution of risk in the population, incorporating individual variability in exposure, absorption, metabolism and excretion rates. An ambitious concept, the "exposome," involves the characterization of the totality of exposures to environmental chemicals using prospective, comprehensive HBM surveillance (Rappaport, 2011).

Biomonitoring can also be used in epidemiological studies in combination with health data to demonstrate an association between the body burden of pollutants and their health effects, or to test other research hypotheses. Novel biomonitoring methods are usually tested and validated in research settings. Sustained national and international surveillance programmes typically use well established biomonitoring techniques (e.g. biomarkers which are known to reflect exposure to the chemical of interest, standardized sampling methods and verified analytical techniques) to collect information on population exposures to environmental hazards that are known to be significant to public health.

Biomonitoring, however, usually does not reveal exposure sources and routes. Therefore, environmental monitoring remains crucial for the development of targeted policy actions.

The results of biomonitoring-based surveillance can be presented in the form of environmental public health indicators or simple numerical summary measures of surveillance data, such as the proportion of heavily exposed individuals. Well designed indicators, based on sound surveillance programmes that use standardized methods, can provide valuable information to policy-makers and the public. Findings from the assessment of such indicators can then guide policy action to reduce or prevent adverse health effects in the general population (reviewed in Egorov, Dalbokova & Krzyzanowski, 2013).

The objectives of analysing HBM-based environmental health indicators include: assessing temporal exposure trends and the effectiveness of policy actions, characterizing geographic patterns of exposure, comparing different population subgroups and identifying vulnerable subpopulations. Presenting and interpreting the data in a clear and understandable manner helps to broaden the reach of the information. It also facilitates the use of a common "language," or a more standardized approach, among different sectors involved in environmental public health policy-making. Advantages of using a standardized approach are consistency and comparability of data across various settings.

Infants and children are especially susceptible to adverse health effects of environmental pollutants, such as lead, methylmercury, arsenic, toluene and polychlorinated biphenyls (PCBs), due to their increased exposure levels and absorption rates, and diminished ability to detoxify many exogenous compounds (Grandjean & Landrigan, 2006).

The aims of this report are to: summarize the available HBM data in the European Region, focusing on exposures in children and women of reproductive age; provide information about the baseline situation in the Region; and describe progress towards the goals set in the Parma Declaration as described below (WHO Regional Office for Europe, 2010):

> *A. Protecting children's health*
>
> *Regional Priority Goal 4: Preventing disease arising from chemical, biological and physical environments.*
>
> *(ii) We aim to protect each child from the risks posed by exposure to harmful substances and preparations, focusing on pregnant and breast-feeding women and places where children live, learn and play. We will identify those risks and eliminate them as far as possible by 2015.*
>
> *(iii) We will act on the identified risks of exposure to carcinogens, mutagens and reproductive toxicants, including radon, ultraviolet radiation, asbestos and endocrine disruptors, and urge other stakeholders to do the same. …*
>
> *D. Knowledge and tools for policy-making and implementation.*
>
> *11. We will contribute to develop a consistent and rational approach to human biomonitoring as a complementary tool to assist evidence-based public health and environmental measures, including awareness-raising for preventive actions.*

2. HBM Concepts and Methodology

2.a Overview of HBM concepts

Internal dose

Internal dose refers to the amount of a chemical (parent compound or its metabolite) that reaches the human tissue of interest. It is assessed using direct measurements (e.g. concentration of chemical in the blood) or estimated using computational internal dosimetry models.

Pharmacokinetics

Pharmacokinetics (PK) refers to an area of pharmacology that studies the fate of intentionally administered substances (e.g. pharmaceutical compounds, hormones, nutrients) or inadvertently administered ones (e.g. industrial chemicals) in a human or animal model. PK quantitatively describes the fate of the administered compound until its complete elimination (via metabolism and excretion) from the body. The most advanced pharmacokinetic models, called the Physiology Based Pharmacokinetic (PBPK) models, quantitatively describe the absorption, metabolism, distribution and elimination (ADME) processes in the human body, with a focus on the effective dose at the expected target site (Bois, Jamei & Clewell, 2010). PBPK models are applied to HBM data interpretation and support chemical risk assessment. PBPK models are the only available method for linking biomonitoring data with exposure.

Types of HBM surveys

Cross-sectional surveys assess the internal concentration of pollutants in the human population at one moment in time. When the survey uses a random sample of the general population of a country, it characterizes nation-wide exposure. In longitudinal surveys, participants are followed over time and multiple biological samples are collected from each individual. The birth cohort is a type of longitudinal survey that involves assessing perinatal exposure (e.g. biomarkers measured in the blood or urine of the pregnant mother, in cord blood, or in breast milk) and following up the children to assess associated health effects occurring later in life.

Interpretation of biomarkers

Biomarkers (either parent compounds or their metabolites) present a time-variable concentration profile that is associated with temporal patterns of exposure and elimination kinetics. These are considerably different for persistent and bioaccumulative compounds when compared to non-persistent ones. Individual exposure to persistent and bioaccumulative compounds can be characterized using a single sample in cross-sectional surveys. This is due to their partitioning into and storage in certain tissues (e.g. adipose tissue) and slow elimination, which result in low sample-to-sample variability in biomarker values during a short time interval. In contrast the temporal variability of biomarker values for rapidly eliminated compounds can be large, depending on recent exposure episodes. In such cases repetitive sampling may be required in order to characterize individual exposure levels.

Individual factors

The use of detailed PBPK models for interpreting biomonitoring data also allows

for the modelling of different sources of inter-individual variability of the ADME process. These sources include: body weight, genetic polymorphisms related to metabolism of xenobiotics, age-dependent maturity of the detoxification pathway, and excretion and elimination rates. Thus parameters that were previously treated as confounders or uncertainty factors (in analysis involving crude HBM data), can now be viewed as analyzable parameters which reflect variations in the susceptibility within a population that is exposed to environmental pollutants.

Biomonitoring equivalents (BEs)

Most standards and guidelines for safe exposure are currently expressed in units of intake, such as acceptable or tolerable daily intake (ADI or TDI), reference dose (RfD), minimal risk level (MRL), or derived no-effect level (DNEL). PBPK can be used to estimate a biomonitoring equivalent (BE) level, which represents the concentration of a chemical or its metabolite in biological specimens and is consistent with the established reference values for intake levels (Aylward, Lakind & Hays, 2008; Boogaard, Hays & Aylward, 2011).

2.b Sample matrices in HBM

Once the chemical is absorbed in the body it can be excreted without transformation, excreted after metabolization or stored in various tissues or bones. While there are many biological matrices that can be used in HBM, chemical-specific factors limit the possibilities. This is because the physicochemical properties of the chemical determine its metabolism and excretion routes, which influence the selection of an appropriate matrix. However, the application of advanced analytical techniques, which have very low limits of quantitation (LOQ), has expanded the possibilities and enabled the use of non-invasive matrices with relatively low concentration of xenobiotics in HBM studies. For example dioxins (which are lipophilic compounds) were measured in adipose tissue containing 65–95% fat in the 1980s but are today measured in serum containing only 0.5–0.6% fat.

Blood is one of the most commonly used matrices in HBM surveys. Blood is the preferred matrix for many chemicals as it is in continuous contact with the whole organism and is in equilibrium with the organs and tissues where chemicals are deposited. Furthermore the procedures for blood sampling are standardized and many people have become used to giving this kind of sample. A disadvantage of using blood in HBM is the need for invasive sampling, which may have an adverse effect on participants' response and compliance rates.

Blood is also the most appropriate matrix for measuring biomarkers of exposure to certain metals. For example most of the information on human exposure to lead is based on the blood lead levels. Lead in urine primarily reflects the amount of lead absorbed recently but it may not be a reliable biomarker of exposure over a longer time interval (Jakubowski, 2012; Lauwerys & Hoet, 2001). Correlations between maternal and umbilical cord blood lead levels, and between maternal and infant's blood lead levels, confirm the transfer of lead from mother to the foetus (Sanders et al., 2009). The level of mercury in blood indicates recent exposure to both organic and inorganic mercury but it does not provide information about historical exposure or variations in exposure (UNEP Chemicals Branch, 2008).

Cadmium in blood primarily reflects exposure during the past 2–3 months with a contribution from a long-term body burden. In contrast cadmium measured in urine primarily reflects the total body burden of cadmium as a result of a much longer history of exposure (Adams & Newcomb, 2014; ATSDR, 2008). Evidence exists, however, that at very low environmental exposures, urinary cadmium is strongly influenced by

a series of factors unlikely to be related to cadmium toxicity or accumulation (Chaumont et al., 2013).

Blood and cord blood, as well as placenta and human milk are usually used for the analyses of persistent, bioaccumulative compounds, such as perfluorinated compounds, organochlorine pesticides, PCBs, dioxins, brominated flame retardants (BFRs), organotins and metals. For lipophilic compounds, such as dioxins, variability in serum lipid concentrations can be accounted for by expressing results as “concentration of chemical per gram of serum lipids”.
Cord blood and/or placenta provides information on both the exposure of mothers and prenatal exposures of their children (Smolders et al., 2009). These matrices cover the prenatal period, a life stage which is characterized by high vulnerability to environmental insults (Jurewicz, Polańska & Hanke, 2013).

Urine is a readily available sample matrix which is easily accessible in large volumes. Samples can be collected directly by the donors which simplifies the fieldwork. Urine is the most useful matrix for analysis of rapidly metabolized and excreted chemicals. Problems related to urine as a biological monitoring matrix are related to the wide variability of urinary excretion rates among individuals, as well as the great temporal variability in urine composition within individuals (Aylward et al., 2014). Two most commonly used solutions are: expressing the results per gram of creatinine and adjusting the measured values for the specific gravity of the measured compounds.

Urinary biomarkers are used for rapidly metabolized and excreted compounds, such as non-persistent pesticides, bisphenol A (BPA) and other phenols, parabens, phthalates, volatile organic compounds (VOCs) and PAHs. Urine is also used to monitor exposure to some metals, such as arsenic and inorganic mercury. Urinary mercury reflects recent exposure to inorganic mercury as well as exposure to organic mercury compounds (Barregard, 1993; Mason, Lawson & Sheu, 2001). In an occupationally non-exposed population, the number of dental amalgam surfaces was found to be the best predictor of elevated urinary mercury (Langworth et al, 1992).

HBM studies can also include analysis of environmental pollutants in other matrices, such as hair, nails, saliva and deciduous teeth. Structure and histogenesis of hair and nails favour their use for biomonitoring of trace elements. Hair samples are used for identifying long-term exposure to metals. Exposure to methyl mercury through fish consumption is very well indicated by the measurement of total merucry in hair (UNEP Chemicals Branch, 2008), which presents the cumulative mid- to long-term average exposure (depending on the length of the hair sample). Recent efforts have supported the use of hair as a matrix for measuring exposure to organic pollutants (Appenzeller & Tsatsakis, 2012). The minimum necessary weight (~50–200 mg) of the material that needs to be collected can be a limiting factor (for example, in newborn babies, or bald individuals). In addition external deposition of chemicals on hair can distort analysis results.

Human nails are largely comprised of keratin-rich proteins, which incorporate trace elements in proportion to dietary intakes and other exposures (He, 2011). Use of nails for biomonitoring offers several advantages: the possibility to integrate a relatively long-term intake with exposure of a single specimen; specimen collection is non-invasive; and sample shipping and storage are easy. Disadvantages of using nails for biomonitoring include the lack of sensitivity for several compounds, potential contamination through the use of medication, nail polish and nail cutters, external deposition of chemicals and the small mass of samples.

Deciduous teeth have been used as markers of children’s exposure to metals such as lead, strontium, zinc and magnesium. In fact high spatial resolution laser ablation inductively coupled plasma mass spectrometry (ICP-MS), when used with dental histology, has delivered useful information on the life-time exposure of children to lead (Shepherd et al., 2012),

shedding light on the epigenetic effects of heavy metals associated with endocrine disruption.

Identifying biomarkers in saliva is a promising approach for HBM, even if only a few substances, thus far, have showed a moderate correlation with exposure data or with established biomonitoring matrices such as blood, plasma and urine. Saliva has been shown to be particularly suitable for substances with low molecular weight such as organic solvents, selected pesticides, cotinine and specific trace elements. Besides the advantage offered by the non-invasive nature of sampling, serious problems and limitations have been identified in the use of saliva for biological monitoring. These are mainly related to the limited sensitivity of salivary biomarkers (Michalke et al., 2014).

Exhaled breath is a non-invasive biomonitoring matrix which facilitates the direct association of inhaled compound concentrations to exhaled concentrations of toxicological relevance. Since a respective biomarker comes directly from the respiratory system, actual internal dose at the tissue of interest can be assessed. However, information is primarily limited to target tissues in the respiratory tract and the applicability domain covers only specific types of compounds (e.g. volatile compounds) for a short exposure regime.

Table 1 summarizes the advantages and limitations of biological matrices that are commonly used in HBM studies to assess environmental exposures in humans.

Table 1. Biological matrices used in HBM studies

Matrix	Population	Advantages	Limitations	Compounds measured in the matrix
Blood, serum, plasma	General	In equilibrium with all organs and tissues. Well established standard operating procedures (SOPs) for sampling.	Invasive; trained staff and special materials required. Volume limitation. Special conditions for transport and shipment.	POPs, metals/trace elements, organic compounds, tobacco smoke. e.g.: alkylphenols, mercury, lead, BFRs, dioxins, water disinfection byproducts, fluorinated compounds, organochlorine pesticides, organophosphate pesticides, phthalates, PCBs, dioxins.
Urine	General	Non-invasive, easy collection, no volume limitation. Allows analysis of metabolite	Composition of urine varies over time.	Metals/trace elements, organic compounds, tobacco smoke. Metabolites of environmental pollutants. e.g.: mercury, cadmium, arsenic, organochlorine compounds, BPA, organophosphate pesticides, parabens, phthalates, PAHs, benzene.
Hair	General, with few exceptions (i.e. neonates)	Non-invasive; minimum training required for sampling. No special requirements for transport and storage. Information about cumulative exposure during previous months. Segmental analysis is possible.	Hair is exposed to the environment and can be contaminated. Potential variations with subject's hair colour, hair care or race.	Metals/trace elements, POPs e.g.: total mercury, methylmercury, arsenic, cadmium, parabens, organochlorine compounds

Table 1 (continued)

Matrix	Population	Advantages	Limitations	Compounds measured in the matrix
Cord blood	Specific	Non-invasive; provides information about mother and child. Well defined SOP for peripheral blood can be used for cord blood.	Only available at birth in maternity ward settings. Ethical constraints. Special conditions for transport and storage.	POPs and other organic compounds, metals/trace elements, tobacco smoke, e.g.: alkylphenols, mercury, lead, BFRs, dioxins, water disinfection byproducts, fluorinated compounds, organochlorine compounds, organophosphate pesticides, phthalates, PCBs.
Breast milk	Specific	Provides information about mother and child. Enriched with lipophilic compounds.	Somewhat invasive. Restricted period of availability. Depuration of chemicals during lactation should be considered.	POPs, metals/trace elements, organic compounds, tobacco, e.g.: alkylphenols, BPA, dioxins, BFRs, fluorinated compounds, PCBs, organochlorine pesticides, lead, cadmium, mercury, phthalates
Amniotic fluid	Specific	Invasive	Limited to women undergoing amniocentesis or Caesarean section.	POPs, organic compounds, metals/trace elements, e.g.: phthalates, mercury, organochlorine pesticides
Placenta	Specific	Non-invasive	Restricted to certain period of life; requires homogenization	Metals/trace elements, POPs, organic compounds, e.g.: mercury, cadmium, lead, organochlorine pesticides, BPA, BFRs, dioxins, PCBs, PAHs, phthalates
Meconium	Specific	Non-invasive, easy collection. Reflects prenatal exposure.	Only available at birth.	Metals/trace elements, POPs, organic compounds, tobacco, e.g.: mercury, cadmium, organochlorine pesticides, PCBs, phthalates
Semen	Specific	Mainly used to measure biomarkers of effect.	Invasive. Only available from males. Less documented for HBM applications	Metals/trace elements, POPs, organic compounds, e.g.: mercury, phthalates, dioxins, PCBs, organochlorine pesticides
Exhaled air	General	Non-invasive. Direct assessment of exposure through air	Limited to volatile chemicals. Difficult sampling, transport and storage.	Metals, disinfection byproducts, e.g.: lead, cadmium, trihalomethanes
Saliva	General	Non-invasive, easy collection	Lower concentrations of analytes than in blood; requires sensitive analytical techniques. Variation in flow rate and composition. The use of stimulant or absorbent pads can interfere with analysis. Less documented for HBM applications.	Metals/trace elements, organic compounds, POPs, tobacco, e.g.: cadmium, phthalates, BPA, PCBs, dioxins

Table 1 (concluded)

Matrix	Population	Advantages	Limitations	Compounds measured in the matrix
Nails	General	Non-invasive, easy collection. No special storage or transport requirements. Provide information about short and long term exposure.	Exposed to the environment and can be contaminated (toenails are less exposed). Less documented for HBM applications.	Metals/trace elements, tobacco, e.g.: arsenic, mercury, cadmium, lead
Deciduous teeth	Specific	Non-invasive. No special requirements for transport and storage.	Low availability; restricted to a certain period of life. Less documented for HBM applications.	Metals/trace elements, organic compounds, tobacco, e.g.: lead, cadmium
Sweat	General	Non-invasive	Difficult collection. Less documented for HBM applications.	Metals/trace elements, organic compounds, e.g.: lead, cadmium

2.c Types of biomarkers

Biomarkers of exposure

Biomarkers of exposure identify and measure chemical residues in tissue or body fluids, metabolites of xenobiotic compounds, or physiological outcomes that occur as a result of exposure. When selecting an appropriate analyte in human specimens it is important to take into account the kinetics of biomarkers of interest. Different matrices reflect exposure over different time periods. Probably the best known example of this phenomenon is that of lead, whose half-life varies from about a month in blood to about a year in soft tissue and to twenty years in bones. As a general rule biomarkers of exposure to compounds that remain stable in the human body (e.g. dioxins, dioxin-like PCBs and metals) are measurements of the original compound concentrations in blood, serum or urine. For chemicals that are metabolized rapidly (e.g. organophosphate pesticides and phthalates), one or more metabolites of the original compound are often used as biomarkers of exposure; these are generally measured in urine.

Biomarkers of effect

Biomarkers of effect reflect quantifiable changes in biochemical, physiologic or other parameters in the organism that occur as a result of exposure.

Ideally, a biomarker of effect should reflect early reversible changes in the organism. Depending on the health endpoint considered, series of biomarkers of effect have been identified that range from biomolecules found in tissue or fluids to physiological measurements, such as lung function tests and arterial imaging. With regard to carcinogenicity, the most commonly studied biomarkers reflect genotoxic effects (Albertini et al., 2000; Bonassi et al., 2005). Cytogenetic endpoints, such as micronuclei induction, chromosome aberrations and sister chromatid exchange, are considered as biomarkers of early carcinogenic (genotoxic) effects and are considered predictive of cancer risk in humans (Bonassi et al., 1995; Brandt & Watson, 2003; Fenech et al., 1999; Smerhovsky et al., 2001). DNA adducts and protein

adducts, especially hemoglobin (Hb) adducts, are better predictors of cancer risk than biomarkers of exposure (Angerer, Ewers & Wilhelm, 2007).

The most common method to estimate DNA damage caused by PCBs, dioxins and furans in human blood cells is the Comet assay (also known as "single-cell gel electrophoresis") (Azqueta & Collins, 2013). It is a simple and sensitive method that measures DNA damage (e.g. strand breaks, DNA adducts, excision repair sites and cross links) at the single cell level.

Biomarkers of inflammatory processes include interleukin-1 beta (IL-1, 1beta), growth related oncogene-alpha (GRO-alpha), monocyte chemoattractant protein-1 (MCP-1), tumour necrosis factor alpha (TNF-alpha) and C-reactive protein (CRP). The enzyme-linked immunosorbent assays (ELISA) and other more recently developed multiplex immunoassays are common measurement methods for cytokines and other biomarkers of inflammation (Leng et al., 2008).

Biomarkers of susceptibility

Biomarkers of susceptibility reflect intrinsic characteristics of an organism that make it more susceptible to the adverse effects of an exposure to a specific chemical substance.

Polymorphisms of relevant xenobiotic metabolising enzymes are used as susceptibility markers. Many of the cytochrome P450 (CYP) enzymes are polymorphic, and some genotypes can be associated with high enzymatic activity. For example, cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) induction (specifically the *2C I462V allele) has been linked to lung cancer (Thier et al., 2003). Moreover, cytochrome P450, family 2, subfamily E, polypeptide 1 (CYP2E1) allelic variants appear to modulate the risk for alcoholic liver disease (Savolainen et al., 1997) and cancer (Uematsu et al., 1991). A polymorphism of N-oxidation has been linked to susceptibility to colon cancer (Kadlubar et al., 1992) and a polymorphism in glutathione-s-transferase has been linked to increased lung cancer risk (Seidegard et al., 1990).

With regard to neurological disorders, biomarkers of genetic susceptibility are rapidly becoming more widely available. Identification of the variant allele in a gene, such as apolipoprotein E (APOE), has been found to be useful in assessing risk and in providing information regarding the pathogenesis of Alzheimer's disease (Mayeux, 2004).

"Omics" biomarkers for research and discovery

During the last decade a combination of advanced techniques, clustered under the name "-omics," has offered new opportunities for enhanced understanding of the exposure-response continuum in health risk assessment. Omics are high throughput techniques that permit the observation and measurement of response modulation at different biological scales (e.g. [epi]genome, transcriptome, proteome, metabolome) in humans. Omics techniques range from next generation sequencing and gene expression microarrays (coupled with quantitative real-time polymerase chain reaction (qRT-PCR)) to liquid chromatography–mass spectrometry (LC-MS) and gas chromatography–mass spectrometry (GC-MS). These integrated platforms can be used for protein- and metabolite-, or DNA- and protein-adduct-, profiling.

Discovery biomarkers may be based on DNA sequencing data, gene expression, and protein and metabolite profiles, as well as on prior information coming from protein-protein interaction databases (the interactome). An example of gene expression-based markers of effect is the up-modulation of chemokine ligand genes after exposure to carbon nanotubes, a marker for lung fibrosis (Sarigiannis et al., 2012). Acute exposure to environmentally ubiquitous VOCs, such as benzene, toluene, ethylbenzene

and xylenes, primarily induces signal transduction, protein metabolism and messenger ribonucleic acid (mRNA) transcription mechanisms. Chronic exposure to VOCs also affects protein biosynthesis and modification, cell proliferation and differentiation and, to a lesser extent, cytokine and chemokine mediated signalling (Sarigiannis et al., 2009).

2.d Objectives and design of HBM surveys

Objectives of HBM surveys

HBM surveys can have a number of objectives, such as: assessing the distribution of exposure; detecting emerging threats; monitoring the effects of policy interventions aimed at reducing or preventing harmful exposures; setting priorities for downstream risk assessment; monitoring spatial patterns and temporal trends; identifying and monitoring contaminated sites; supporting epidemiological research; and serving the development of the "exposome" concept.

HBM programmes provide information that is essential for identifying chemicals that need to be assessed with regard to potential health risks in specific population subgroups or areas. In particular, longitudinal biomonitoring surveys that cover all societal groups, including vulnerable subpopulations (e.g. people of low socioeconomic status [SES]), provide a unique opportunity to monitor spatial patterns and temporal trends of population exposure to chemicals of concern.

Targeted HBM surveys can help to monitor the actual exposure of the population living near contaminated sites. An example of this approach is the HBM surveillance in the vicinity of toxic waste sites in the region of Campania, Italy (Abbott, 2014). Surveys that involve biomarkers of health effect, as well as biomarkers of exposure, can quantify early signals that are predictive of adverse health outcomes.

Analysis of HBM data, in connection with environmental monitoring data, as well as pertinent data on lifestyle or nutrition, can reveal major sources of exposure, describe exposure pathways, and identify risk factors, providing support to targeted interventions. All aspects of the survey design, such as sample size, selection of biomarkers, questionnaire content, and data analysis and interpretation, depend on the research questions.

Selection of biomarkers

The selection of biomarkers depends on the aim of the study. It should be driven mainly by scientific criteria, such as expected health outcomes (based on information from international organisations such as the International Agency for Research on Cancer (IARC); see also the European Union (EU) list of endocrine disrupters); available guidelines (e.g. German HBM values, BEs, biomonitoring "margins of safety"); expected exposure ranges based on published results of national and international HBM studies; and availability of valid analytical techniques with limits of detection that are low enough to measure the expected levels in the population. Further, practical considerations, such as the complexity of the field work and the costs of analysis, may be important for the selection of biomarkers.

Survey design and sample size

Well designed HBM surveys that use appropriate sampling, laboratory analysis, data management and processing techniques are powerful tools that serve a multitude of purposes in environment and health science and policy-making. Integrated approaches involving human biological monitoring provide useful information to assess the distribution of

exposures in different societal strata and detect emerging threats to public health.

The survey size (the number of individuals in the survey or sample size) depends on the survey objectives and research hypothesis. A minimum of 120 randomly selected individuals per population group is recommended for cross-sectional surveys to allow for the estimation of group-specific reference values with sufficient precision and meaningful comparison of population groups (Poulsen, Holst & Christensen, 1997).

Data collection on exposure factors and health outcomes

Questionnaires in HBM surveys are used to collect necessary information for the interpretation of biomarkers, e.g. data on personal characteristics, lifestyle, indoor and outdoor environments. The design of questionnaires should be based as much as possible on standard questions from previous studies, and newly designed questionnaires should be tested in the target population. Interviews conducted by survey personnel generally provide higher quality of data than self-administered questionnaires. Computer-assisted personalized interviews (CAPI) reduce the workload for input and allow built-in quality controls (QCs).

Routinely collected medical data should also be obtained when possible. Examples are data from school health examinations and maternity records (which include neonates' birth weight, length, head circumference, and gestational age). Collection of these data requires informed consent from the participants and agreements with the institutions involved (e.g. schools, hospitals).

2.e Ethical aspects of HBM surveys

Ethical and scientific standards for carrying out biomedical research on human subjects have been developed and established in international guidelines, including the Declaration of Helsinki, the International Ethical Guidelines for Biomedical Research Involving Human Subjects adopted by the Council for International Organizations of Medical Sciences (CIOMS), and the WHO and International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice. Within Europe, the Oviedo Convention on research on biological material of human origin (Council of Europe, 1997) and the Data Protection Directive (95/46/EC) (EU, 1995) are instrumental for the protection of study subjects involved in biomedical research. Compliance with these guidelines helps to ensure that the dignity, rights, safety, and well-being of research participants are promoted and that the results of the investigations are credible.

The Oviedo Convention and its Additional Protocol are documents open for signature and ratification by all Member States of the Council of Europe. The European Court of Human Rights uses the Oviedo Convention as an expression of European human rights standards, even in cases involving countries that have not signed or ratified the convention. The Data Protection Directive 95/46/EC regulates the processing of personal data within the EU. Samples and data obtained in a HBM study are considered "sensitive personal data". The Directive imposes the practice of informed consent, including the right to know one's own results, and requires notification of the national data protection authority.

Written consent is defined as consent that is informed, freely given, explicit, specific and documented. It has to be obtained from each study participant prior to the enrolment in the study. The consent form should include: the identity of the data controller and his/her contact address and affiliation, the reason for the collection of the data, and the recipients or categories of recipients of the data. Information should also be provided about: the purpose of the study; the

overall plan; possible risks and benefits; the opinion of the ethics committee; the right to refuse consent and withdraw consent at any time without having to give reasons or being subject to any form of discrimination; the right to access the data; the right to rectification of data; and the right not to know one's own results.

2.f Laboratory analysis of biomarkers – overview of methods and costs

Methods

The concentration of organic compounds in the biological samples and the complex composition of the matrix have to be taken into account when selecting an analytical method. Specific standardized procedures for isolating and pre-concentrating analytes are necessary to maximize recovery. Sample preparation and clean-up are needed in order to: avoid chemical interference and enrich the target chemicals to detectable levels.

ICP-MS is the most appropriate technique for the detection of trace metals and metalloids in urine and blood. Mercury is usually determined separately using different techniques such as direct mercury analyser integrating sample thermal decomposition, amalgamation and subsequent detection using atomic absorption spectrometry. This is appropriate for blood and hair samples but not recommended for urine samples, which must first be chemically decomposed using acid digestion and then analysed using cold vapour atomic absorption spectrometry (CVAAS).

Liquid-liquid extraction (LLE) and solid-phase extraction (SPE) are classic methods used to extract organic chemicals from liquid samples. SPE has many advantages compared to LLE such as: improved selectivity, specificity and reproducibility; lower solvent use; shorter sample preparation time; and ease of operation and automation. Based on the features (e.g. polarity) of the target compound and the sample matrix, different SPE sorbents may be selected. Microextraction techniques, such as solid-phase microextraction (SPME), stir-bar sorptive extraction (SBSE) and liquid-phase microextraction (LPME), allow high enrichment and reduced solvent consumption. In recent years, extraction methods have been based on liquid partitioning with ultrasonic extraction (USE), microwave-assisted extraction (MAE; used to enhance extraction efficiency), pressurized liquid extraction (PLE; used to reduce extraction time and solvent use and to increase recovery) or supercritical fluid extraction (SFE; used to extract non-polar or slightly polar analytes, resulting in minimal clean-up of the extract), which has replaced the Soxhlet process (Sosa-Ferrera, Mahugo-Santana & Santana-Rodriguez, 2013).

For the quantitative analysis of organic compounds, mass-based analytical methods, such as LC-MS and liquid chromatography time-of-flight mass spectrometry (LC-TOF-MS) show very good sensitivity and accuracy.

Costs

The cost of analysis of metals in biosamples is typically less than one hundred Euros, while the cost of analysis of organic compounds can reach hundreds of Euros, depending on the chemical investigated. The cost of analysis of PCBs and dioxins in blood samples is in the range of €500 to €800 per sample. Analysis can include 20–30 related compounds simultaneously. Cost of analysis of perfluorinated compounds (PFCs), flame retardants and pesticides in blood is around €200 per sample for multiple compounds of the same chemical family. The cost of analysis for compounds identified in urine (mostly

metabolites) is about €100 for pesticides (e.g organophosphates); about €120 for phthalates (including the urine metabolites of phthalates); about €100 per sample for BPA. The prices are similar for identifying urine metabolites of PAHs but are slightly lower for VOCs. Analyses of metabolomes start from about €200 per sample for targeted analysis; untargeted analyses are somewhat more expensive.

Unbiased (hypothesis-neutral) transcriptome analysis involves the monitoring of gene expression at a genome-wide scale. It can be done using microarrays or next generation sequencing. Microarrays can be found at market prices ranging from €60 to €220 each. Prices can be higher when the arrays are custom-produced to target specific genes. Next generation sequencing offers several advantages over microarrays: it has reduced background, increased sensitivity, improved dynamic range and greater density of information. However, sequencing is time-consuming, expensive and bioinformatically challenging. It runs at a cost of less than €200 per sample, even though the capital cost for purchasing the sequencer itself can be from €200 000 to €400 000 in 2014 prices.

2.g Interpretation of biomarker data

Statistical values

At the initial stage of data analysis (descriptive statistics), basic statistical values are calculated for each biomarker: minimum and maximum values, percentage of subjects having the biomarker value above the LOQ or above the limit of detection (LOD), and geometric mean (GM). Percentile values, the values of a variable below which a certain percent of observations fall, may also be calculated: 50th percentile (P50; median), 90th percentile (P90) and 95th percentile (P95). Percentages of results exceeding reference values or health-based values may also be reported.

Health-related values

HBM data can be interpreted via comparing the measured biomarker levels to health-relevant biomonitoring reference values. In this context, the German Human Biomonitoring Commission has derived reference values for several compounds (Schulz et al., 2007a). These values that have been determined based on either exposure-effect relationships (e.g. for cadmium, lead, mercury and pentachlorophenol) or derived from TDI values. When the evaluation is based on epidemiological studies, the health-based HBM value is derived through linking the concentration of pollutant in a specific biological matrix with the onset of adverse health effects. There are two levels of HBM values derived by the German Human Biomonitoring Commission, namely HBM-I and HBM-II. The HBM-I value represents the xenobiotic's concentration in human biological materials below which, according to the current knowledge, there is no risk of adverse health effects and no need for action. The HBM-I value is, therefore, a control value. The HBM-II value represents the concentration of a xenobiotic in human biological materials above which there is an increased risk of adverse health effects. The HBM-II is an intervention or action level threshold. If a concentration is higher than the HBM-I value but lower than the HBM-II value, then potential sources of exposure should be identified and, if possible, reduced or eliminated at an acceptable cost.

Due to the limited number of studies associating HBM data to adverse outcomes, only a few health-related HBM values have been determined. The current list of health-based HBM values is availbale at the German HBM Commmission's web site (UBA, 2015). Examples of such values for selected pollutants are provided in Table 2.

Table 2. German Human Biomonitoring Commission reference HBM values for pentachlorophenol, di(2-ethylhexyl)phthalate (DEHP), bisphenol A (BPA), cadmium, lead and mercury

Parameter and medium	Population group (age range)	HBM-I value	HBM-II value	Reference
Pentachlorophenol in serum	General population	40 µg/l	70 µg/l	Schulz et al., 2007a
Pentachlorophenol in urine	General population	25 µg/l or 20 µg/g creatinine	40 µg/l or 30 µg/g creatinine	
Sum of the metabolites of DEHP: 5-oxo- and 5-OH-MEHP in urine	Children aged 6–13	500 µg/l		HBM-Kommission, 2007
	Women of reproductive age	300 µg/l		
	Males ≥ 14 years, general population	750 µg/l		
BPA in urine	Children	1 500 µg/L		HBM-Kommission, 2012
	Adults	2 500 µg/L		
Cadmium in urine	Children and adolescents	0.5 µg/L	2 µg/L	Schulz et al., 2011
	Adults	1 µg/L	4 µg/L	
Lead in blood	General population	Suspended	Suspended	Wilhelm et al., 2010
Mercury in urine	Children and adults	5–7 µg/ g creatinine	20 µg/L or 25 µg/g creatinine	Schulz et al., 2007a
Mercury in blood	Children and adults. The value was derived for women of reproductive age but it is recommended for all population groups.	5 µg/L	15 µg/L	Schulz et al., 2007a

Source: adapted from Schulz et al. (2011:156), with additions. Reproduced with permission from Elsevier.

BEs are defined as the concentration of a chemical or metabolite in a biological matrix (blood, urine, human milk, etc.), consistent with defined exposure guidance values or toxicity criteria. These include reference doses (RfD) and reference concentrations (RfC), MRLs and TDIs, which have been defined by using the knowledge about the toxicokinetic properties of the chemical (Boogaard, Hays & Aylward, 2011). The application of BEs is based on the assumption that intake and excretion are in equilibrium. This ensures the coherence between the guidance values for chronic exposure and the estimated BE (Angerer et al., 2011). Use of reliable physiology based biokinetic (PBBK) models is the most convenient way to translate external exposure reference values into BEs. The BE derived for several compounds are given in Table 3.

Table 3. Biomonitoring equivalent (BE) values for selected pollutants

Environmental Chemical	Matrix	Analyte	BE value	Intake-based reference value	Reference
DDT/ Dichlorodiphenyl-dichloroethylene (DDE)/ dichlorodiphenyl-dichloroethane (DDD)	Blood	(DDT only) (DDT/DDE/DDD)	30 000 ng/g lipid 40 000 ng/g lipid	70 µg/l FAO/ WHO (10 µg/kg/day)	Kirman et al., 2011
Hexachlorobenzene	Blood	Hexachloro benzene	16 ng/g lipid	Health Canada (0.05 µg/kg/ day)	Aylward et al., 2010
Dioxin Toxic equivalency factor (TEQ)	Blood	Dioxin TEQ	15 ng/g lipid	ATSDR[a] LOAEL[b] (0.12 ng/kg/ day)	Aylward, Lakind & Hays, 2008
Hexabromocyclo-dodecane	Blood, breast milk	Hexabromocyclo dodecane	190 000 ng/g lipid	EU Draft (2 mg/kg/day)	Aylward & Hays, 2011
Deltamethrin	Blood	Deltamethrin	20 µg/L (adults) 2µg/L (children)	EC (10 µg/kg/day)	Aylward et al., 2011
	Urine	Dimethylcyclo propane carboxylic acid	50 µg/L (adults) 7µg/L (children)		
2,2',4,4',5-pentabromodiphenyl ether (BDE 99)	Blood	BDE 99	520 ng/g lipid	USA EPA (0.1 µg/kg/ day)	Krishnan et al., 2011
Cyfluthrin	Urine	4-fluoro-3-phenoxybenzoic acid	400 µg/L	FAO/WHO ADI (10 µg/kg/day)	Hays et al., 2009
Triclosan	Urine	total triclosan (free plus conjugates)	2 600 µg/L	EC (120 µg/kg/ day)	Krishnan et al., 2010b
BPA	Urine	BPA-glu	2 000 µg/L	EFSA (50 µg/kg/day)	Krishnan et al., 2010a
Di-2(ethylhexyl) phthalate (DEHP)	Urine	MEHP[c], MEHHP[d], and MEOHP[e]	660 µg/L	EFSA (50 µg/kg/day)	Aylward et al., 2009b
		MEHP, MEHHP, MEOHP, and 5cx-MEPP[f]	1 000 µg/L		
		MEHP, MEHHP, MEOHP, 5cx-MEPP, and 2cx-MMHP[g]	1 100 µg/L		

Table 3 (continued)

Environmental Chemical	Matrix	Analyte	BE value	Intake-based reference value	Reference
Diisononyl phthalate – (DiNP)	Urine	Oxidative (OH-, oxo-, and carboxy-MiNP - monoisononyl phthalate) metabolites	15 µg/L (children 6–11 years) 10.7 µg/L (adolescents 11–16 years) 12.7 µg/L (men >16 years) 10.6 µg/L (women >16 years)	EFSA (150 µg/kg/day)	Hays et al., 2011
		MiNP	0.7 µg/L (children 6–11 years) 0.5 µg/L (adolescents 11–16 years) 0.6 µg/L (men >16 years) 0.5 µg/L (women >16 years)		
di-n-butyl phthalate – (DBP)	Urine	monobutyl phthalate (MBP)	0.2 µg/L	EFSA (10 µg/kg/day)	Aylward et al., 2009a
benzylbutyl phthalate (BzBP)	Urine	monobenzyl phthalate (MBzP)	12 µg/L	EFSA (500 µg/kg/day)	Aylward et al., 2009a
diethyl phthalate (DEP)	Urine	mono-ethyl phthalate (MEP)	18 µg/L	EFSA (800 µg/kg/day)	Aylward et al., 2009a
Benzene (for chronic non-cancer exposure)	Blood Urine	Benzene	0.15 µg/L 0.16 µg/L	USA EPA Chronic Inhalation Exposure (RfC)	Hays et al., 2012
	Blood Urine		1.29 µg/L 1.42 µg/L	Texas Commission on Environmental Quality (TCEQ)	
	Blood Urine		0.29 µg/L 0.33 µg/L	ReV California Acute Reference Exposure Levels (CAL REL)	
	Blood Urine		0.04 µg/L 0.05 µg/L	ATSDR chronic inhalation MRL	
Benzene cancer risk-specific exposure levels	Blood Urine	Benzene	0.058–0.204 µg/L 0.125–0.286 µg/L	USA EPA, risk-specific concentrations (1E-04 risk – 13.0–45.0 µg/m^3)	Hays et al., 2012
	Blood Urine		0.58–2.04 ng/L Not calculated	USA EPA, risk-specific concentrations (1E-06 risk – 0.13–0.45 µg/m^3)	
	Blood Urine		0.204 µg/L 0.286 µg/L	TCEQ, Effects Screening Levels (ESL) cancer (1E-04 risk – 44.6 µg/m^3)	
	Blood Urine		2.04 ng/L Not calculated	TCEQ, ESL cancer (1E-06 risk – 0.446 µg/m^3)	

Table 3 (concluded)

Environmental Chemical	Matrix	Analyte	BE value	Intake-based reference value	Reference
Toluene)	Blood	Toluene	50 µg/L 40 µg/L 3 µg/L 3 µg/L 30 µg/L	USA EPA chronic RfC (128 mg/m^3) Health Canada chronic inhalation TDI (150 mg/m^3) WHO air quality guideline (332 mg/m^3) ATSDR chronic inhalation MRL (132 mg/m^3) ATSDR acute MRL (150 mg/m^3)	Aylward, Barton & Hays, 2008
Cadmium	Urine	Cadmium	1.2 µg/L 1.0 µg/g creatinine	FAO/WHO (10 µg/kg/day) EFSA (2.5 µg/kg/week)	Hays et al., 2008 EFSA, 2009
Arsenic, inorganic	Urine	Inorganic arsenic, monomethylated arsenic, and dimethylated arsenic	6.4 µg/L	ATSDR (0.3 µg/kg/day)	Hays et al., 2010

[a] ATSDR = Agency for Toxic Substances and Diseases Registry
[b] LOAEL = lowest-observed-adverse-effect level
[c] MEHP = mono-(2-ethylhexyl) phthalate
[d] MEHHP = mono-(2-ethyl-5-hydroxyhexyl)phthalate
[e] MEOHP = mono-(2-ethyl-5-oxohexyl) phthalate
[f] 5cx-MEPP = mono(2-ethyl-5-carboxypentyl)phthalate
[g] 2cx-MMHP = mono-[2-(carboxymethyl)hexyl]phthalate

The BE values for human milk levels of POPs are based on the intake reference values, such as tolerable daily intake TDI, RfD or minimum risk level (MRL) assuming that the average concentration of lipid in human milk is 3.5% and average milk consumption in infants is 125 g milk/kg bw/day (Table 4).

Table 4. BE values for POPs in human milk

Environmental Chemical	Matrix	Analyte	BE value	Intake-based reference value	Reference
PCDD/PCDF/ PCB (TEQs)	Human milk	PCDD/PCDF/ PCB	0.2–0.9 pg/g lipid	WHO TDI (1-4 pg/kg bw day)	WHO, 2000
PCDD/PCDF/ PCB (TEQs)	Human milk	PCDD/PCDF/ PCB	0.2 pg/g lipid	USA EPA RfD (0.7 pg/kg bw day)	EPA, 2010
PCDD/PCDF/ PCB (TEQs)	Human milk	PCDD/PCDF/ PCB	0.2 pg/g lipid	ATSDR MRL subchronic 1 pg/kg bw day	ATSDR, 1999
Total PCBs	Human milk	PCBs	7 ng/g lipid	ATSDR MRL subchronic 0.03 µg/kg bw.d	ATSDR, 2000
DDT	Human milk	DDT	2 300 µg/ kg lipid	WHO TDI (10 µg/kg bw day)	FAO/WHO, 2001

Source: adapted from WHO & UNEP (2013:20)

The German HBM Commission has also derived reference HBM values, known as RV95 values, based on the 90th percentile of the biomarker values in the reference (unexposed) population (Ewers et al., 1999). Different RV95 values might be obtained for different population subgroups due to age and other factors, such as smoking.

HBM data in exposure reconstruction

HBM data can be used for exposure reconstruction, i.e. the quantification of exposure components resulting in the observed biomarker concentrations. Several techniques have been developed in this direction at increasing levels of complexity, ranging from exposure conversion factors (ECF) (Tan et al., 2006), to combined maximum likelihood estimates, coupled with physiologically based biokinetic (PBPK) modelling approaches with synthetic biomarker data based on Bayesian statistics (Georgopoulos et al., 2009). Exposure reconstruction allows assessing the magnitude, timing and sources of exposure, based on information on exposure factors and conditions. This information is usually provided by study participants who complete an activity diary or exposure recollection questionnaire. In this way, biomarker levels, which reflect internal exposure, are translated into external exposure levels. These levels can either be paired with clinical observation in order to derive exposure response relationships, or compared with known regulatory thresholds.

2.h Communication and presentation of HBM data

Communication is an integral part of a HBM programme and involves engagement with many stakeholders through the course of the project. Focused and timely communication is essential when conducting HBM studies. Those who conduct research have an obligation to the survey participants and the general public to be transparent and honest with regard to the design and implementation of the survey, and application of its results. Furthermore, communication strategies need to ensure ethically acceptable practices taking in account relevant political issues.

Aims of a communication strategy can vary depending on the objectives of the study and the target audience. Examples of communication strategy aims include: promoting public awareness of environmental health issues using HBM as a tool, enhancing study recruitment, specifying the study's goals and limitations, ensuring transparency for stakeholders, disseminating individual and collective results, conveying the public health significance of the results at the population level, and safeguarding translation of the results into precautionary and preventative policy.

A communication strategy should be part of the project design and it should be integrated in deadlines and milestones for the project. It should be documented and seen as a work-in-progress that is subject to regular reviews, ensuring that it adapts and remains sensitive to the on-going evaluation of communications activities. Communication strategies need to be based on a good understanding of the needs of the target audience. Preliminary analysis can assist with the development of tailored messages that use appropriate language and channels of communication. Social scientists and technology/media specialists should be consulted with at an early stage in this process.

At the start of the project, a stakeholder mapping exercise can help with the development of a communication strategy framework. Each stakeholder group requires specific messages and approaches to ensure the success of communication efforts. A communication

strategy needs to be adapted according to different needs and expectations of stakeholder groups and target audiences.

Table 5 lists possible communication strategies according to a target audience.

Table 5. Examples of communication strategies according to target audience type

Target audience	Preferred/appropriate communication approach
General public	Media – news articles Web site
Target population	Media – news articles Letters Web site
Study participants	Letters Face to face Web site
Media	Press release Symposium
Scientific community	Flyers, posters, banners Publication in peer review journals Oral / poster presentations of work at scientific congresses Symposium
Policy-makers	Stakeholder alert Factsheet Symposium or workshop

Communication of results to survey participants and maintaining the confidentiality of personal data

Study participants should receive their individual results and/or collective results that they have requested. The information material provided for the participants during enrollment informs them that they have the right not to know their own results. Explanation of individual results must be as clear as possible in order to be understood by individuals of various education levels and technical backgrounds and avoid unwarranted alarms.

Maintaining the confidentiality of individual results is a legal obligation. Before carrying out a study or communicating its results, consideration needs to be given to the meaning of results and their potential health relevance. Uncertainties regarding the public health significance of the results need to be communicated properly and ethical guidelines have to be followed.

It is important to convey if there is a lack of scientific knowledge or understanding with regard to specific results and if further research is required. Results could be compared to available health-based guidance values or standards. If an individual result indicates a high exposure level, information should be provided about appropriate next steps the participant should take.

Communication of results to the general public

The group level aggregated results can be made publically available after ensuring that no link can be made with

personal (individual level) data. These can stimulate efforts to assess potential sources of exposure and reduce exposure as appropriate. Comparison with other population groups helps to interpret results and evaluate population-specific interventions.

Communication of results to policy-makers

Each country has specific policy needs, which make it important to engage with policy-makers. Developing a one-page factsheet, which concisely explains the results and their relevance to national policies, is an appropriate first step. A symposium or workshop format gives researchers and policy-makers an opportunity to discuss the data in relation to policy needs and their public health significance. Policy-makers will be better equipped to develop evidence-based interventions if HBM studies provide pertinent information on trends and to link temporal changes in exposure to previous interventions.

3. Examples of HBM surveys

3.a Examples of international HBM surveys

National Health and Nutrition Examination Survey (NHANES) in the United States

The largest continuous national surveillance programme involving HBM is the National Health and Nutrition Examination Survey (NHANES), which has been conducted by the Centers for Disease Control and Prevention (CDC), the National Center for Health Statistics (NCHS) of the United States of America since 1971 (Yetley & Johnson, 1987; Wright et al., 2007). NHANES is designed as a series of annual cross-sectional surveys. Starting with NHANES II (1976–1980), the CDC began measuring blood lead levels in the American population. NHANES III (1988–1994) included about 40 000 people from 81 counties across the United States. Data collection in the current format began in 1999, and since that point NHANES remains a continuous annual survey. NHANES uses a stratified, multistage, probability-cluster sampling design to select a representative sample of the civilian American population. Each year approximately 7000 randomly-selected residents across the United States are enrolled. Chemicals that are measured include: phenols, metals, organochlorine (OC) pesticides, phthalates, cotinine, PBDEs and other brominated flame retardants, PCBs and dioxin-like chemicals, PAHs, PFCs and VOCs. Most chemical analytes are measured in subsets of NHANES participants. The individual-level data are widely used in research projects, while statistical summaries provide information for policy-makers and the public. NHANES does not provide information about geographical regions and exposure levels in the very young. Another limitation, especially with regard to the interpretation of data on non-persistent chemicals, is that only one sample per person at one point in time is taken (spot sample).

WHO survey of POPs in human milk in the European Region

The WHO/UNEP Human Milk survey involves biomonitoring of POPs in human milk using standardized recruitment, sampling, laboratory analysis, and data presentation protocols. Human milk was selected for the survey because it provides information on the cumulative exposure of the mother as well as the current exposure of the infant. The main objective of this continuous biomonitoring programme is to examine temporal trends in participating countries. The first round of the survey took place in 1987–1988, while the last (fourth and fifth) rounds took place in 2008–2009 and 2010–2011.

National surveys are designed using the guidelines for national protocol development. In each country, at least 50 milk samples from healthy, primiparous (i.e. has had only one pregnancy longer than 20 weeks of gestation) women under 30 years of age need to be collected within 3–8 weeks after the child's birth. The women need to exclusively breastfeed a single child (twin births excluded), and they need to have been living in the same area for at least 10 years. Women with unusual exposure history, such as living near known POP hot spots, are excluded. Each woman provides at least 50 mL of milk. Samples are divided in two 25 mL portions. The first portion is used locally for analysis of analytically "simple" POPs, such as marker PCBs and organochlorine pesticides. The second portion is brought to a specimen pool to be combined with the samples of all other study participants. The pooled

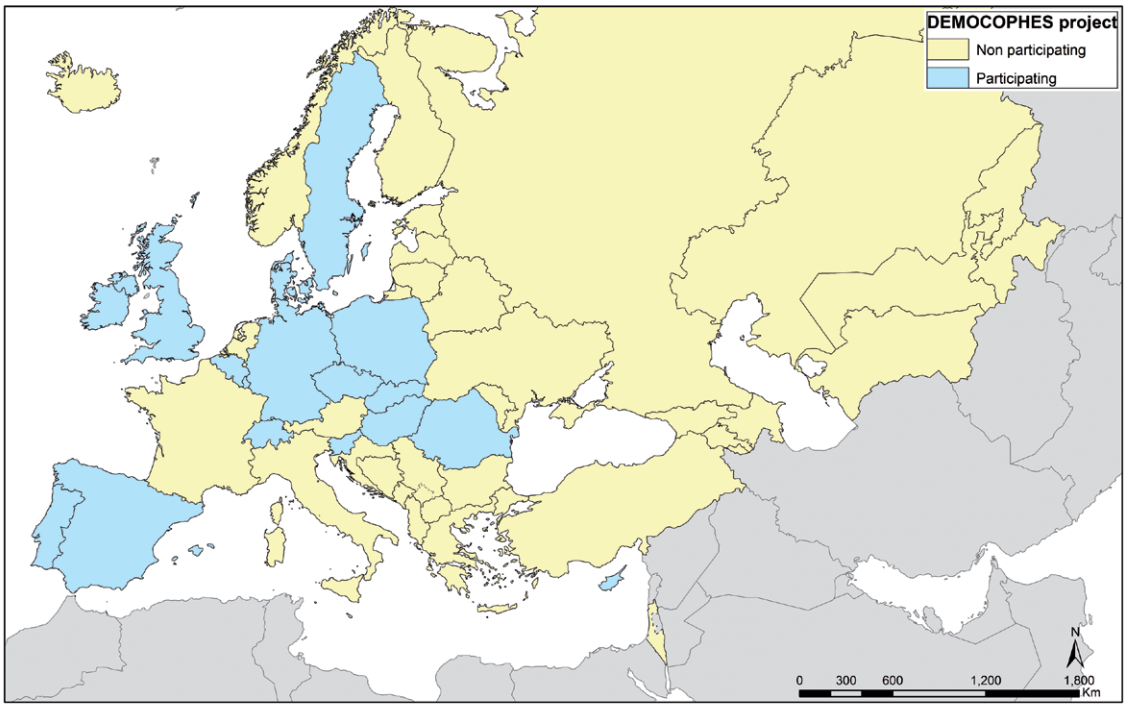
samples are then sent to the reference laboratory (currently the State Institute for Chemical and Veterinary Analysis of Food, in Freiburg, Germany) for the analysis of analytically "complex" POPs, such as polychlorinated dibenzodioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and dioxin-like PCBs. The gas chromatography–high resolution mass spectrometry (GC-HRMS) technique is used to quantify the concentrations of individual congeners. Some results of the WHO/UNEP Human Milk survey are presented in Section 4 below.

DEMOCOPHES survey in the EU

The DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale (DEMOCOPHES) project was a major international HBM survey that took into account cultural differences, ethics, available resources and expertise in various European countries (Becker et al., 2013; Casteleyn et al., 2015; Schindler et al., 2014). The project LIFE09 ENV/BE/000410 (EU, 2013) was 50% co-funded by the EC programme, "LIFE+," while the rest of the funding was provided by each participating country.

The DEMOCOPHES project demonstrated the feasibility of a harmonised approach to HBM in Europe. It was implemented in 17 European countries (Fig. 1) in close collaboration with another EC-funded project, the Consortium to Perform Human biomonitoring survey on a European Scale (COPHES), a scientific consortium that developed harmonized analytical methodologies and survey protocols. All national cross-sectional surveys aimed at assessing exposures to mercury, cadmium, cotinine and phthalates, and used human biomarkers and questionnaire data. In addition, exposure to bisphenol-A (BPA) was analysed in six countries.

Fig. 1. Countries which participated in DEMOCOPHES



The designations employed and the presentation of this material do not imply the expression of any opinion whatsoever on the part of the Secretariat of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers and boundaries. Dotted and dashed lines on maps represent approximate borders for which there may be not full agreement.

Cartography by Pierpaolo Mudu (WHO)
Data Source and map production:

Each national survey aimed to enroll a sample of 120 children, from 6 to 11 years old, and their mothers, up to the age of 45 years. Subjects residing in cities and rural areas were recruited using stratified sampling.

Each national team involved about 15 people working in collaboration with specialized experts. The national teams adapted the EU "common protocol" to local conditions and realities, ensuring that the comparability of results among participating countries is not jeopardized. Each country had to decide whether to recruit through schools or population registers and to delineate criteria, defining both rural and urban areas. Survey documents were submitted to ethics committees, as well as to privacy and data protection authorities for approval. All relevant information on protocol modifications at a national level was reported to the European survey coordinators. This information helped to develop recommendations for further development of harmonized HBM protocols.

National teams were trained to conduct recruitment, sampling and interviewing. Surveys were conducted from September 2011 to February 2012. Hair and morning urine samples were collected from almost 4000 study subjects. Half of them were from urban areas and half were from rural areas. The mothers who were interviewed provided data on residential environment, nutrition, smoking behaviour, other exposure-relevant behaviour, occupation, and socio-demographic factors.

For the laboratories analysing DEMOCOPHES samples, effective capacity-building and quality assurance (QA) and control processes were essential for obtaining comparable HBM measurements. This was achieved through the inter-laboratory comparison investigations (ICIs) and External Quality Assessment Scheme (EQAS) organized by COPHES (Esteban et al., 2014; Schindler et al., 2014). During the project, two ICI rounds and two EQUAS rounds were carried out to identify qualified laboratories. Only those laboratories that had been successful in one ICI and one EQUAS, or in two EQUAS, rounds were identified as "qualified" to analyse the samples. In early 2012, 16 laboratories conducted analysis of mercury in hair, 14 analysed urinary cadmium, 14 laboratories analysed creatinine, nine analysed cotinine, seven analysed phthalates, and five analysed bisphenol-A.

Human samples are precious and their collection is a labour-intensive and costly effort. Thus, appropriate specimen handling, transport, and storage are important considerations. Unused biological material is stored at minus 80°C and remains available for use in subsequent phases of the study or in complementary analysis, in agreement with national and European regulations for data protection and ethics. Storage of these samples for a minimum of ten years is foreseen.

The results of the chemical analysis and the questionnaires were gathered in a database for analysis and interpretation at the national level. After cleaning all the data, national experts performed the statistical analysis of the measurements and of the questionnaire data. The cleaned data were transferred to a European central database for statistical analysis and interpretation at the European level by COPHES. Preliminary results of DEMOCOPHES are presented in Section 4 of this report.

Participants of DEMOCOPHES were informed about their personal measurement results according to their wishes. National survey webpages are available at the project web site (EU, 2013). A press kit with a summary of results is also available (EU, 2013). All national results and reports were disseminated through national workshops and press releases, and presented on webpages for national surveys.

DEMOCOPHES has demonstrated that it is feasible to produce data that can be compared across borders if harmonised and standardised protocols are used and if internal and external QA is guaranteed.

3.b Examples of national and subnational cross-sectional surveys

Belgium

The HBM programme in Flanders (the Dutch-speaking part of Belgium) involved consecutive rounds of monitoring, with the characterization of the exposure distribution in the general population and the identification of reference values (Schoeters et al., 2012b).

The first Flemish Environment and Health Study (FLEHS I) (2002–2006) included only classical pollutants with well known health effects and validated analytical methods, such as heavy metals, POPs, benzene and PAHs. The survey was conducted in eight areas in Flanders with typical pollution pressure (two urban, two rural and four industrial areas). It involved about 4600 individuals, including mother-child pairs, 14 and 15 year-old students and adults between 50 and 65 years of age. FLEHS I demonstrated that living in areas with different environmental pressures yields a different fingerprint of pollutants in the body, thus indicating the importance of regional, local, and context-specific environmental policies and priorities (Maervoet et al., 2007; Den Hond et al., 2009 and 2011; Dhooge et al., 2010 and 2011).

In the second survey, FLEHS II (2007–2011), the aims were twofold: 1) to generate Flemish reference values for a large number of pollutants, and 2) to perform surveillance in two hotspot areas. Neonates and adolescents were again included, and adults between 20–40 years old were targeted in order to study fertility, which was a major research topic in FLEHS II. The survey involved 200 school students, 200 adults and 250 mother-child pairs who were recruited using a stratified random sampling scheme. The exposure biomarkers included metals, classic POPs, perfluorinated compounds, brominated flame retardants, musks, BPA, metabolites of phthalates, parabens and pesticides. Biomarkers of effect were selected on the basis of expected health outcomes of the chemicals under investigation (Den Hond et al., 2013; Koppen et al., 2009; Morrens et al., 2012; Schoeters et al., 2012; Vrijens et al., 2014). In the same period, HBM surveys were conducted in two industrial hotspot areas: one near a stainless steel manufacturing facility and one in the neighbourhood of a metal shredder. A participatory process was used to select these two exposure hot spots. The results of the hotspots were compared with the Flemish reference values for individuals of the same age group and with health-based reference values (Croes et al., 2014; Vrijens et al., 2014).

The ongoing FLEHS III survey (2012–2015) has a similar blueprint as FLEHS II: it aims to assess Flemish reference values for a large number of pollutants. The survey includes one exposure hotspot. The selection of the biomarkers was conducted using a formal multi-criteria ranking, and with the involvement of external experts. Since aging is a major topic within the current research programme, the adult group was defined as 50–65 years old.

France

A national HBM programme has been in development since 2008. It was introduced into law in August 2009 and included in the 2nd National Environment and Health Plan (2009–2013). French Ministries of Health and Environment are funding the programme, while the French Institute for Public Health Surveillance (InVS) is in charge of implementing the programme. It includes cross-sectional and longitudinal birth cohort studies (the latter is described in the next subsection). The “Esteban cross-sectional survey” involves a representative sample of 5000 individuals, ages 6 to 74 years old, residing in continental (mainland) France. This includes about 1000 children, ages 6 to 17 years old. The HBM programme’s

aims are to: establish reference values for the levels of biomarkers of exposure to chemical agents; analyse predictors of exposure; assess temporal trends in biomarkers levels (by comparing with previous surveys); and monitor the impact of public health policies and regulations aimed at reducing environmental exposures to chemicals. Implementation began in April 2014 with recruitment and a test phase. Afterward full scale data collection will take place for the duration of one year in order to take into account seasonal patterns of exposures. Data will be collected from participants who complete a questionnaire and donate biological samples (blood, urine and hair), which are stored in a biobank at -80°C for future analysis.

Germany

The German Environmental Surveys (GerESs) are nationwide population surveys, which have been carried out in Germany periodically since 1985 (Schulz et al., 2007b). The first survey (GerES I) was carried out in 1985–1986 in the former Federal Republic of Germany on 2700 adults. It was followed by GerES IIa in 1990–1991 in the western part of Germany and GerES IIb in 1991–1992 in the eastern part, with a total sample size of approximately 4000 adults and 730 children. In 1998, the third GerES (GerES III) involved 4800 adults in both the eastern and western part. The 2003–2006 survey (GerES IV) focused exclusively on children 3–14 years of age (n = 1790).

The participants of GerES surveys were randomly selected from the subject database of the National Health Interview and Examination Surveys (NHIES). Samples were representative with regard to age, gender, community size and region (east Germany/west Germany). Starting with GerES III, immigrants were included. Interviews and sampling were conducted in the households of the subjects by survey technicians. To account for seasonal effects fieldwork was conducted over a period of one year (three years in GerES IV). The first two surveys focussed mainly on heavy metals. The third and fourth surveys also included organic compounds, such as various pesticides, PAHs, PCBs, BPA and phthalates.

HBM activities on the federal level were always closely connected to the risk assessment of chemicals and chemicals regulation. At the end of the 1970s the first German Chemicals Legislation was developed (Chemicals Act, “Chemikaliengesetz” [ChemG], 1980) and entered into force in 1982. In parallel, the 1979 test operation of the Environmental Specimen Bank (ESB) started, and in 1985 the ESB was established as a permanent monitoring instrument and an archive for human specimens in order to investigate time trends of environmental exposures and to study the fate of chemicals in humans and the environment (Kolossa-Gehring et al., 2012).

ESB is a major component of the German environmental observation system providing a scientific basis for decision making by the German Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety (BMUB), and for monitoring the efficacy of such actions. Biological samples (whole blood, blood plasma, 24-hour urine and scalp hair) are collected annually from approximately 60 male and 60 female students at each of the four university cities of Münster, Ulm, Halle, and Greifswald. Samples are stored in walk-in chambers under cryogenic conditions at a temperature below –150 °C. ESB enables retrospective monitoring of phthalates, bisphenol, heavy metals, and perfluorinated compounds. It provides a continuous historical record of human exposure in Germany, and allows for the assessment of temporal trends and spatial patterns of exposure.

Russian Federation

A pilot HBM survey in maternities was conducted in collaboration with WHO in 2013–2014. It applied a standardized

protocol developed by the WHO European Centre for Environment and Health (ECEH) for monitoring the implementation of the Parma Declaration commitments. The aim of the survey in maternities was to assess prenatal exposures to selected priority pollutants in the general population and in exposure hot spots in volunteer Member States. Environmental pollutants and biomarkers were selected at WHO technical meetings, using a set of pre-defined criteria. At the first stage the survey protocol included biomarkers of exposure to mercury (total mercury in maternal hair, urine and cord blood), lead (in cord blood), cadmium (in maternal urine) and arsenic (in maternal urine). Biological samples, exposure questionnaires and medical records were collected from mothers of newborn children. Mothers were recruited from maternity wards. The survey had a randomized clustered design with two arms to assess prenatal exposures in the general population and in an industrially contaminated area.

The Russian Federation volunteered to pilot test the draft survey methodology. The general population arm involved a representative sample of women recruited at randomly selected maternity wards in the Moscow Region. The industrially contaminated area was defined as parts of an industrial city with a lead acid battery plant and other sources of emissions of metals, using a previously complied map of metal-contaminated soil.

The survey demonstrated that exposures to mercury were relatively low. Only two countries (Hungary and Poland) which participated in DEMOCOPHES had lower hair mercury levels than the participants of the Moscow Region study (Egorov et al., 2014). The results also showed that exposure to lead of participants living in an industrially contaminated area have declined substantially since the previous surveys in the early 2000s. Current cord blood mercury levels are similar to the levels of individuals living in control cities. The survey demonstrated that the levels of total arsenic in urine were higher than in the NHANES survey in the United States. Elevated levels of arsenic were strongly associated with consumption of bottled mineral water during the last trimester of pregnancy (manuscript in preparation). These results warrant further investigation to determine the sources of arsenic exposure and propose policy actions to remove contaminated products from the market.

Spain

The national HBM survey, BIOAMBIENT.ES, was conducted in the framework of the strategy for monitoring POPs and other environmental chemicals in the Spanish population. It was adopted in 2007 by the Spanish Ministry of Agriculture, Food and Environment, and it was implemented nation-wide. The survey was linked to annual occupational health exams. It included study participants of various occupations and aimed to recruit a nationally representative sample of the Spanish population. Participants were workers older than 18 years old who were residents of Spain for at least five years. The selection was done through a stratified cluster sampling, covering all geographical areas and economic sectors. In order to ensure a proper seasonal distribution, four sampling periods per year were defined: January–March, April–June, July–September, and October–December (Esteban et al., 2013). The final sample size was almost 2000 individuals, age 18 to 67 years old, who were recruited between March 2009 and July 2010. The participants donated samples of first-morning urine, blood, serum and scalp hair. The attention was focused on chemicals that persist in the environment, bio-accumulate through the food chain, and are of public health concern due to their recognized toxicity.

In this programme, mercury was measured in hair, blood and urine. Other metals were measured in urine and blood; PFCs, PBDEs, PCBs and organochlorine pesticides were measured in serum, and PAH metabolites and cotinine were measured in urine.

Sociodemographic data and information on living and environmental conditions were collected via questionnaire (Pérez-Gómez et al., 2012). Complete results of the occupational health exams were also abstracted for data analysis. Preliminary results of BIOAMBIENT.ES are already available (Cañas et al., 2014; Huetos et al., 2014; Bartolomé et al., 2015), although data analysis is still in progress. The results confirmed the high fish consumption in Spain and, correspondingly, a high exposure to methylmercury. Exposures to lead and cadmium were not found to be major problems in Spain, as measured exposure levels were in the same range or lower than those reported in similar studies from neighbouring European countries. Levels of PCBs have decreased over the last 20 years and are now similar to those in Germany and are even lower than those in France (Huetos et al., 2014). Exposures to PAHs are in the same range or lower than in neighbouring countries (Bartolomé et al., 2015).

3.c Examples of national birth cohort studies

Among many birth cohorts studies in Europe, the four biggest in terms of population size (Guxens et al., 2012; Vrijheid et al., 2012) are briefly discussed below.

France

The "Etude Longitudinale Francaise depuis l'Enfance (ELFE)" (French Longitudinal Study of Children) survey involves a nationally representative cohort of children. It was launched in April 2011 (Vandentorren et al., 2009). About 20 000 children will be followed from birth to adulthood to characterize the impact of environmental exposures and the socioeconomic context on health and behaviour. Environmental stressors measured in the clinical and biological component of the cohort include heavy metals, volatile organic compounds, pesticides, POPs, phthalates, environmental tobacco smoke, moulds, air pollutants, electromagnetic field, ultraviolet (UV) radiation, ionizing radiations and noise. The main health outcomes to be investigated include neurodevelopment, fertility, puberty and sexual development, asthma and allergies, hearing loss, obesity and growth. Data on school achievements have also been collected. The survey also includes the collection of samples of: mothers' venous blood and urine before delivery; cord blood and umbilical cord during delivery; maternal scalp hair and breast milk; and a portion of the baby's first stools after delivery. The project aims at assessing the consequences of prenatal and early childhood exposure to pollutants (lead, mercury, PCBs, pesticides), phthalates, and BPA on children's neuro-cognitive and reproductive development. As of June 2014, preliminary descriptive results for lead and mercury exposure indicate decreasing temporal trends in exposures compared to previous results obtained in similar populations in France.

Denmark

The Danish National Birth Cohort (DNBC) includes data from about 100 000 pregnant women and children who were recruited from March 1996 to November 2002 (Olsen et al., 2001). Data collection covered all geographic regions of the country. Candidates for the cohort were all pregnant women in Denmark who, at their first visit to the general practitioner, wanted to carry their pregnancy to term and who spoke Danish. Exposure information from the women was collected by computer-assisted telephone interviews four times: twice during pregnancy, once when their children were six months old, and once when their children were 18 months old. Measured biomarkers focused on perfluorinated compounds. A biological bank had been set up with blood taken from the mother twice during pregnancy, cord blood taken shortly after birth and

blood samples from children collected within six months after the delivery.

Norway

The Norwegian Mother and Child Cohort Study (MoBa) is an ongoing long-term prospective cohort study of about 110 000 pregnant Norwegian women and their children recruited from 1999 to 2008 (Magnus et al., 2006). The target population of the study is all women who give birth in Norway. Each pregnant woman was asked to provide biological specimens (urine and blood) and complete a series of questionnaires. Blood samples were also taken from the participating fathers. During and after birth umbilical cord samples were taken from the baby. As of October 2012 a total of 68 900 paternal sample sets were registered. In addition 94 500 maternal sample sets were taken at around week 17 of pregnancy and 85 100 maternal sample sets were taken after delivery. 90 700 children's sample sets were registered. Measured biomarkers include metabolites of organophosphate pesticides, phthalates and BPA in pooled urine specimens.

Spain

The Spanish Environment and Childhood Research Network ("Infancia y Medio Ambiente" [INMA]) includes several Spanish cohorts of pregnant women and their children from various cities such as Valencia, Sabadell, Asturias and Guipúzcoa. The recruitment period started in 1997 and finished in 2008. A total of almost 4000 pregnant women had been recruited. Supplemental data have been collected using questionnaires, clinical records, physical examinations and environmental monitoring. Various biomarkers including metals, polybrominated and organochlorine compounds, BPA and phenols, phthalates and PAHs have been analysed in blood, placenta, urine, saliva, breast milk, hair and nails (Guxens et al., 2012; INMA, 2015).

3.d Examples of ongoing epidemiological studies in Europe aimed at characterizing complete exposures to environmental toxicants

The Cross-Mediterranean Environment and Health Network (CROME) project, funded under the LIFE+ (2007–2013) programme (CROME, 2015), aims to demonstrate an integrated methodology for the interpretation of HBM data that will allow researchers to quantitatively assess the impact of acute/chronic chemical exposure (e.g. to neurological toxicants, carcinogens) on human health. The project started in July 2013 and will end in December 2016. The methodology involves linking environmental monitoring, HBM data and epidemiological observations using physiologically-based toxicokinetic (PBTK) and toxicodynamic (PBTD) models. Associations between observed health outcomes and the measured/estimated markers of exposure are assessed using advanced statistical models and causal diagrams. The latter use the biomarker values measured in different biological matrices (urine and/or blood) in order to estimate, through a lifetime PBTK model, the biological effective dose in the target tissue (which is consistent with the biomarker level measured). Health impact is estimated through survey-weighted logistic multivariate regression, adjusting for different covariates (age, sex, socioeconomic status). CROME methodology and tools will be applied and integrated into the decision-making processes of the competent authorities in the four demonstration sites (Greece, Italy, Slovenia and Spain), allowing researchers to assess different levels of environmental exposure, age windows, and socioeconomic and genetic variability.

The main objective of the Health and Environment-wide Associations based on Large population Surveys (HEALS), the EU project funded within the 7th Framework Programme for Research and Technological Development (FP7), is to refine an integrated methodology for EU-wide environment and health assessments (HEALS, 2015). This involves refining the application of the corresponding analytical and computational tools for performing environment-wide association studies. The project started in October 2013 and will last five years. The HEALS approach brings together and organizes environmental, socioeconomic, exposure, biomarker and health effect data. It includes the procedures and computational sequences necessary for applying advanced bioinformatics to ensure that environmental exposure-health associations are studied comprehensively.

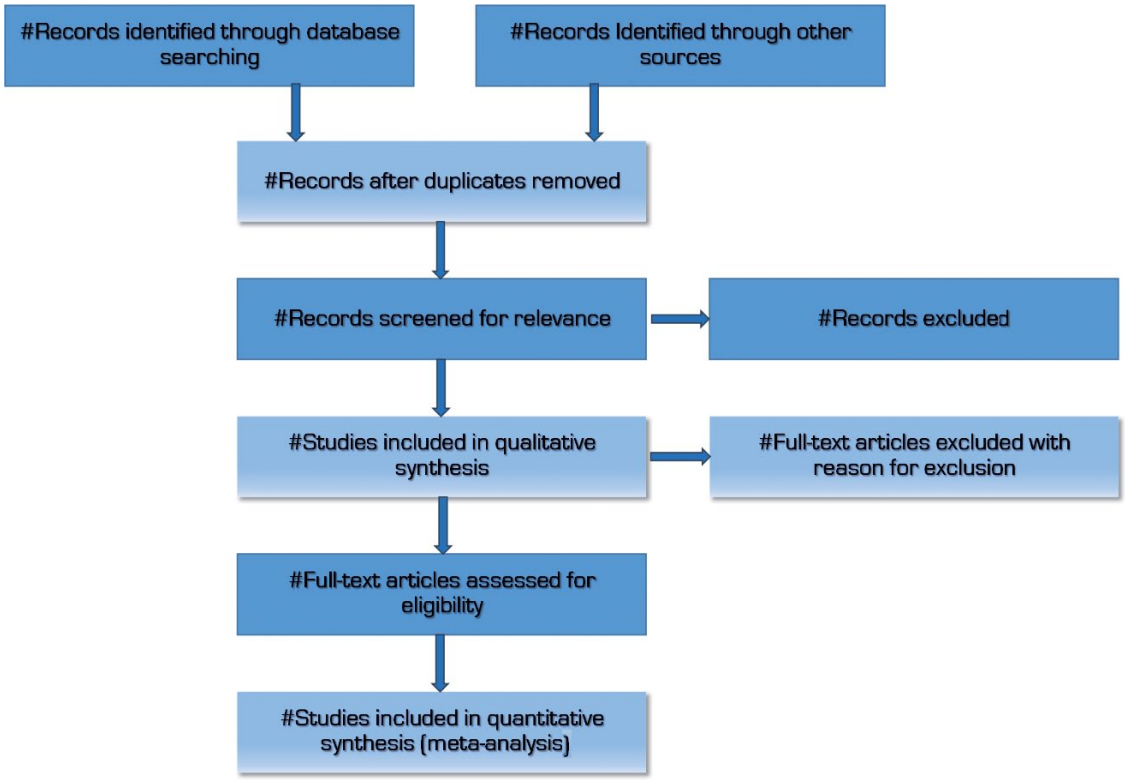
The overall approach will be verified and refined in a series of population studies across Europe, including twin cohorts, which will assess different levels of environmental exposure, age windows of exposure, and socioeconomic and genetic variability. The HEALS approach will be applied in a pilot environment and health examination surveys of children, including singletons and sets of twins, with matched singletons from ten EU Member States (the Exposure and Health Examination Survey [EXHES] Study). Focus is on susceptibility windows during growth (including pregnancy) and development, and on the distribution of the burden of environment-related diseases. There will be a focus on vulnerable populations such as the young, elderly, socioeconomically disadvantaged, and ethnic minorities. HEALS aims to reduce exposure measurement error by providing a more reliable “time–geography of exposure”, shifting the current paradigm from a population to an individual level. The reasons are to contribute to unravelling the exposome while simultaneously identifying, characterizing and quantifying exogenous and endogenous exposures and modifiable disease risk factors.

4. Overview and interpretation of available HBM data in the WHO European Region

4.a Outline of review methodology

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology (Moher et al., 2009) was used to carry out the systematic review presented here (Fig. 2). PRISMA helps to achieve transparent and complete reporting when the amount of relevant literature sources is large.

Fig. 2. The PRISMA flow diagram, depicting the flow of information through the different phases of a systematic review



Source: reprinted and adapted from Moher et al. (©2009:1009) with permission from Elsevier.

Scopus and PubMed online databases were searched for HBM surveys. Publications reviewed needed to fulfill specific matching criteria:

- the review was limited to the WHO European Region; and
- for most pollutants, only results from national HBM surveys were included. Smaller subnational surveys were only included for pollutants with limited available national data, such as VOCs and PAHs.

Relevant publications were identified using a systematic search in Scopus and PubMed. For most pollutants, multiple search terms were used.

For completeness, the results of the literature search were supplemented with publications known to the search team, but which are not listed in PubMed and Scopus, such as reports published by government agencies or international organizations. In addition, bibliographies of publications identified during the previous steps were searched for additional references. Then the search was repeated using additional search terms (e.g. abbreviations of chemicals), which were found in manually identified sources.

The results of national surveys were summarized in tables, which are intended to provide a general overview of the situation in the WHO European Region. If data were presented in publications in a graphical form only, data values were extracted from the plots using specialised software Engauge Digitizer. For some chemical families, which includes multiple compounds (e.g. phthalates), the data on the most abundant or most public health-relevant chemicals were included in summary tables. The data were grouped by the sample matrix (e.g. urine, blood) and by units of analysis.

For the sake of brevity, the data on some organic pollutants were summarized as arithmetic means and ranges for country-level summary values (geometric means [GM] or medians from national surveys). Mean values were estimated only if data were available for three or more countries. The data on organic pollutants were also summarized by geographical subregions in accordance with the United Nations statistical classification (UN, 2014). The Member States of the WHO European Region belong to six geographical subregions: eastern, northern, western and southern Europe, and central and western Asia.

4.b Metals

Many metals are known to have adverse impacts on human health via various toxicological mechanisms. Lead, mercury, cadmium and arsenic are some of the most common toxic metals found in the environment, with well characterized adverse health effects as demonstrated by extensive data on human exposures in Europe.

Lead

There is convincing evidence of lead prenatal neurotoxicity (Andersen, Nielsen & Grandjean, 2000), which interferes with the brain growth process, adversely affects the structural integrity of the nervous system (Blake, 2004; Rodier, 1995), and causes subclinical brain dysfunction at doses much lower than those affecting adult brain functions (Grandjean & Landrigan, 2006). Such latent subclinical impairments at the early life stage have also been linked with overt neurological diseases in ageing individuals (Grandjean & Landrigan, 2006; Landrigan et al., 2005).

Adverse health effects caused by lead exposure include intellectual and behaviour deficits in children, deficits in fine motor function, hand-eye coordination, and reaction time; and decreased performance on intelligence tests (Sanders et al., 2009). The

developmental effects of lead occur during a critical time window at the age of less than two years (Sanders et al., 2009). Recent findings reviewed by the CDC showed that children's physical and mental development can be affected by low level lead exposure (blood lead levels < 100 µg/L) (Sanders et al., 2009). Lead was also found to produce lifelong changes in behaviour: decreased attention span, increased impulsivity, heightened aggressiveness, and impaired motor coordination, memory and language skills (Grandjean & Landrigan, 2006).

Lead is among the most potent nephrotoxic environmental pollutants (Nordberg, Fowler & Nordberg, 2007). Renal damage induced by lead primarily affects the cellular and functional integrity of the proximal tubules. The risk of nephrotoxicity at low exposure levels, which are found in most industrialized countries, is not yet characterized (Chaumont et al., 2012).

Sources of lead exposure include: contaminated ambient air, foods, drinking-water, soil, and dust (Agency for Toxic Substances and Disease Registry [ATSDR], 2007b). Drinking water in houses containing lead pipes may contain lead, especially if the water is acidic. Plumbing that contains lead may be found in public drinking-water systems and in houses that are more than 20 years old. Fruits, vegetables, and grains grown in lead-containing soil may contain levels of lead in excess of background levels. Cigarette smoke may also contain small amounts of lead. The principal source of lead exposure for children is hand-to-mouth contact after exposure to lead-containing soil or dust in urban areas. Dust is contaminated mostly by flaking lead-containing paint from older buildings or bridges or by industrial releases (ATSDR, 2007b; Landrigan & Todd, 1994).

There has been a significant worldwide decrease of blood lead levels over the last 20 years, due to: the elimination of lead in petrol, the corresponding decline of lead levels in ambient air, and other exposure control measures (Jakubowski, 2012). Adult blood lead levels in Germany have declined almost two-fold, from the highest level (GM 62 µg/L) observed in the first national surveys in 1985–1986 to the GM 32 µg/L level observed in the last survey in 1998. There was also a two-fold decline in German children: from a GM of 32 µg/L in 1990–1992 to a GM of 16 µg/L in 2003–2006 (Table 6). However, the ages of children examined were not consistent, which could confound the comparison. Data for other countries, which have been available since 2001, show comparable, relatively low blood levels, ranging from 9 µg/L in neonates from Belgium to 30 µg/L in children age 8–10 years old in the Czech Republic.

The HBM-I value for lead, which was previously set at 100 µg/L for children younger than 12 years old and women of childbearing age, was suspended in 2010. Based on the recent findings, the German Biomonitoring Commission concluded that setting any "effect threshold" would be arbitrary. In other words there is no "safe" lead exposure level. This is because even low level exposure to lead (below 100 µg/L blood lead level) has been associated with adverse health effects and no threshold for adverse effects has been identified (Sanders et al., 2009). Thus, the goal is to reduce exposures to lead to the lowest level possible.

Table 6. Summary of available HBM data on lead

Country	Study	Population (N)	Blood Pb (ng/mL)	Urine Pb (µg/g creat.)	Reference
Belgium (Flanders)	FLEHS first survey (2003)	Adolescents 14–15 y.o. (1679)	22 MED 45.4 P90		Schroijen et al., 2008; Schoeters et al., 2012a
	FLEHS second survey (2007–2011)	Adolescents 14–15 y.o. (1679)	22 MED 45.4 P90		
		Adolescents 14–15 y.o. (207)	14.8 GM 27.6 P90		
		Mothers 20–40 y.o. (235)	11.1 GM 18.9 P90		
Germany	GerES I (1985–86)	Adults 25–69 y.o. (2347)	61.7 GM 114 P95		Kolossa–Gehring et al., 2012; Schulz et al., 2007b
	GerES II (1990–92)	Adults 18–79 y.o. (3966)			
		Children 6–17 y.o. (713)			
	GerES III (1998)	Adults 18–69 y.o. (3974)			
	GerES IV (2003–2006)	Children 3–14 y.o. (1560)			
France	ENNS (2006–2007)	Adults 18–74 y.o. (1949)	25.7 GM 73 P95		Frery et al., 2012
Italy	PROBE (2008–2010)	Adolescents 13–15 y.o. (252)	9.5 GM 29.4 P95		Pino et al., 2012
Spain	BIOAMBIENT.ES (2009–2010)	Adults 18–65 y.o. (1880)	24.0 GM 47.4 P90 56.8 P95		Cañas et al., 2014
Czech Republic	CZ-HBM (2001–2003)	Children 8–10 y.o. (333)	31 GM 54 P95		Cerná et al., 2012; Batáriová et al., 2006
		Adults 18–58 y.o. (1188)	33 GM 72 P95		
	CZ-HBM (2005–2009)	Children 8–10 y.o. (723)	22 GM M 19 GM F		
		Adults 18–58 y.o. (1227)	23 GM M 14 GM F		
Slovenia	Pilot HBM (2007–2009)	Adults 20–40 y.o. (274)	18.4 GM 40.3 P95		Snoj Tratnik, Mazej & Horvat, 2012

y.o. = years old
F = female
M = male
MED =median

Cadmium

Cadmium (Cd) is a potent nephrotoxic environmental pollutant (Nordberg et al., 2007). High level exposure to cadmium can cause adverse renal effects in vulnerable individuals. However, the risk of nephrotoxicity at low exposure levels, as found in most industrialized countries, is poorly characterized (Chaumont et al., 2012). Cadmium accumulates in the body with age, inducing bone, cardiovascular, hepatic and lung damage. It has been classified by the IARC as a known human carcinogen and by the United States of America EPA as a probable human carcinogen (EPA, 2014a). Exposure occurs primary through tobacco smoke and dietary intake.

The passage of cadmium through the placenta into the foetus is rather limited. It has been reported that exposure to low levels of cadmium during pregnancy is associated with low birth weight and, possibly, congenital malformations. However, maternal smoking is a powerful confounder of this association, which may not have been fully controlled for in previous studies (reviewed by Järup, 1998).

A major source of cadmium exposure among the general population is smoking (active as well as passive), as tobacco leaves accumulate high levels of cadmium from the soil. Direct measurement of cadmium levels in body tissues confirms that smoking roughly doubles cadmium body burden in comparison to not smoking (ATSDR, 2008). For non-smokers, food is generally the largest source of cadmium exposure. People who regularly consume shellfish and organ meats (kidney, liver) are at higher risk of exposure (ATSDR, 2008).

Population-based reference values for cadmium in blood derived from German HBM surveys are < 0.3 µg/L for children and 1µg/L for non-smoking adults (Schulz et al., 2011). The HBM-I and HBM-II values set by the German Human Biomonitoring Commission are 0.5 µg/L and 2.0 µg/L in urine of children, and 1.0 µg/L and 4.0 µg/L in urine of adults (Table 2). Based on the available HBM data, the exposure of the majority of the European population is below the health-based values.

In most surveys, children and neonates had GM levels around 0.1 µg/L in blood and below 0.1 µg/L in urine, while blood levels in adolescents (based on data from Belgium and Italy) were 0.2–0.4 µg/L (Table 7). In adults, blood GMs were between 0.3 and 0.6 µg/L, while urine GMs were between 0.2 and 0.3 µg/g creatinine. Lower levels were generally found in children compared to adults, presumably because cadmium accumulates in the human body with age, and also because of higher exposure in adults due to smoking.

Mothers tended to have higher levels of cadmium than their children. Levels of cadmium in the general population seem to persist at approximately the same level for years.

Nevertheless increased exposure levels have been found in some subpopulations. According to the data from national surveys, the HBM I level was exceeded in a substantial proportion of the population of the Czech Republic, where 5% of adults studied had urine levels of cadmium above 1.29 µg/g creatinine (P95 value). German adults also had high exposures, where the P95 urine level was 1.27 µg/L in 1990–1992 (Table 7). A proportion of the adolescent population exceeded the 1 µg/L blood cadmium in Belgium, while a proportion of adults in the Slovenian Pilot HBM survey also exceeded that level (Table 7).

In the recently completed DEMOCOPHES survey (EU, 2013) no mothers or children had a urine cadmium level that exceeded the corresponding HBM-II thresholds (Berglund et al., 2014; Mørck et al., 2014b; Smolders et al., 2014). However, 0.24% of children exceeded the HBM-I value. Also, 1.1% of mothers (including 0.6% of non-smoking and 3.1% of smoking mothers) exceeded the 1 µg/g creatinine threshold set by the European Food Safety Authority (EFSA) (Berglund et al., 2014).

Table 7. Summary of available HBM data on cadmium

Country	Study	Population (N)	Blood Cd (µg/L)	Urinary Cd (µg/g creat.)	Urinary Cd (µg/L)	Reference
Belgium (Flanders)	FLEHS first survey (2003)	Adolescents 14–15 y.o. (1679)	0.39 MED 1.26 P90			Schoeters et al., 2012a; Schroijen et al., 2008
	FLEHS second survey (2007–2011)	Neonates (241)	0.073 GM 0.160 P90			
		Mothers 20–40 y.o. (235))	0.312 GM 0.728 P90			
		Adolescents 14–15 y.o. (207)	0.210 GM 0.471 P90			
France	ENNS (2006–2007)	Adults 18–74 y.o. (1930)		0.29 GM 0.91 P95		Frery et al., 2012
Italy	PROBE (2008–2010)	Adolescents 13–15 y.o. (252)	0.26 GM 0.74 P95			Pino et al., 2012
Spain	BIOAMBIENT.ES (2009–2010)	Adults 18–65 y.o. (1880)		0.20 GM 0.56 P90 0.75 P95	0.27 GM 0.76 P90 1.03 P95	Argelia Castaño, personal communication
	ISCIII pilot study (2009–2010)	Adults 23–66 y.o		0.25 GM 0.55 P90 0.71 P95		Castaño et al., 2012
Czech Republic	CZ-HBM (2001–2003)	Children 8–10 y.o. (333)				Batáriová et al., 2006; Cerná et al., 2012
		Adults 18–58 y.o. (1188)	0.6 GM 3.0 P95	0.29 GM 1.29 P95		
	CZ-HBM (2005–2009)	Children 8–10 y.o. (723)				
		Adults 18–58 y.o. (1227)				
Slovenia	Pilot HBM (2007–2009)	Adults 20–40 y.o. (274)	0.28 GM 1.2 P95			Snoj Tratnik, Mazej & Horvat, 2012
EU (17 countries)	DEMOCOPHES (2010–2012)	Children 6–11 y.o. (1844)		0.065 GM 0.181 P90	0.071 GM 0.220 P90	Berglund et al., 2014; Den Hond et al., 2015
		Mothers < 45 y.o. (1844)		0.24 GM 0.59 P90 in smokers (N = 360) 0.18 GM 0.42 P90 in non-smokers (N = 1272)	0.219 GM 0.620 P90	

Among the countries which took part in DEMOCOPHES, the levels of cadmium in adults were by far the highest in Poland (with the GM level of 0.42 µg/g creatinine and P90 of 1.29 µg/g creatinine in smoking women, and GM of 0.36 µg/g creatinine and P90 of 0.83 µg/g creatinine in non-smoking women). The main reason for this might be that farmers there used fertilizers with high cadmium contents (Berglund et al., 2014). The levels of cadmium in Polish children were lower than in the United Kingdom and Luxembourg.

Mercury

Mercury (Hg) is an important neurotoxin (Rodier, 1995; Andersen, Nielsen & Grandjean, 2000; Blake, 2004). Exposure to the organic form of mercury, methyl mercury (MeHg), causes subclinical brain impairment at low doses, with the higest vulnerability at the prenatal development stage (Grandjean & Landrigan, 2006). Chronic exposure to low-levels of MeHg can lead to neuropsychological dysfunctions in the domains of language, attention, and memory, and to a lesser extent in visual-spatial and motor functions (Grandjean et al., 1997). Humans are mainly exposed to organic mercury through consumption of aquatic food, while exposure to inorganic or elemental mercury occurs mainly through inhalation during occupational activities or from dental amalgam release.

In contrast to MeHg, remarkably little is known about the developmental neurotoxicity of elemental mercury or inorganic mercury compounds (Davidson, Myers & Weiss, 2004). Although elemental mercury passes through the placenta, it accumulates much less in the foetal brain than in the brain of the mother (Clarkson, 2002). In addition, children are rarely exposed to mercury vapour or inorganic mercury, as these exposures occur mainly in occupational settings (Davidson, Myers & Weiss, 2004).

The 2.3 µg/g guidance value for mercury in hair, based on the tolerable daily intake (TDI) limit, was defined by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) at its 67th meeting in 2006 (FAO/WHO, 2006). The RfD of 0.1 µg/kg body weight per day, established by the United States EPA, corresponds to the hair mercury concentration of about 1 µg/g hair for children and women of child-bearing age (National Research Council, 2000). More recent research involved analysis of data from studies of developmental neurotoxicity at low exposure levels to estimate an even lower biological limit of 0.58 µg/g hair (Bellanger et al., 2013).

Mercury in hair

The most important source of non-occupational human exposure to mercury is fish and other aquatic foods (Horvat, Šlejkovec & Falnoga, 2012; National Research Council, 2000). Most of the mercury consumed in fish or seafood is in the organic form of highly absorbable monomethyl mercury (National Research Council, 2000), which accumulates in hair. Mercury in the hair of people who do not consume fish are normally below 0.5 µg/g. Blood levels are about 250 times lower than in hair (Horvat, Šlejkovec and Falnoga, 2012). Higher values of mercury are usually found in mothers compared to children.

The combined results of the DEMOCOPHES project showed that the GM level of mercury in the hair of mothers was 0.23 µg/g and the P90 level was 1.20 µg/g. Levels in children were lower: GM level of 0.15 µg/g and P90 level of 0.80 µg/g (Table 8). In the combined study population, 1.4% of the children and 3.4% of the mothers had mercury levels above the FAO/WHO health-based guidance value of 2.3 µg/g. About 8.1% of the children and 12.7% of the mothers had mercury levels above the 1.0 µg/g level corresponding to the United States EPA's RfD of 0.1 µg/kg body weight per day (National Research Council, 2000).
The data from the DEMOCOPHES and national HBM surveys showed that a substantial proportion of the population have hair mercury concentrations above the United States EPA guidance value of 1.0 µg/g. Recently, Bellanger et al. (2013) analysed the hair mercury data

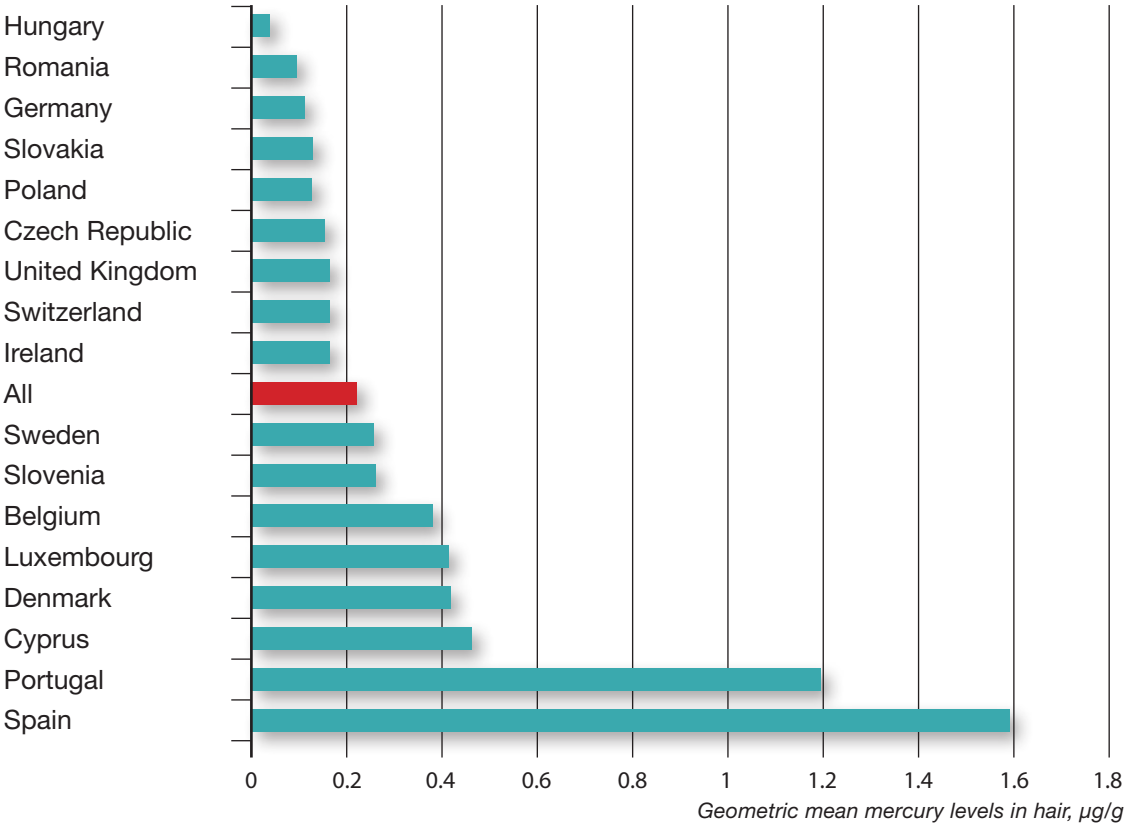
for reproductive age women in Europe. The authors estimated that more than 1.8 million children (35%) are born every year in the EU to mothers whose hair mercury level exceeds the reference level of 0.58 µg/g, and 900 000 (17%) children are born to mothers whose hair mercury level exceeds 1.0 µg/g.

Exposure varied substantially among European populations, with the highest biomarker values found in Spain and Portugal (Fig. 3), where people eat large quantities of seafood (EU, 2013; Castaño et al., 2014; Den Hond et al., 2015; Smolders et al., 2014). Countries in central and eastern Europe have relatively low exposure levels, which is likely due to low seafood consumption. In France, which did not participate in DEMOCOPHES, GM levels in hair were 0.59 µg/g and 0.37 µg/g, for adults and children, respectively (Table 8).

Mercury in blood

Blood mercury level reflects exposure through ingestion of contaminated fish or drinking water, inhalation of elemental mercury vapour in ambient air, and exposure through dental amalgams and medical treatments. The blood mercury GMs in most national surveys in Europe were below or around 1 µg/L. However, in some subpopulations exposure levels exceeded the health-based HBM-I value of 5 µg/L (Table 8).

Fig. 3. Mercury levels in hair samples of mothers (results of DEMOCOPHES survey)



Source: DEMOCOPHES data not adjusted for covariates from Den Hond et al. (2015:256).

Urinary mercury

Urinary mercury reflects exposure mainly to inorganic and elemental mercury. In the general population, the main source of exposure is amalgam dental fillings. The German Human Biomonitoring Commission's reference value (ReV) for adults without dental amalgam fillings is

1 µg/L in urine (Schulz et al., 2011). The corresponding ReV for children without amalgam fillings is 0.4 µg/L (Schulz et al., 2011). The health-based HBM-I guidance value for mercury in urine is 7 µg/L or 5 µg/g creatinine. GM levels in adults in most countries (except Spain) are below the reference value for adults. Significant differences in mercury levels were observed in the urine of children between the periods of 1990–1992 and 2003–2006. While older surveys reported GM levels that exceeded the reference value, more recent surveys generally reported P90 levels below 0.4 µg/L. This significant decline in mercury urine concentration in children, which was not evident in adults, is most probably associated with the reduction of dental amalgam use in children. The HBM-I level was exceeded only in the Czech Republic, where adults were reported to have a urine P95 level of 6.8 µg/g creatinine. Furthermore, children from the Czech Republic had the highest P95 values among the available national surveys (Table 8).

Overall, exposures to mercury in the European population have been stable during the past 20 years. Mercury levels were generally higher in adults than in children, most probably due to the bio-accumulative nature of this metal. The highest levels of mercury in hair and blood samples were measured in coastal populations with high levels of fish consumption (reviewed by Višnjevec, Kocman & Horvat, 2014).

Table 8. Summary of available HBM data on total mercury and methyl mercury (MeHg)

Country	Study	Population (N)	Total mercury				MeHg	Reference
			Blood (ng/mL)	Urine (µg/g creat.)	Urine (µg/L)	Hair (µg/g)	Hair (µg/g)	
Belgium (Flanders)	FLEHS first survey (2007-2011)	Mothers 20–40 y.o. (242)				0.35 GM 0.82 P90	0.26 GM 0.65 P90	Schoeters et al., 2012a
		Adolescents 14–15 y.o. (206)				0.19 GM 0.47 P90	0.12 GM 0.35 P90	
Germany	GerES I (1985–1986)	Adults 25–69 y.o. (2519)						Kolossa-Gehring et al., 2012; Schulz et al., 2007b
	GerES II (1990–1992)	Adults 18–79 y.o. (4287)	0.5 GM 2.0 P95		0.53 GM 3.7 P95			
		Children 6–17 y.o. (812)	0.33 GM 1.4 P95		0.54 GM 3.9 P95			
	GerES III (1998)	Adults 18–69 y.o. (4822)	0.61 GM 2.4 P95		0.4 GM 3.0 P95			
	ENNS (2006–2007)	Children 3–14 y.o. (1552)	0.23 GM 0.3 P90		<0.1 GM 0.3 P90			

Table 8 (concluded)

Country	Study	Population (N)	Total mercury				MeHg	Reference
			Blood (ng/mL)	Urine (µg/g creat.)	Urine (µg/L)	Hair (µg/g)	Hair (µg/g)	
France	ENNS (2006–2007)	Adults 18–74 y.o. (365)				0.59 GM 1.90 P95		Frery et al., 2012
		Children 3–17 y.o. (1364)				0.37 GM 1.20 P95		
Italy	PROBE (2008–2010)	Adolescents 13–15 y.o. (252)	0.84 GM 3.55 P95					Pino et al., 2012
Spain	ISCIII pilot study (2009–2010)	Adults 23–66 y.o. (175)		1.23 GM 2.72 P90 3.30 P95		2.12 GM 5.09 P90		Castaño et al., 2012
Czech Republic	CZ-HBM (2001–2003)	Children 8–10 y.o. (333)	0.43 GM 1.44 P95	0.45 GM 4.18 P95				Batáriová et al., 2006; Èerná et al., 2012
		Adults 18–58 y.o. (1188)	0.82 GM 3.45 P95	0.61 GM 6.8 P95				
	CZ-HBM (2005–2009)	Children 8–10 y.o. (723)						
		Adults 18–58 y.o. (1227)	0.6 GM 0.75 GM					
Austria	2008-2010	Children 6–11 y.o. 50)					6 MED	Hohenblum et al., 2012
		Adults 25–50 y.o. (100)					64 MED	
Slovenia	National HBM survey (2007–2009)	Adults 20–40 y.o. (274)	1.07 GM 4.03 P95	0.50 GM 3.44 P95		0.23 GM 0.89 P95		Snoj Tratnik, Mazej & Horvat, 2012
17 EU countries	DEMOCOPHES (2010–2012)	Children 6–11 y.o. (1844)				0.15 GM 0.80 P90		EU, 2013; Smolders et al., 2014
		Mothers < 45 y.o. (1844)				0.23 GM 1.20 P90		

Arsenic

The toxicity of arsenic (As) and its compounds depends on the form (inorganic/organic) and the oxidation state of arsenic. The toxicologically relevant arsenic (TRA) species include arsenious acid (As[III]), arsenic acid (As[V]), monomethylarsonic acid (MMA), dimethylarsinic acid (DMA) and trimethylarsine oxide (TMAO). The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) concluded that inorganic arsenic is genotoxic and a known human carcinogen. Therefore, exposure should be "as low as is reasonably practicable" (ALARP).

On the other hand, dietary exposure to organic arsenic is unlikely to constitute a risk to health. The most prevalent effects consistently reported at low level subchronic arsenic exposure involve skin changes, such as hyperpigmentation and hyperkeratosis (Tsuji et al., 2004). Other effects that have been reported for subchronic exposure include gastrointestinal disturbances, peripheral neuropathy, liver effects, vascular disease (leading to gangrene) and haematological disorders (Liu& Waalkes, 2008; Tsuji et al., 2004). Carcinogenicity is the most serious consequence of chronic arsenic exposure.

Health effects of subchronic arsenic exposure in children are similar to those in older age groups. Children do not appear to be more sensitive than adults. Thus exposure studies in adults may be relevant for deriving reference levels for children, although differences in dose-per-body-weight should be considered (Tsuji et al., 2004).

Exposure to toxic arsenic species (through food, water or dust particles) is reflected in measurement of arsenic in urine, where DMA predominates (Šlejkovec et al., 2008). Therefore, the most common biomarker of exposure to inorganic arsenic is urinary DMA, and also MMA (Alyward et al., 2014). The major form of dietary arsenic, which predominates in seafood, is the non-toxic organic, arsenobetaine (Hughes, 2006). Elevated concentrations of this compound can be found in urine up to three days after consumption of seafood (Navas-Acien et al., 2011). Some types of seafood (especially mussels, shrimp and some fish) can be rich in DMA, arsenosugars, and inorganic arsenic (e.g. algae and animals which feed on them) (Cullen et al., 1989). Blood levels of arsenic do not appear to be a reliable indicator of chronic exposure to low levels of arsenic, due to the fast clearance of arsenic in blood (ASTDR, 2007).

The general population is exposed to arsenic most commonly through fish and other seafood (Hughes, 2006). In contrast to mercury, arsenic is mostly present in non-toxic organic forms in fish and shell fish, which are much less harmful to humans than inorganic arsenic (Horvat, Šlejkovec and Falnoga, 2012). The most important source of exposure to inorganic arsenic is drinking-water (Hughes, 2006). Levels of inorganic arsenic in drinking-water depend on the geochemical conditions of the area (Nordstrom, 2002). For example, in some areas in eastern Croatia, ground water has high concentrations of arsenic. Urinary arsenic is most frequently used as a biomarker to assess environmental exposure to arsenic. The ReVfor total arsenic in urine, according to the findings of the German HBM survey, is 15 µg/L for children and adults who did not eat fish during 48 hours prior to sample collection (Schulz et al., 2011).

The GM levels of total arsenic in European populations were from 0.5 µg/L to 1 µg/L in blood and from 4µg/g to 16 µg/g creatinine in urine. TRA species in urine were reported only for Belgium and France, where the GMs and P95s were comparable between the countries (Table 9). There was no obvious difference observed between children/adolescents and adults.

Table 9. Summary of available HBM data on arsenic (toxicologically relevant species including inorganic arsenic and its metabolites)

Country	Study	Population (N)	Total arsenic			TRA species	Reference
			Blood (ng/mL)	Urine (µg/g creat.)	Urine (µg/L)	Urine (µg/g creat.)	
Belgium (Flanders)	FLEHS first survey (2007-2011)	Neonates (241)	0.54 GM 2.18 P90				Schoeters et al., 2012a
		Mothers 20–40 y.o. (235)	0.64 GM 2.04 P90	15.9 GM 71.4 P90		3.7 GM 10.7 P90	
		Adolescents 14–15 y.o. (207)	0.62 GM 2.12 P90	9.3 GM 49.0 P90		3.6 GM 8.0 P90	
Germany	GerES I (1985–1986)	Adults 25–69 y.o. (2542)			9.02 GM 37.5 P95		Kolossa-Gehring et al., 2012; Schulz et al., 2007b
	GerES II (1990–1992)	Adults 18–79 y.o. (4001)	0.5 GM 2.0 P95		6.33 GM 30.2 P95		
		Children 6–17 y.o. (731)	0.33 GM 1.4 P95		6.01 GM 27.5 P95		
	GerES III (1998)	Adults 18–69 y.o. (4052)	0.61 GM 2.4 P95		3.87 GM 19.3 P95		
	GerES IV (2003–2006)	Children 3–14 y.o. (1734)	0.23 GM 0.3 P90		4.4 GM 11.0 P90		
France	ENNS (2006–2007)	Adults 18–74 y.o. (1515)		11.96 GM 61.29 P95		3.34 GM 8.9 P95	Frery et al., 2012
Italy	PROBE (2008–2010)	Adolescents 13–15 y.o. (252)	0.82 GM 3.69 P95				Pino et al., 2012
Slovenia	Pilot HBM (2007–2009)	Adults 20–40 y.o. (274)	0.74 GM 2.98 P95				Snoj Tratnik, Mazej & Horvat, 2012

4.c Organic pollutants

Selected organic pollutants and their metabolites studied in HBM surveys in the WHO European Region are discussed below. They are grouped in accordance with the biological sample matrices in which they were primarily analysed: compounds that are persistent were commonly identified in blood and human milk, while non-persistent chemicals were usually detected in urine.

Organic compounds identified in blood and human milk

Pefluorinated compounds (PFCs)

Polyfluorinated alkylated substances consist of a hydrophobic alkyl chain of varying length (typically from four carbon atoms (C4) to C16) and a hydrophilic end group. The hydrophobic part may be fully

or partially fluorinated. Fully fluorinated compounds are called perfluorinated substances. The hydrophilic end group can be neutral, or positively or negatively charged. The resulting compounds are non-ionic, cationic or anionic surface active agents due to their amphiphilic character. Examples of anionic end groups are the sulfonates (-SO3-), which include perfluorooctanesulfonic acid, also known as perfluorooctane sulfonate (PFOS), the carboxylates (-COO-), which include perfluorooctanoic acid, also known as perfluorooctanoate (PFOA).

Because of their extraordinary properties (chemically inert, non-wetting, very slippery, nonstick, highly fire resistant, very high temperature ratings, highly weather resistant, etc.), they are applied in fluoropolymer-coated cookware, sports clothing, extreme weather-resistant military uniforms, food handling equipment, medical equipment, motor oil additives, fire-fighting foams, paint and ink as well as water-repellent products.

PFOS and PFOA are weakly lipophilic, water soluble and bind preferentially to proteins. Based on the results of animal experiments, their acute toxicity is considered moderate. Toxic effects observed in long-term animal tests include hepatotoxic effects and altered lipid metabolism. Tumor growth has also been observed in animal experiments. Epidemiological studies have indicated effects of PFCs on glucose, urea, and/or uric acid metabolism, as well as immunotoxicity and potential carcinogenicity (EPA, 2014b). Recent epidemiological studies reported inconsistent associations between environmentally relevant serum PFC levels and neurodevelopmental defects (Strom et al., 2014), risk of miscarriage (Darrow et al., 2014) and cancer in humans (Chang et al., 2014).

Available data from national studies in the WHO European Region are summarized in Table 10. Arithmetic mean serum levels of PFOS and PFOA in pregnant women in Denmark were 35.3 ng/g lipids and 5.6 ng/g lipids, respectively (Fei et al., 2007). In a recent study in the same country (Halldorsson et al., 2012), the median levels for PFOS and PFOA were 21.7 ng/g lipids and 3.7 ng/g lipids, respectively. In Germany, PFOS levels have been decreasing since 1986, while PFOA levels started to decrease only after 2006 (UBA, 2012). The highest PFOS levels in human milk (65.2 ng/g lipids) were detected in the Republic of Moldova. The results are summarized by geographic subregion in Table 10 and Table 11. Since there are no health-based values for PFOA and PFOS, the interpretation of these results is limited to the assessment of temporal and geographic patterns.

Table 10. Summary of available HBM data on PFOS and PFOA in blood and in human milk

Country – study	Population group	Matrix	Compound	Unit	Geometric mean or median level	Arithmetic mean level	Reference
Denmark – Danish National Birth Cohort	Pregnant women	Plasma	PFOA	ng/g lipid		5.6	Fei et al., 2007
Denmark – Aarhus Birth Cohort	Pregnant women	Serum	PFOA	ng/g lipid	3.7		Halldorsson et al., 2012

Table 10 (concluded)

Country – study	Population group	Matrix	Compound	Unit	Geometric mean or median level	Arithmetic mean level	Reference
Germany – ESB	Students (before the year 2000) – Münster	Plasma	PFOA	µg/L	5.2		UBA, 2012
Germany – ESB	Students (2000 and later) – Münster	Plasma	PFOA	µg/L	4.5		
Norway – MoBa	Pregnant Women	Blood	PFOA	ng/g lipid	2.2		Whitworth et al., 2012
United Kingdom – ALSPAC*	Mothers of girls (8–13 years)	Serum	PFOA	ng/g lipid	3.7		Christensen et al., 2011
United Kingdom – ALSPAC*	Girls	Serum	PFOA	ng/g lipid	3.7		Maisonet et al., 2012
Denmark – Danish National Birth Cohort	Pregnant women	Plasma	PFOS	ng/g lipid		35.3	Fei et al., 2007
Denmark – Aarhus Birth Cohort	Pregnant women	Serum	PFOS	ng/g lipid	21.5		Halldorsson et al., 2012
Georgia – UNEP/POPS/ COP.6/INF/33	Mothers	Human Milk	PFOS	ng/g lipid	27.2		WHO & UNEP, 2013:42
Germany – ESB	Students (before the year 2000) – Münster	Plasma	PFOS	µg/L	20.7		UBA, 2012
Germany – ESB	Students (2000 and later) – Münster	Plasma	PFOS	µg/L	9.5		
Lithuania – UNEP/POPS/ COP.6/INF/33	Mothers	Human Milk	PFOS	ng/g lipid	29.3		WHO & UNEP, 2013
Moldova – UNEP/POPS/ COP.6/INF/33	Mothers	Human Milk	PFOS	ng/g lipid	65.2		WHO & UNEP, 2013
Norway – MoBa	Pregnant Women	Blood	PFOS	ng/g lipid	13.0		Whitworth et al., 2012
United Kingdom – ALSPAC*	Mothers of girls (8–13 years)	Serum	PFOS	ng/g lipid	19.8		Christensen et al., 2011
United Kingdom – ALSPAC*	Girls	Serum	PFOS	ng/g lipid	19.6		Maisonet et al., 2012
Tajikistan – UNEP/POPS/ COP.6/INF/33	Mothers	Human Milk	PFOS	ng/g lipid	11.1		WHO & UNEP, 2013

* Avon Longitudinal Study of Parents and Children

Table 11. PFOS and PFOA in blood and in human milk: arithmetic means (min-max) of country-level GM or median values

Country (Subregion)	PFOS in blood (ng/g lipids)	PFOA in blood	PFOS in human milk (ng/g
Germany (western Europe)	15.1	4.9	
Denmark, Norway, United Kingdom (northern Europe)	20.3 (13 – 28.4)	3.5 (2.2 – 4.7)	
Lithuania (northern Europe)			29.3
Moldova (eastern Europe)			65.2
Georgia and Tajikistan (Central and Western Asia)			19.2 (11.1 – 27.2)

Source: compiled from Fei et al. (2007); UBA (2012); WHO & UNEP (2013:42); Whitworth et al. (2012).

Organochlorine pesticides

Elevated levels of organochlorine pesticides, such as DDT, have been linked with late-onset Alzheimer's disease (Richardson et al., 2014), especially for a susceptible population of individuals carrying the apolipoprotein E-e4 allele (ApoE4). Long-term oral administration of hexachlorocyclohexane (HCH) pesticides (α-HCH, β-HCH, γ-HCH) to laboratory rodents has been reported to induce liver cancer (ATSDR, 2005).

Levels of dichlorodiphenyltrichloroethane (DDT) and its metabolites dichlorodiphenyldichloroethane (DDD) and dichlorodiphenyldichloroethylene (DDE) were measured in blood samples in a few studies (Table 12). In all cases the identified levels (within the range of 100 ng/g lipids) were lower than the BE value of 40 000 ng/g lipid for the sum of DDT/DDE/DDD derived by Kirman et al. (2011).

Table 12. DDT and DDE in human blood: arithmetic means (min-max) of country-level GM or median values

Country (Subregion)	DDT (ng/g lipid blood)	DDE (ng/g lipid blood)
France (western Europe)	4.0	100
Belgium (Flanders) – FLEHS study (western Europe)		110 (neonates'/mothers' cord blood) 94 (adolescents' serum) 423 (adults' serum)

Source: compiled from Fréry et al. (2010); Schoeters et al. (2012a)

According to the results of the WHO/UNEP Human Milk Survey (WHO & UNEP, 2013), levels of DDT in pooled samples of human milk (Table 13, Fig. 4 and Fig. 5)in all participating countries except Tajikistan were below the milk BE level of 2300 ng/g lipids (Table 4). The high level in Tajikistan may reflect the wide use of DDT during the 1950s–1970s, and the fact that the use of DDT continued until the early 1990s in spite of the DDT ban issued in 1969–1970 by the former Soviet Union

(FSU) government (Li et al., 2006). Data on neighbouring FSU countries, which had similar patterns of DDT application, are not available.

The results of the WHO/UNEP Human Milk Survey show a steady temporal decline of DDT levels in human milk, which is likely the result of the worldwide DDT ban (Fig. 5).

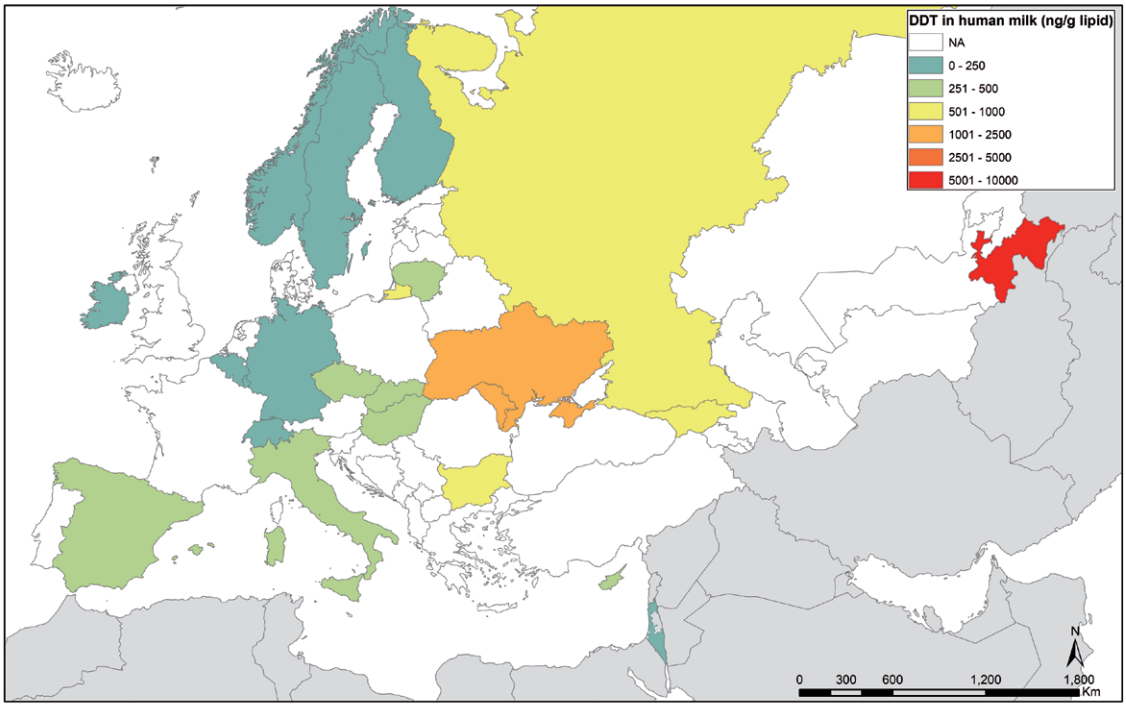
Table 13. DDT in human milk: arithmetic means (min-max) of country-level arithmetic mean values

Subregion	DDT (ng/g lipids)
eastern Europe[1]	773 (400 – 1847)
western Europe[2]	160 (127 – 185)
northern Europe[3]	131 (54 – 275)
southern Europe[4]	438 (383 – 492)
western Asia[5]	376 (183 – 599)
central Asia[6]	8502

1 Bulgaria, Czech Republic, Hungary, Republic of Moldova, Russian Federation, Slovakia, Ukraine
2 Belgium, Germany, Luxembourg, Switzerland
3 Finland, Ireland, Lithuania, Norway, Sweden
4 Italy, Spain
5 Georgia, Cyprus, Israel
6 Tajikistan

Source: data from WHO & UNEP (2013:30)

Fig. 4. DDT levels in human milk in the Member States of the WHO European Region: data from the WHO/UNEP Human Milk Survey in 2000–2012 (average values from all survey rounds)



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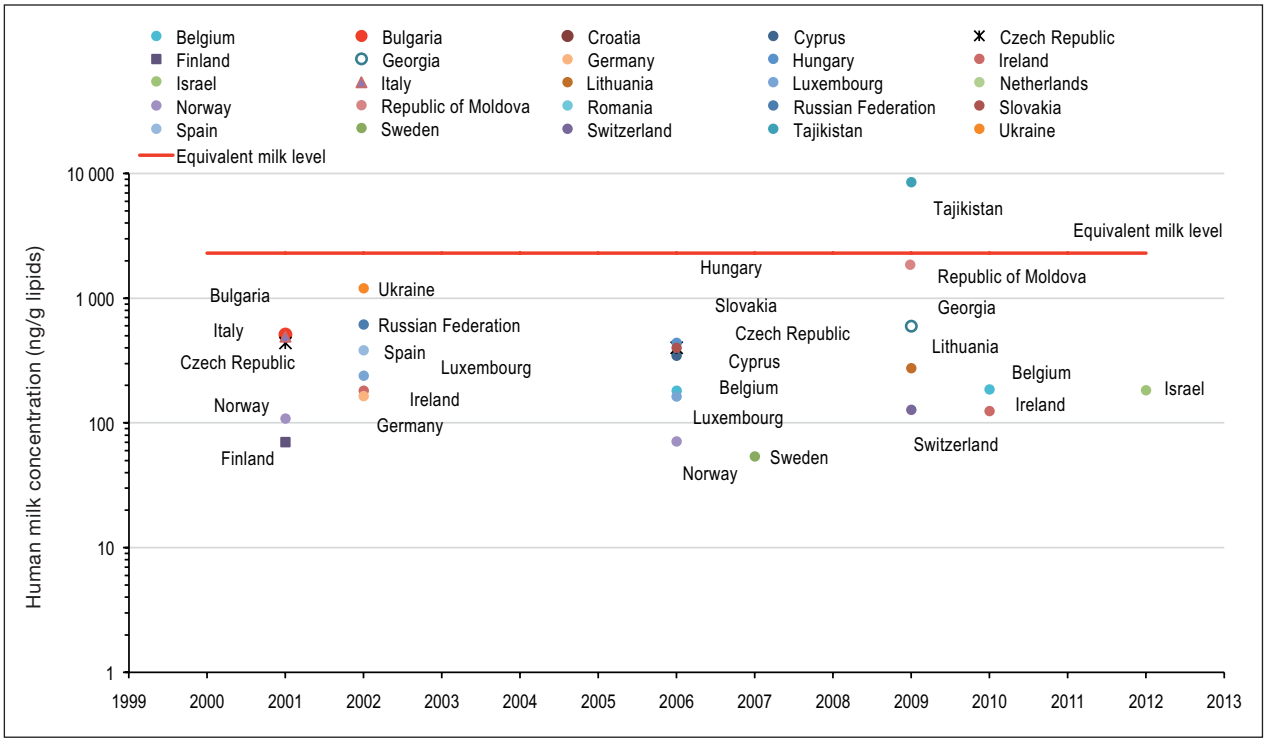
Map production:
Cartography by Pierpaolo Mudu (WHO)

Source: data from WHO & UNEP (2013:30)

Fig. 5. Temporal pattern in DDT levels in human milk in the WHO European Region: data from the WHO/UNEP Human Milk Survey in 2000–2012



Source: data from WHO & UNEP (2013:30)

Higher β-HCH levels in human milk have been found in eastern Europe and central Asia compared to southern, western and northern Europe (Table 14).

Table 14. HCHs in human milk: arithmetic means (min-max) of country-level arithmetic mean values

Subregion	α-HCH (ng/g lipid milk)	β-HCH (ng/g lipid milk)	γ-HCH (ng/g lipid milk)
eastern Europe[1]	3.0 (1.5–5.5)a	146 (7.0–481)b	2.4 (0.4–13)a
western Europe[2]		11 (2.0–16)	0.6 (0.4–1.1)
northern Europe[3]		10 (2.5–17)	0.7 (0.4–1.0)
southern Europe[4]		59 (58–60)	0.8 (0.4–1.7)
western Asia[5]	1.6 (Georgia)	42 (10–95)	0.5 (0.5–0.5)
central Asia[6]	4.2	229	0.9

1 a. Bulgaria, Republic of Moldova, Russian Federation, Ukraine;
b. Bulgaria, Czech Republic, Hungary, Republic of Moldova, Russian Federation, Slovakia, Ukraine
2 Belgium, Germany, Luxembourg, Switzerland
3 Ireland, Lithuania, Norway, Sweden
4 Italy, Spain
5 Cyprus, Georgia, Israel
6 Tajikistan

Source: data from WHO & UNEP (2013:35–37)

The data on α-HCH and β-HCH levels in serum samples are presented in Table 15. Reflecting the bioaccumulation properties of β-HCH, serum levels of this compound in Catalonia, Spain, were found to be increasing with age from 29.3 ng/g lipid in yound adults (18 to 29 y.o.) to 252.8 ng/g lipid in 60–74 y.o. individuals while level in all adults was 83.0 ng/g lipid (Porta et al., 2010).

Table 15. HCHs in human serum: arithmetic means (min-max) of country-level GM or median values

Country (Subregion)	α-HCH in blood (ng/g lipid)	β-HCH in blood (ng/g lipid)
Czech Republic (eastern Europe)		13 (adults)
France (western Europe)	0.6 (adults)	30 (adults)
Denmark (northern Europe)		2.0 (mothers) 2.0 (children 6–11 y.o.)
Spain (southern Europe)		83 (adults, Catalonia) 15 (pregnant women)

Source: compiled from Fréry et al. (2010); Llop et al. (2010); Porta et al. (2010); Černá et al. (2012); Mørck et al. (2014a)

The elevated levels of POPs in some countries of eastern Europe and central Asia may pose an increased risk of endocrine disruption-related health outcomes to populations living in these areas. Examples include disorders with the timing of puberty, infertility, and the development/function of reproductive organs. Damgaard et al. (2006) found that exposure to POPs, as measured in milk, was associated with congenital cryptorchidism.

Polychlorinated dibenzodioxins (PCDDs), dibenzofurans (PCDFs) and biphenyls (PCBs)

PCDDs, PCDFs and dioxin-like PCBs, hereafter called "dioxins", are an important class of POPs that have similar toxicological properties. Endocrine disrupting effects of dioxins are likely due to a combination of several mechanisms, such as altered steroidogenesis, reduced expression of receptors for sex steroids and luteinizing hormone (LH), and the inactivation of steroid hormones (Svechnikov et al., 2010). Maternal exposure to dioxins has been linked to a long-lasting modification of thyroid function in children, while exposure during infancy has been linked to altered spermatogenesis and hormonal status in adult men. Dioxins also act as nongenotoxic cancer promoters (Cheng et al., 2006; Matés et al., 2010).

PCDD/PCDFs are formed during waste incineration, home heating, and the production of organic chemicals containing chlorine, such as organochlorine pesticides and PCBs. These compounds remain stable in the environment for a long time, travel thousands of kilometers in the atmosphere and accumulate in the food chain, even in areas where major emission sources do not exist, such as the Arctic (WHO, 2003). The main route of exposure (more than 90%) in the general population is through food products, such as dairy products, meat and fish (WHO, 2002). For breastfed infants, the main source of exposure is mother's milk.

WHO has developed the Toxic Equivalency Factors (TEFs) to quantify the relative potency of PCDDs/PCDFs and dioxin-like PCBs compared to the most toxic dioxin congener, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Using this scheme, the overall toxicity of the mixture of dioxins is presented as the Toxic

Equivalency Quantity (TEQ), expressed in concentration units. The physical meaning of TEQ is the concentration of TCDD, which would have the same potency as the mixture analysed.

The previously published statistical analysis of available data demonstrated that breast milk concentrations of DDT, total PCBs and dioxins (expressed in TEQ units) have been decreasing by 50% every 4, 14 and 15 years, respectively, following the first order kinetic (Noren & Meironyte, 2000).

The results of the WHO/UNEP Human Milk Survey also showed that exposure levels to these compounds are continuously decreasing over time despite their persistence and bioaccumulation potential (WHO & UNEP, 2013). This decrease may be a result of the implementation of the Stockholm Convention on Persistent Organic Pollutants (UNEP, 2011). The results (Table 16) are compared to the thresholds proposed by WHO as safety standards for dioxin-like compounds, expressed as TEQs and calculated as BE human milk levels (Table 3).

Although the levels of most POPs have been declining over time, the levels of PCBs and dioxin-like compounds are one to two orders of magnitude above the human milk safety value proposed by WHO. In contrast to organochlorine pesticides, levels of dioxins are higher in Europe compared to countries of western and central Asia which participated in the WHO/UNEP Human Milk Survey (Table 16). This may reflect the more extensive use of consumer products and widespread solid waste incineration, as well as the higher consumption of meat and fish, in some countries in Europe.

Table 16. Dioxin-like PCBs, PCDDs and PCDFs and non dioxin-like PCBs in human milk: arithmetic means (min-max) of country-level arithmetic mean values

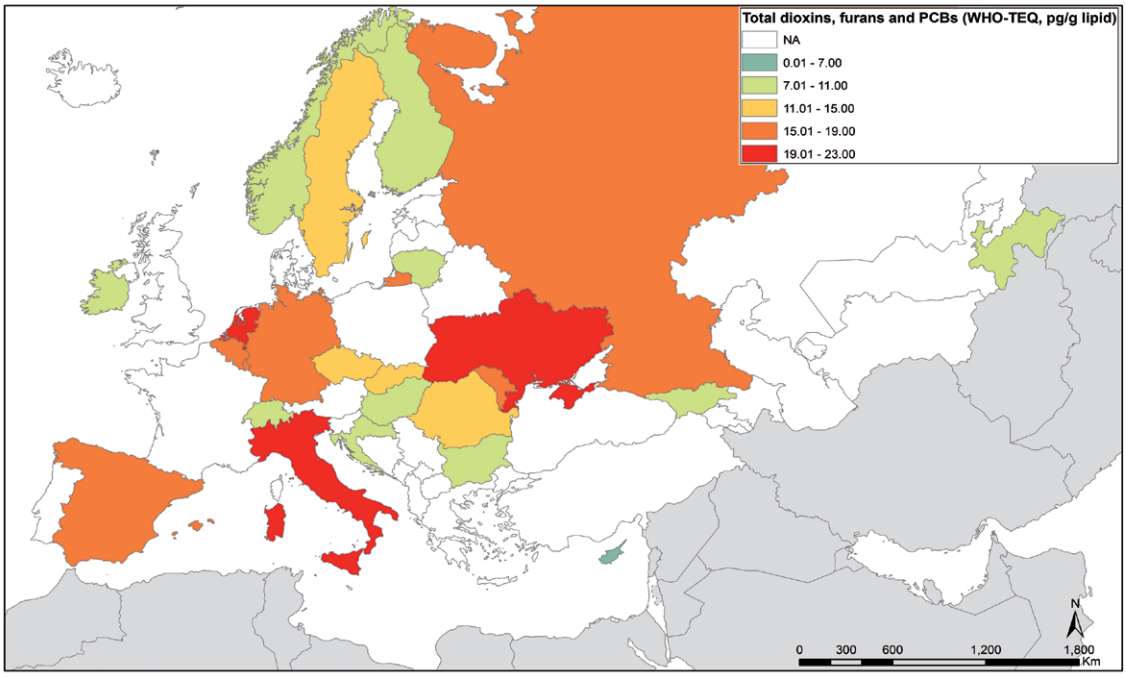
Subregion	PCBs-PCDDs-PCDFs in WHO TEQ units (pg/g lipids)	PCBs-PCDDs-PCDFs TEQ threshold (pg/g lipids)	PCBs (ng/g lipids)	PCBs threshold (ng/g lipids)
eastern Europe[1]	13 (5.9–19)	0.2	152 (34–376)	0.7
western Europe[2]	14 (10–19)		136 (69–221)	
northern Europe[3]	8.9 (6.7–12)		63 (24–90)	
southern Europe[4]	15 (10–20)		210 (136–252)	
western Asia[5]	7.4 (5.8–8.9)		28 (27–29)	
central Asia[6]	7.3		20	

1 Bulgaria, Czech Republic, Hungary, Republic of Moldova, Romania, Russian Federation, Slovakia, Ukraine
2 Belgium, Germany, Luxembourg, Netherlands, Switzerland
3 Finland, Ireland, Lithuania, Norway, Sweden
4 Croatia, Italy, Spain
5 Georgia, Cyprus
6 Tajikistan

Source: data from WHO & UNEP (2013:27–28)

Fig. 6 shows the available results of WHO/UNEP Human Milk Survey concentrations of PCDDs/PCDFs and dioxin-like PCBs, expressed in WHO TEQ units (WHO & UNEP, 2013). The physical meaning of TEQ is the concentration of the most toxic dioxin congener, TCDD, which would have the same potency as the mixture of dioxins, furans and dioxin-like PCBs analysed. Fig. 7 shows that the concentrations of dioxins in human milk have steadily declined across the WHO European Region.

Fig. 6. Concentrations of dioxins (WHO TEQ units) in human milk: data from the WHO/UNEP Human Milk Survey in 2000–2012 (average values from all survey rounds)



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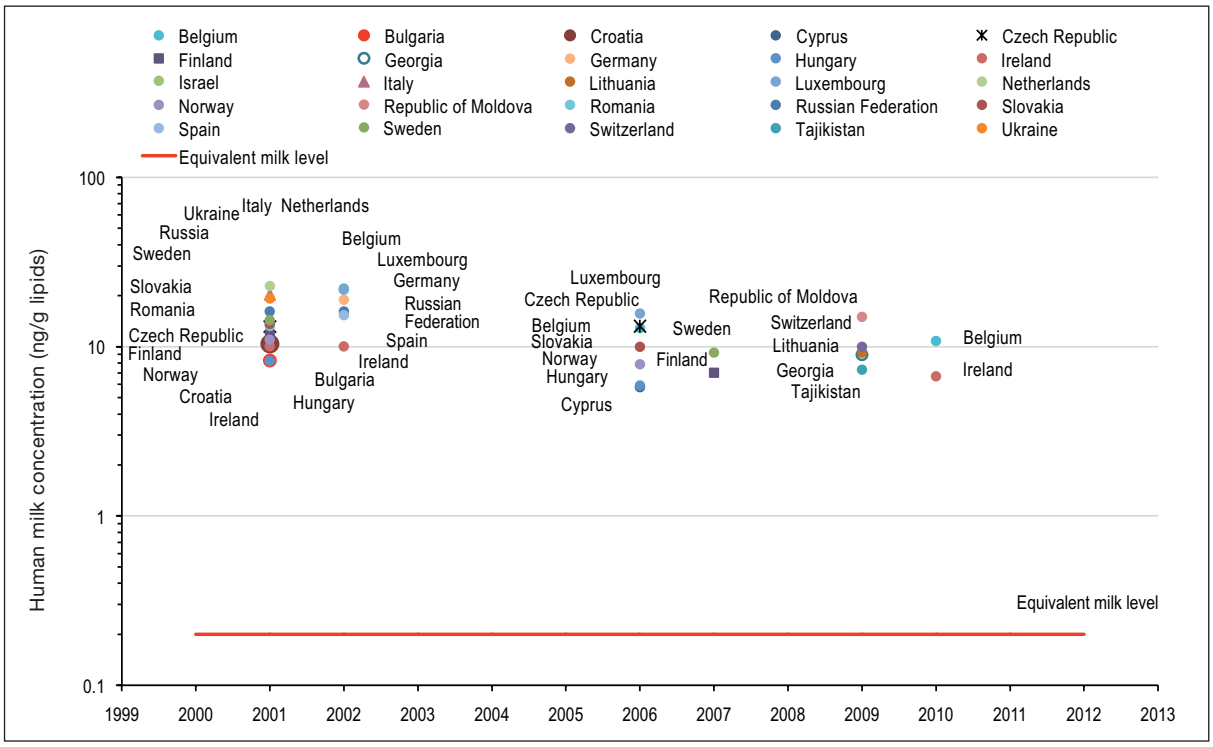
Map production:
Cartography by Pierpaolo Mudu (WHO)

Source: data from WHO & UNEP (2013:25)

Fig. 7. Temporal trends of PCDDs/PCDFs/PCBs in human milk in different countries

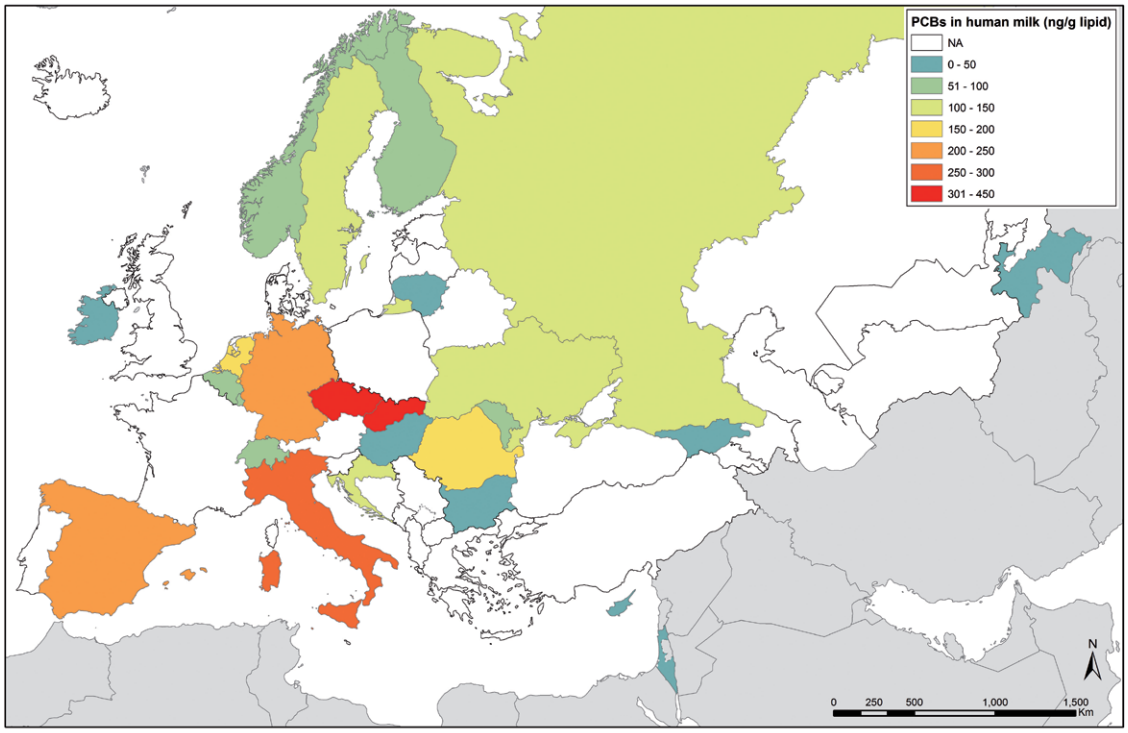


Source: data from WHO & UNEP (2013:27)

The typical average daily intake of breast milk fat, in exclusively breast fed infants during the first six months of life, ranges from three to six g/kg of body weight. Hence, the daily intake of dioxins in most European infants still greatly exceeds the BE value of 1 pg TEQ/kg of body weight (ATSDR, 1999; WHO, 2000). These compounds still pose significant, albeit poorly characterized, risks associated with endocrine disruption.

Fig. 8 presents a cross-sectional summary of the data on total non-dioxin–like PCBs from the WHO/UNEP Human Milk Survey in 2000–2012 (WHO&UNEP, 2013). Fig. 9 shows a temporal trend in the blood level of the most abundant PCB congener, PCB 153, in several countries. This graph demonstrates a steady decline over time. It should be noted that methodologies of surveys conducted in different years might not be fully consistent with each other. In Spain, the apparent decline from 2002 to 2005 likely reflects not only a declining trend over time but also higher levels of PCB 153 in older individuals (who participated in the 2002 survey).

Fig. 8. Total non dioxin-like PCBs in human milk: data from the WHO/UNEP Human Milk Survey in 2000–2012 (average values from all survey rounds)



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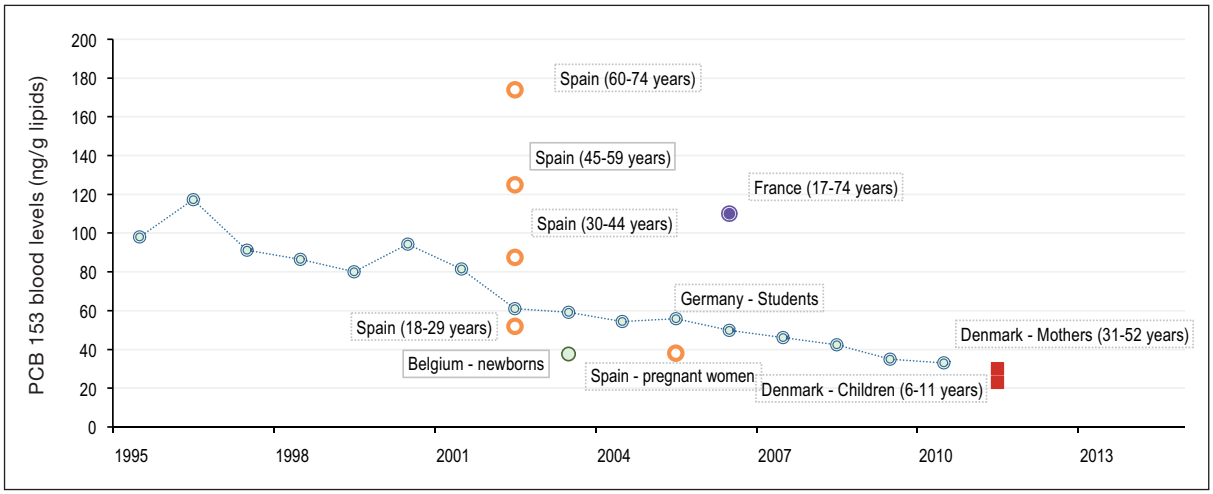
Map production:
Cartography by Pierpaolo Mudu (WHO)

Source: data from WHO & UNEP (2013:28)

Fig. 9. Temporal trends of PCB 153 across different countries and population groups (1995–2010)



Source: compiled from Casas et al. (2011); Vandentorren et al. (2011); Olsén et al. (2012); Bertelsen et al. (2013).

The surveillance of dioxins and PCBs in breast milk needs to be continued and expanded to monitor the implementation of the Stockholm Convention (UNEP, 2011) and the Parma Declaration (WHO Regional Office for Europe, 2010), which formalized Member States' commitment to protecting children's environmental health by reducing exposure to hazardous substances such as endocrine disruptors.

Polybrominated diphenyl ethers (PBDEs)

PBDEs include 209 possible congeners with different numbers and positions of bromine atoms in the molecular structure. Similarly to PCBs, they are named under the International Union of Pure and Applied Chemistry (IUPAC) system, based on the position and number of the bromine atoms. PBDEs have been used as flame retardants for decades in a wide range of products, such as plastics, electronics and textiles. They have been distributed in three commercial mixtures of congeners with different levels of bromination (penta-BDE, octa-BDE and deca-BDE), which are named after the dominating homologue group. The pentabromo formulation is dominated by BDE-47, BDE-99 and BDE-100 congeners. It has been mainly employed as an additive of polyurethane foams in furniture, carpets and bedding. The octabromo mixture is dominated by BDE-183, followed by BDE-153 and BDE-154. This octa-BDE mixture is used in flame-retardant thermoplastics such as polystyrene. The decabromo product is essentially composed of decabromodiphenyl ether (BDE-209) and has been predominantly used for textiles and electronic products such as televisions and computers. According to the PBDE global market demands in 2001, the deca-BDE formulation was the dominant one (83%), followed by penta-BDE (11%) and octa-BDE (6%) (La Guardia, Hale & Harvey, 2006). Currenlty, the penta- and octa- varieties are banned in the EU due to their toxicity and bioaccumulating properties. Deca-BDE continues to be produced.

Adverse health effects of human exposure to PBDEs include endocrine disruption (Darnerud 2003; Herbstman et al., 2008; Legler 2008; Turyk et al., 2008), developmental neurotoxicity (Herbstman et al., 2010; Gascon et al., 2011). Environmental exposures to PBDEs during pregnancy may lead to delayed mental and psychomotor development in infants (Czerska et al., 2013).

Levels of PBDEs found in human milk across different European subregions are summarized in (Table 17). The highest

levels of PBDEs in human milk were found in northern Europe, followed by western and southern Europe, and the lowest levels of PBDEs were found in two countries of western Asia and eastern Europe (WHO & UNEP, 2013). Since PBDE levels are associated with consumer products use, higher SES appears to drive exposure levels. In addition, indoor PBDE levels might be higher in northern Europe, due to the lower ventilation favoured in colder climatic areas.

Levels of PBDEs in human milk are generally at a level of a few ng/g lipid, and far below the BE value of 520 ng/g lipid for human blood (levels in milk and blood are similar in ng/g lipid units) (Krishnan et al., 2011). It should also be noted that the levels of PBDEs in human samples in Europe are strikingly lower than those found in the USA, where the GM level of only one congener, BDE 47, in human serum is 20.5 ng/g lipid (CDC, 2009).

Table 17. Total PBDEs in human milk: arithmetic means (min-max) of country-level GM or median values

Subregion	Sum PBDEs (ng/g lipid)
eastern Europe[1]	1.0
western Europe[2]	3.0 (1.5 – 4.1)
northern Europe[3]	4.4 (2.6 – 8.3)
southern Europe[4]	2.1 (1.5 – 2.6)
western Asia[5]	1.3

1 Czech Republic
2 Belgium, Germany, Luxembourg, Switzerland
3 Finland, Ireland, Norway, Sweden
4 Croatia, Italy, Spain
5 Cyprus

Source: data from WHO & UNEP (2013:41)

Organic compounds and associated metabolites identified in urine

Non-persistent pesticides and herbicides

Organophosphorus or organophosphate pesticides (OPPs) are widely used in commercial agriculture, in household applications and for the treatment of head lice in humans and ecoparasites in domestic animals (Aprea et al., 2000; Curl, Fenske & Elgethum, 2003; Barr et al., 2004). Organophosphorus compounds, including phosphates, phosphonates, phosphinates and phosphorothioates, can be classified according to their chemical structure (Gupta, 2005). Most OPPs have low solubility in water, a high oil-water partition coefficient and low vapor pressure (Kavvalakis & Tsatsakis, 2012). Examples of OPPs include Malathion, Parathion, Dimethoate, Chlorpyrifos and Diazinon.

OPPs exert their acute effects by inhibiting acetyl cholinesterase in the nervous system, resulting in respiratory, myocardial and neuromuscular transmission impairment. Therefore, the main targets are the nervous, respiratory and cardiovascular systems. Some OPPs are also known to interfere with reproductive system function, especially in males. OPPs are mutagenic, carcinogenic, cytotoxic, genotoxic, teratogenic and immunotoxic (Çakir & Sarikaya, 2005; Giordano et al., 2007; Kang et al., 2004).

Pyrethroids are synthetic chemical insecticides that are widely used because of their relative safety for humans, high

insecticidal potency at low dosages and rapid knock-down effects (WHO, 2005). Although more than 1000 pyrethroids have been made, only a few are used in households, mosquito control and agriculture. In malaria-endemic zones, pyrethroid insecticides are used to impregnate mosquito nets and clothing for the prevention of malaria (Government of Canada, 2009). Pyrethroids are synthetic forms of pyrethrins, which are natural insecticides derived from the extract of chrysanthemum flowers. There are two types of pyrethroids that differ in chemical structure and symptoms of exposure. Natural pyrethrins are esters of a cyclopropanecarboxylic acid and a cyclopentenolone alcohol. Structural modifications of these moieties have produced the diverse pyrethroids currently available.

Pyrethroid insecticides are considered less toxic to humans compared to other classes of insecticides, although they do have neurotoxic effects at high doses (Shafer, Meyer & Crofton, 2005; WHO, 2005). Accidental exposure to pyrethroids can lead to several symtoms such as paraesthesiae, nausea, vomiting and abdominal pain (Bradberry et al., 2005). Pyrethroids can cross the placental barrier and are known to interfere with hormonal and neurological development, and adversely affect the immune system as well as other physiological functions (Bell, Hertz-Picciotto & Beaumont, 2001; Chanda & Pope, 1996; Hanke et al., 2003; Muto et al., 1992).

Common herbicides include chloroacetanilide herbicides (acetochlor, alachlor, metolachlor) and triazines, such as atrazine. Chloroacetanilides are a family of herbicides widely used in crop production to control grassy weed growth by interfering with the weed's protein synthesis. Human alveolar (lung) A549 cells, when exposed to acetochlor, have been shown to experience negative changes. This is due to acetochlor's up-regulation of pro-apoptotic proteins and activation of extracellular signal-regulated kinase (ERK), resulting in elevation of reactive oxygen species (ROS) generation in a time-dependent manner (Zerin, Song & Kim, 2015). Exposures to atrazine have been linked with fetal developmental defecits, such as fetal growth restriction and small head circumference (Chevrier et al., 2011). Based on a recent review of epidemiologic evidence, atrazine may also have carcinogenic effects (Boffetta et al., 2013).

Data on urinary levels of OP pesticides (Table 18) are very limited. The available data on urinary dialkylphosphate (DEP) metabolites in France (Fréry et al., 2010), Germany (Becker et al., 2006) and the Netherlands (Ye et al., 2008) show similar levels of exposure to organophosphate (OP) pesticides and limited spatial variability based on urinary diethyl thiophosphate (DETP) and dimethyl dithiophosphate (DMDTP) (which are their major metabolites). However, levels of dimethylthiophosphate (DMTP) in the Netherlands were substantially higher. The data were retrieved from studies conducted in the last few years. Assessing temporal trends in exposure is problematic. Additional data need to be collected in a more harmonised manner (e.g. measuring similar DEP metabolites). HBM surveys need to be accompanied by a collection of ancillary data on exposure sources, in order to attribute the variability in OP metabolites to the respective pesticides, and to assess spatial and temporal patterns in population exposure.

Only one national survey involving measurements of urinary biomarkers of herbicides was identified through literature search: the mother-child cohort study in France, "Perturbateurs Endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance" (PELAGIE) (Chevrier et al., 2014). The results show that median levels of acetochlor, alachlor, metolachlor, atrazine and metabolites of triazine in urine samples from pregnant women were below the corresponding LOQs, which ranged from 0.002 µg/L to 0.315 µg/L for different analytes. Residence in a rural area or residential proximity to corn crops was associated with relatively higher urinary levels of certain herbicides. The lack of BE values and the scarcity

of biomonitoring data for non-persistent pesticides (OPPs and pyrethroids) and herbicides (chloroacetanilide herbicides such as acetochlor, alachlor, metolachlor and triazines such as atrazine), obscure the assessment of health risks associated with exposure to these compounds. However, in vitro evidence shows increased levels of ROS generation after exposure to chloroacetanilide herbicides (Zerin, Song & Kim, 2015). Moreover, cohort studies provide evidence of environmentally relevant exposure levels associated with adverse health outcomes. Exposure to atrazine was linked to fetal developmental defects (Chevrier et al., 2011) and in-utero exposure to chlorpyrifos was linked to attention deficit hyperactivity disorder (ADHD) in school-age children (Fortenberry et al., 2014).

Table 18. Urinary levels (country means) of sum of total dialkyl phosphate (DAP) metabolites of OP pesticides (dimethylphosphate, dimethylthiophosphate, dimethyldithiophosphate, dimethyl, diethylphosphate, diethylthiophosphate, diethyldithiophosphate) and 3,5,6-trichloro-2-pyridinol (TCPy) metabolite of the crystalline OP insecticide, chlorpyrifos

Country (subregion)	Total DAP (µg/L)	TCPy (µg/L)
Netherlands (northern Europe)	25.2	1.2
Norway (northern Europe)	24.2	0.99

Source: Ye et al. (2008 and 2009)

Bisphenol A (BPA)

BPA is a plastic monomer, which at room temperature exists as a white solid. It is frequently used as a starting substance in epoxy-phenolic resins and as a monomer in the manufacture of polycarbonate (PC) plastics. Epoxy resins are used as an inner protective lining in canned food and drinks, and bottle caps. PC is commonly used in plastic consumer products, such as baby bottles, reusable water bottles, plastic tableware and food storage containers. Furthemore, BPA is used as an additive in other plastics, which are used, for example, in dental sealants and children's toys (Mørck, 2012). The industrial production volume is approximately 2.9 billion kilograms of BPA per year, making BPA one of the most commonly produced chemicals in the world (Mørck, 2012).

When polymers of BPA in plastic products are exposed to changes in heat or acidic conditions during use – for example, during heating in a microwave – the ester bond linking monomers of BPA can be hydrolysed. This results in the release of free BPA monomers that migrate into the food products or the environment. Food products are the major source of BPA exposure in all age groups in non-occupationally exposed individuals (Dekant & Völkel, 2008). Air and dust are also a potential source of human BPA exposure, as well as dermal contact with thermal paper, which is used in purchase receipts (Mørck, 2012).

Due to BPA's ability to interact with cellular receptors, it is defined as an endocrine disrupting chemical (EDC). A recent review, based on reports related to BPA's effects on female and male reproductive systems in humans and animals, concluded that BPA is a reproductive toxicant (Peretz et al., 2014). Exposure to BPA may disrupt the development of the fetus and young child as a consequence of its interaction with oestrogen, androgen and thyroid receptors (Mørck, 2012). BPA exposure in adults may be associated with reduced ovarian response, reduced fertilization success and embryo quality, implantation failure, miscarriage, premature delivery, altered male sexual

function, reduced sperm quality, altered sex hormone concentrations, polycystic ovary syndrome (PCOS), altered thyroid hormone concentrations, blunted immune function, type-2 diabetes, increased cardiovascular disease risk (due to hypertension and elevated cholesterol levels), altered liver function, obesity, albuminuria, oxidative stress and inflammation, and altered epigenetic markers and gene expression. Exposure to BPA during gestation could result in increased spontaneous abortion, abnormal gestation time, low birth weight, increased male genital abnormalities, and childhood obesity. Particularly strong are the associations between early BPA exposure and altered behaviour and disrupted neurodevelopment in children, as well as increased probability of childhood wheeze and asthma (Rochester, 2013). BPA may increase cancer susceptibility through developmental reprogramming. However, due to the paucity of data, BPA is currently not classified as a carcinogen (Keri et al., 2007).

BPA urinary concentrations are age-dependent, reflecting the differences in consumer exposure to food packaging material (e.g. canned food, milk formula, use of plastic baby bottles). The restriction of BPA use in baby bottles in EU countries was introduced in 2011. This policy action and the increase in public awareness about BPA's potential adverse health effects have resulted in a decline of measured BPA levels. In the most recent studies, urinary BPA levels were about 2 µg/L (Table 19). The differences in BPA levels among the different geographic regions are not significant. In all cases, the levels of urinary BPA, were three orders of magnitude lower than the BE value of 2,300 µg/L derived by Krishnan et al. (2010a), which is based on the respective TDI of 50 µg/kg of body weight set by EFSA. However, several epidemiological studies have identified associations between urinary BPA and several endocrine disruption-related adverse outcomes (Rochester, 2013). These indicate the need for more longitudinal/prospective-type studies with increased sample sizes (Patel et al., 2014) in order to verify the adverse effects of BPA at environmentally low concentrations.

BPA is a compound that has sparked extensive scientific and political debate. Sweden banned the use of BPA and substances containing BPA in varnishes and coatings in packaging intended for children up to three years of age in January 2013 (EU, 2012).

A critical issue related to the potential health effects of BPA is related to the so-called "low-dose hypothesis", which states that low-dose exposures can act in a nonlinear manner. This means that there is no "safe" exposure level. Toxicological studies have shown that low dose exposure to BPA may result in effects that are not always apparent at higher doses (Vandenberg et al., 2012).

Table 19. Glucuronidated BPA in urine: arithmetic means (min-max) of country-level GM or median values

Subregion	BPA-Glu (µg/L)
western Europe[1]	2.0 (1.4 – 2.6) in adults 2.3 (1.8 – 2.7) in children
northern Europe[2]	1.8 (1.2 – 3.2) in adults 1.6 (0.7 – 2.3) in chidlren
southern Europe[3]	1.9 (1.4 – 2.2) in adults 2.9 (1.8 – 4.2) In children

1 Belgium, Germany, Luxemburg, France (adults only)
2 Denmark, Netherlands (adults only), Sweden
3 Slovenia, Spain

Source: compiled from Becker et al. (2009); Casas et al. (2011); Covaci et al. (2014); Frederiksen et al. (2014); Olsén et al. (2012); UBA (2012); Vandentorren et al. (2011); Ye et al. (2008)

In the recent DEMOCOPHES survey, the levels of BPA in urine were measured in 6 to 11 year-old children and their mothers in six countries – Belgium, Denmark, Luxembourg, Slovenia, Spain and Sweden (Covaci et al., 2014). The measured country-level GM values for mothers (N = 639) ranged from 1.3 µg/L in Sweden to 2.6 µg/L in Belgium. The average GM in Europe was 1.8 µg/L. The P90 levels ranged from 3.5 µg/L to 8.7 µg/L, while the overall maximum value was 456 µg/L. This was far below the health guidance value for adults of 2500 µg/L urine (EU, 2013; Covaci et al., 2014). The measured country-level GM values for children (N = 653) ranged from 1.5 µg/L in Sweden to 2.6 in Slovenia. The average GM in Europe was 2.0 µg/L. The P90 levels ranged from 4.1 µg/L to 14.9 µg/L, while the overall maximum value was 822 µg/L (Covaci et al., 2014). These levels were also much lower than the HBM-I guidance value for children of 1500 µg/L urine.

The levels in children and mothers were rather similar in all countries except Slovenia, where the GM level in children was the highest among the six countries. The BPA level in mothers in Slovenia, however, was well below the DEMOCOPHES mean.

Parabens

Parabens are preservatives that, since the 1930s, are used in a wide range of pharmaceuticals and personal care, cosmetic, food, and children's products. Parabens and their salts are used as preservatives because of their bactericidal and fungicidal properties. They are detected in waste water, rivers, soil and house dust. Although parabens are still widely considered to be safe, health concerns have been raised for endocrine disrupting effects at high exposure levels. Parabens are esters of para-hydroxybenzoic acid. The most commonly used parabens are: methylparaben, ethylparaben, propylparaben, and butylparaben.

Parabens are known to cause allergic reactions including skin irritation and contact dermatitis in sensitive or already damaged skin (Kirchhof & de Gannes, 2013). Paraben levels in human samples are strongly associated with the use of paraben-containing consumer and cosmetic products. These chemicals have estrogenic activity, which was demonstrated in vitro and in vivo. Estrogenicity appears to increase with side chain length (Boberg et al., 2010; Kirchhof & de Gannes 2013). Parabens and their metabolites are suspected to cause endocrine disrupting effects (Boberg et al., 2010; Smith et al., 2013). Moreover, paraben-containing antiperspirants have been suspected of increasing breast cancer incidence (Abbas et al., 2010). It has been hypothesized that parabens may promote breast cancer development when they are found in high concentrations in breast tissue (Abbas et al., 2010; Harvey & Everett, 2004; Kirchhof & de Gannes 2013). While some studies have found no clear associations between urinary paraben levels and male or female reproductive health (Meeker et al., 2011; Smith et al., 2013), a study by Kirchhof and de Gannes (2013) suggests that exposure to parabens may negatively impact the male reproductive system. Urinary levels of propyl and butyl parabens have been associated with allergic sensitization (Savage et al., 2012). Overall, there is insufficient evidence of serious health effects from exposure to parabens to warrant government regulations of these chemicals (Kirchhof & de Gannes, 2013). No BE values are available for parabens.

Parabens are metabolised rapidly; thus, individual HBM data only reflect recent exposure events (Koch et al., 2014). In Denmark, higher levels (Table 20) of urinary methyl paraben (MeP) (10 µg/L) and ethyl paraben (EtP) (0.9 µg/L) were found in 5–9 year-old children compared to 14–20 year-old individuals (5.4 and 0.4 µg/L for MeP and EtP, respectively) (Frederiksen et al., 2014). Urinary levels of MeP and ethyl paraben (EtP) in pregnant women and four year-old children were significanty higher in Spain, (191 µg/L and 150 µg/L, respectively) than in Denmark (Casas et al., 2011). In contrast the levels in Danish pregnant women and four year-old children were 8.8 µg/L and 8.1 µg/L, respectively (Frederiksen et al., 2014).

The SES of the population is likely to be a key determinant of the use of personal care products containing parabens. Denmark banned parabens in products made for children in 2010. Recently the EC has amended Annex II of the EU Cosmetics Regulation, adding five parabens (isopropylparaben, isobutylparaben, phenylparaben, benzylparaben and pentylparaben) to the list of substances prohibited in cosmetic products. Thus, taking into account their rapid biokinetics and metabolism these compounds would not be expected to be found in future HBM studies conducted in EU Member States. Yet, this is not the case for other parabens and, consequently, continued HBM of the remaining authorised parabens and their metabolites is necessary.

Table 20. Urinary levels of methyl paraben (MeP) and ethyl paraben (EtP)

Country (subregion)	MeP (µg/L)	EtP (µg/L)
Denmark (northern Europe)	10.0 (5–9 y.o. children) 5.4 (14–20 y.o. individuals)	0.9 (5–9 y.o. children) 0.4 (14–20 y.o. individuals)
Spain (southern Europe)	191.0 (Pregnant women) 150.0 (4 y.o. children)	8.8 (Pregnant women) 8.1 (4 y.o. children)

Source: adapted from Casas et al. (2011); Frederiksen et al. (2014)

Phthalates

Phthalates are dialkyl- or alkylarylesters of ortho-benzenedicarboxylic acid (phthalic acid). They are man-made chemicals that are produced worldwide in millions of tons each year. The long chain phthalates, di(2-ethylhexyl) phthalate (DEHP), di-iso-nonyl phthalate (DiNP), di-iso-decyl phthalate (DiDP) and di(2-propylheptyl) phthalate (DPHP), are used primarily in polyvinyl chloride (PVC) polymer and plastisol applications. DEHP is also the major plasticizer for PVC-containing medical devices such as bags for blood or parenteral nutrition, tubing and catheters. Short chain phthalates, such as dimethyl phthalate (DMP), diethyl phthalate (DEP), butyl benzyl phthalate (BBzP), di-n-butyl phthalate (DnBP, and di-iso-butyl phthalate (DiBP), are often used as industrial solvents and lubricants, additives in the textile industry, pesticide formulations, personal care products, paints and adhesives. DEP and DnBP are also used in the pharmaceutical field as a constituent of the enteric coating of some medications. DiBP is used in dispersion adhesives in paper and cardboard packaging. During recycling processes DiBP can end up in paper and paper packaging, allowing it to have contact with food, which is later ingested by humans.

Some phthalates, such as DEHP, DnBP, DiBP, BBzP, dipentyl phthalate (DPP) and DiNP, are developmental and reproductive toxicants in rodent models, particularly affecting male reproductive development. Although phthalates do not exhibit intrinsic hormonal activity they modulate the endogenous production of fetal testicular testosterone and also influence the production of insulin-like factor 3 and follicle-stimulating hormone (Koch & Angerer, 2012; Latini, 2005).

Recent epidemiological studies suggested that exposure to some phthalates at typical environmental levels may be associated with a decreased anogenital distance in male infants, reduced reproductive hormone levels in adult men, reduced semen quality, DNA damage in sperm, abdominal obesity, insulin resistance, conduct or attention-deficit hyperactivity disorders, and less “male-typical” behaviour in young boys (Koch & Angerer, 2012). The most critical window of exposure is

during the inutero development, at the androgen (testosterone) regulated sexual differentiation phase, which occurs at the end of the first trimester of pregnancy (Koch & Angerer, 2012).

Possible correlation between phthalates exposure and allergy and asthma is currently under investigation (Braun, Sathyanarayana & Hauser, 2013; Jaakkola & Knight, 2008; Tsai, Kuo & Ko, 2012). Recent evidence from cohort studies shows that pre- and early post-natal phthalate exposure affects child psychomotor development (Polanska et al., 2014) and that gender might be a modifier of the intensity of adverse health effects (Tellez-Rojo, 2013).

In the EU, DEHP, DnBP, DiBP and BBzP are prohibited from being used in cosmetics due to their classification as substances that are potentially carcinogenic, mutagenic or reproductive toxicants. Despite that ban, DEHP can still be found in products sold in Europe (Koch & Angerer, 2012). Consumption of convenience food, use of personal care products and indoor exposure to vinyl floors and wallpaper have all been linked to higher phthalate levels in urine.

The results of the DEMOCOPHES survey are summarized in Table 21. Phthalate metabolites were generally found at higher levels in children compared to mothers, with the exception of mono-ethyl phthalate (MEP), which is not regulated and is mainly used in cosmetics. A possible explanation is children's relatively higher intake: they are more exposed to dust, playing nearer to the ground; they have more frequent hand-to-mouth contact; and they eat more than adults in relation to their weight. The GM and P90 levels of DEHP metabolites are substantially lower than the respective HBM-I guidance values of 500 µg/L for children and 300 µg/L for women of reproductive age (see Table 2), and for BE values obtained from other sources (see Table 3).

The highest GM level of phthalates in urine of children was found in Slovakia and the lowest level in Luxembourg (Fig. 10). In general, urinary DEHP metabolites levels tended to be higher in eastern Europe compared to western Europe. Comparison of exposure to DEHP with average gross domestic product (GDP) per capita shows that exposure to restricted phthalates is negatively correlated with affluence (Fig. 11). This correlation might be due to a consumer preference towards cheaper imported plastic materials in countries with lower GDP per capita.

The time series data from the German ESB and other national surveys revealed a continuous decline of mono-(2-ethylhexyl) phthalate (MEHP) (a major DEHP metabolite) from 1988 to 2008, when levels decreased from 9 µg/L to 3 µg/L in Germany (UBA, 2012), likely due to the continuous restriction of DEHP use

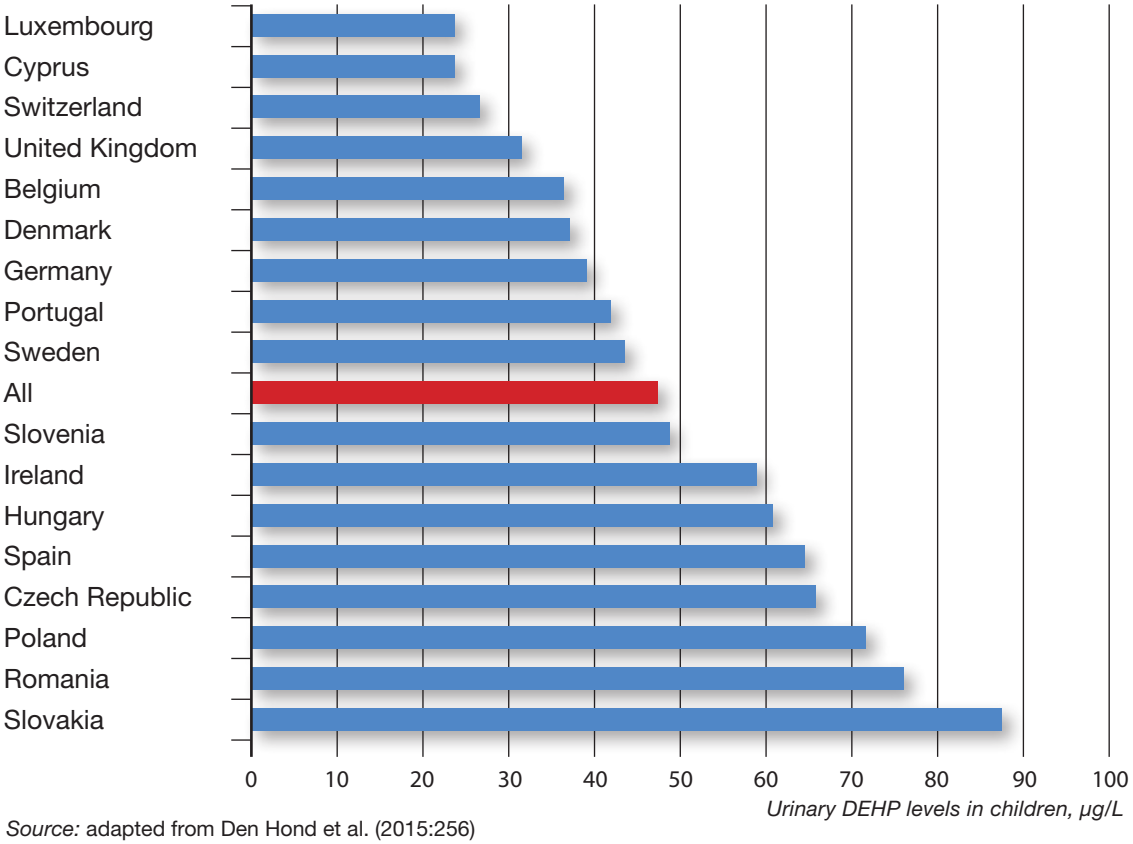
Table 21. Summary of DEMOCOPHES results at the European level for metabolites of phthalates: mean, P90 and health guidance values, µg/L

	Children		Mothers	
Biomarker	**Mean**	**P90**	**Mean**	**P90**
DEHP metabolites	48	141	29	93
MnBP	35	98	24	68
MBzP	7.1	28	4.5	18
MEP	34	160	48	259
MiBP	45	135	30	89

Source: adapted from EU (2013)

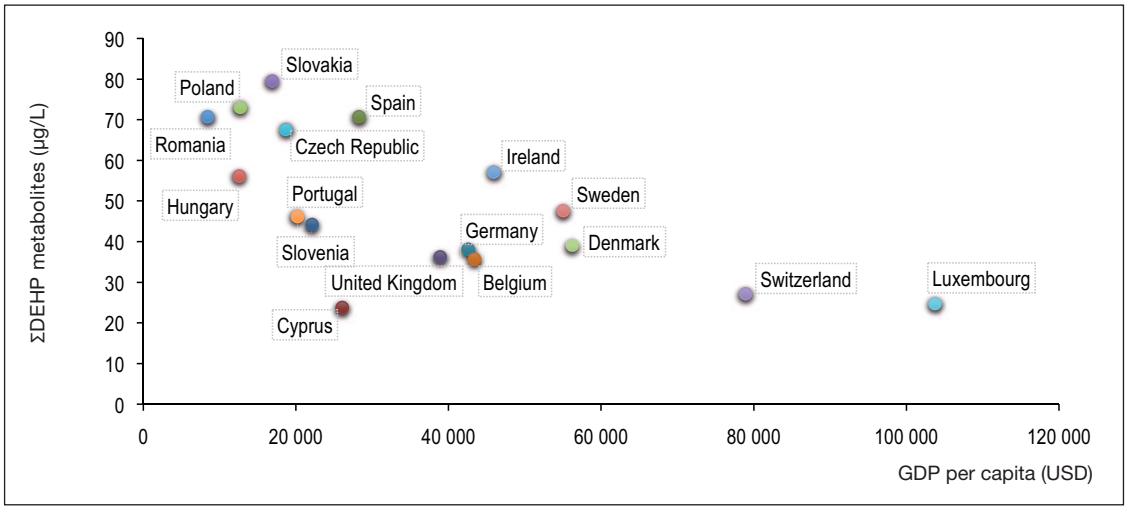
(Fig. 12). In contrast, MiNP levels have increased over the last 15 years. Differences in the temporal trends among the different phthalates are attributed to changes in production and usage patterns, reflecting the continuously evolving legislative framework on the use of phthalates. One result of this regulatory environment is the progressive replacement of DEHP by DiNP (Goen et al., 2011).

Fig. 10. Geometric mean levels of DEHP metabolites in urine of children: unadjusted DEMOCOPHES data



Source: adapted from Den Hond et al. (2015:256)

Fig. 11. Negative association between GDP per capita and total DEHP metabolites in urine of mothers



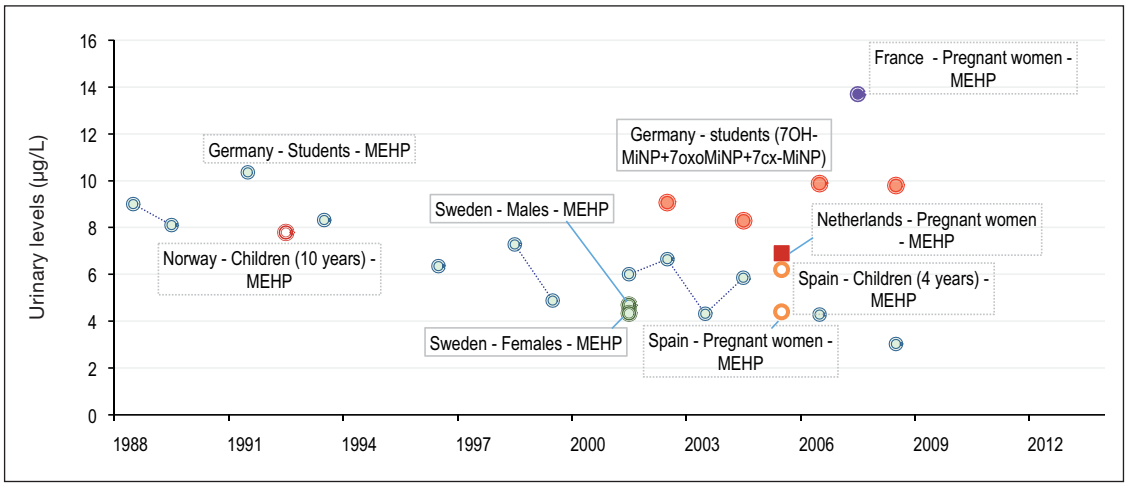
Source: compiled from World Bank (2013); EU (2013)

Data on phthalates from studies other than DEMOCOPHES are limited mostly to countries of western and northern Europe. The available publications provide data on different metabolites of phthalates in different age groups. An overview of the available data on urinary MEHP levels is presented in Table 22. The complete lack of data from lower income countries is an important issue given the strong inverse association between GDP per capita and exposure to phthalates.

Table 22. Data on MEHP from selected studies in Europe, µg/L

Country - study	Population group	Matrix	Analyte	GM or median level	Reference
France – ELFE	Pregnant women	Urine	MEHP	13.7	Vandentorren et al., 2011
Germany – Duisburg Birth Cohort Study	Mothers	Urine	MEHP	4.6	Kasper-Sonnenberg et al., 2012
Germany – Duisburg Birth Cohort Study	Children	Urine	MEHP	4.0	
Germany – ESB	Students (before the year 2000) – Münster	Urine	MEHP	7.8	UBA, 2012
Germany – ESB	Students (2000 or later) – Münster	Urine	MEHP	5.0	
Germany – GerES	3–14 years old	Urine	MEHP	8.5	Koch et al., 2011
Germany – GerES	3–5 years old	Urine	MEHP	4.6	
Germany – GerES	6–8 years old	Urine	MEHP	6.2	
Germany – GerES	9–11 years old	Urine	MEHP	6.8	
Germany – GerES	12–14 years old	Urine	MEHP	7.8	
Netherlands – Generation R	Pregnant women (18–41 years old)	Urine	MEHP	6.9	Ye et al., 2008
Norway – ECA	Children (10 years old)	Urine	MEHP	7.8	Bertelsen et al., 2013
Spain – INMA	Pregnant women	Urine	MEHP	4.4	Casas et al., 2011
Spain – INMA	Children (4 years old)	Urine	MEHP	6.2	
Sweden – PIVUS	Male Seniors (70 years old)	Serum	MEHP	4.7	Olsén et al., 2012
Sweden – PIVUS	Female Seniors (70 years old)	Serum	MEHP	4.3	

Fig. 12. Time trend for the urinary concentrations of a DEHP metabolite, MEHP (blue dots), and a DiNP metabolite, MiNP (red dots)



Source: compiled from Ye et al. (2008); Casas et al. (2011); Vandentorren et al. (2011); Olsén et al. (2012); UBA (2012); Bertelsen et al. (2013).

German ESB data for phthalates show that for DiNP, which has replaced DEHP as a plasticiser, the levels of the sum of the three major metabolites (7OH-MiNP, 7oxoMiNP and 7cx-MiNP) (UBA, 2012), are close to the respective BE values of 10.6 µg/L for women of reproductive age and are also close to the level of 15.0 µg/L for children derived by Hays et al. (2011) (see Table 3).

It is important to ensure that future HBM surveys in Europe effectively monitor the DEHP substitutes, such as DiNP, and their associated metabolites.

VOCs

The organic compounds that have a boiling point between 50oC and 260oC are classified as VOCs. The most commonly found VOCs are benzene, toluene, ethylbenzene, xylenes, styrene, and terpenes (such as a-pinene and limonene). These chemicals are used widely in a large variety of household products such as paints, varnishes, waxes, solvents, detergents, and cleaning products. These chemicals are also emitted during the use of photocopiers and printers (Cox, Little & Hodgdon, 2002; Hodgson et al., 2000; Katsoyiannis, Leva & Kotzias, 2008; Wilke, Jann & Brödner, 2004; Yu et al., 2006;). VOCs are associated with a variety of adverse health effects. The most important compound, benzene, is a carcinogen causing Acute Myeloid Leukemia (AML). It can also cause neurological defects at high exposure levels, which can be found in occupational settings.

Substantial differences in urinary levels of unmetabolized benzene (Table 23), which is the most reliable marker of benzene exposure, were demonstrated in a study of smokers vs. non-smokers in Italy (Fustinoni et al., 2005). Another study showed no significant differences between subjects exposed to municipal solid waste incinerator fumes and unexposed subjects (Ranzi et al., 2013). In Germany ten times higher levels of S-phenylmercapturic acid were found in smokers (1.31 µg/gr creatinine) compared to non-smokers (0.12 µg/gr creatinine) (Schettgen, Musiol & Kraus, 2008). In addition, Wilhelm et al. (2007) studied the influence of exposure to industrial sources (i.e. hot spots) on children's health in North Rhine Westphalia, Germany, and found no significant differences in urinary S-phenylmercapturic acid levels between the levels of exposed and unexposed children. The GM values of exposed children were below the LOD of 0.2 µg/L.

Table 23. Benzene (unmetabolized) and its metabolite, S-phenylmercapturic acid (S-PMA), in urine: arithmetic means (min-max) of country-level GM or median values

Subregion/ country	Benzene (ng/L)	S-PMA (µg/gr creatinine)	S-PMA (µg/L)
Germany (western Europe)		0.12 (non-smokers) 1.31 (smokers)	< 0.2 (non-smokers living in industrial hot spots) < 0.2 (non-smokers living outside industrial hot spots)
Italy (southern Europe)	155 (non-smokers in 2005) 560 (smokers in 2005) 117 (non-smokers in 2013) 128 (non-smokers living near waste incinerators in 2013)		

Source: compiled from Fustinoni et al. (2005); Wilhelm et al. (2007); Schettgen, Musiol & Kraus (2008); Ranzi et al. (2013)

A key factor that affects exposure to benzene is residential proximity to heavily trafficked streets (Karakitsios et al., 2010) and gasoline stations (Karakitsios et al., 2007). The reduced levels of urinary unmetabolized benzene reflect the progressive decline of ambient air benzene in Europe during the last decade. This is likely a result of the decline of emissions from mobile sources due to the continuous renewal of the traffic fleet in Europe and improvements in internal combustion engine technology (Karakitsios et al., 2013). Considering that exposures to benzene are common, the scarce HBM data provide only limited information on the distribution of risks and main sources of exposure. Long-term exposure to benzene in individuals living near gasoline stations and other hot spots remains a concern.

As traffic emissions decline, other sources of benzene become relatively more important, such as benzene emissions from indoor sources, including side-stream smoke, combustion of biomass for heating and cooking, and emissions from building materials. Considering that benzene traffic emissions and indoor/outdoor air exchange rates are higher in southern Europe, it is not surprising that indoor benzene levels are also higher in the south than in the north of Europe (Sarigiannis et al., 2011). Indoor combustion sources, such as kerosene heaters, may also be an important source of exposure to benzene in Members States where such heating practices remain common (Lam et al., 2012). The lack of HBM data from countries with limited resources, where exposure levels may be higher than in resource-rich countries, is a serious limitation of this analysis.

Polyaromatic hydrorcabons (PAHs)

Polycyclic Aromatic Hydrocarbons (PAHs) are a class of environmentally persistent organic compounds which are mainly formed through incomplete combustion of organic molecules. PAHs are composed of two or more fused aromatic rings, with a pair of carbon atoms shared between rings. They consist of carbon and hydrogen only. PAHs are solids with high melting and boiling points, low volatility at room temperature and very low aqueous solubility. They are highly lipophilic and soluble in organic solvents. Their toxicity has been evaluated by several national and international organizations, such as the ATSDR, the United States EPA, the International Programme on Chemical Safety (IPCS), the European Commission Scientific Committee on Food (SCF) and JECFA. The following 16 PAHs (Table 24) have been defined to be of the greatest concern with regard to potential exposure and adverse health effects (EPA, 1977; EU, 2005).

Table 24. The 16 PAHs of greatest public health significance

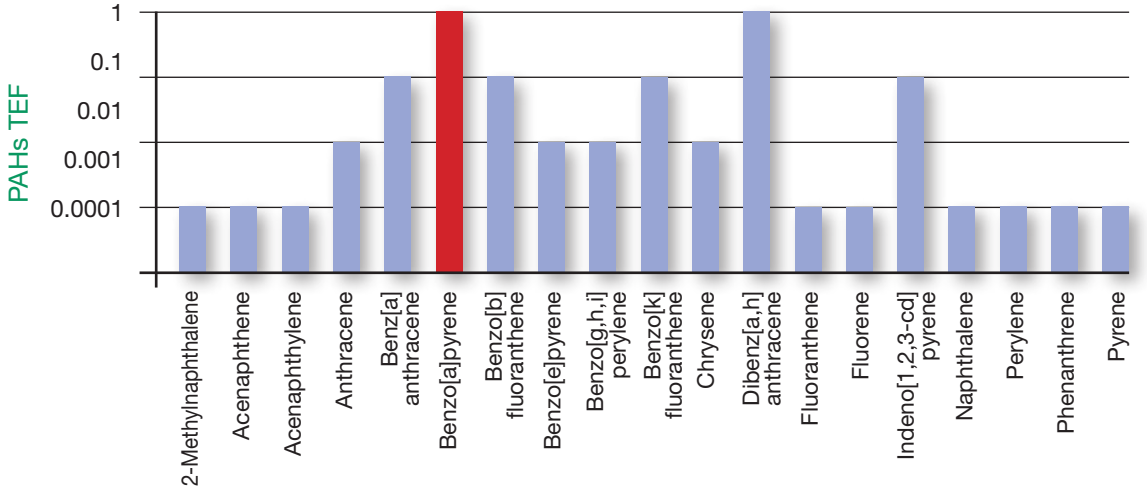
Subregion/country	Benzene (ng/L)	S-PMA (µg/L)
benz[a]anthracene	chrysene	dibenzo[a,l]pyrene
benzo[b]fluoranthene	cyclopenta[cd]pyrene	indeno[1,2,3-cd]pyrene
benzo[j]fluoranthene	dibenz[a,h]anthracene	5-methylchrysene
benzo[k]fluoranthene	dibenzo[a,e]pyrene	benzo[c]fluorene
benzo[ghi]perylene	dibenzo[a,h]pyrene	
benzo[a]pyrene	dibenzo[a,i]pyrene	

Toxicological studies demonstrated that PAHs can cause various types of cancers. Increased risks of lung, skin, and bladder cancers in humans have also been observed in workers who were occupationally exposed to PAHs (Liu & Waalkes, 2008). The mechanism of PAH-induced carcinogenesis is believed to be via the binding of PAH metabolites to deoxyribonucleic acid (DNA) at sites that are critical for the regulation of cell differentiation or growth. Cells with rapid replicative turnover, such as those in bone marrow, skin, and lung tissue, are more likely to be affected.

Exposures to PAHs can occur through various pathways including inhalation and food intake. Since PAHs are considered carcinogens, there is no threshold under which exposure is safe. Thus, there are no BE values for PAHs. The maximum levels of benzo(a)pyrene and the sum of benzo(a)pyrene, benz(a)anthracene, benzo(b)fluoranthene and chrysene are regulated in food stuff according to Commission Regulation (EU) No 835/2011 (EC, 2011a). However, there are no other legal instruments regulating the production and/or use of PAHs.

In the Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons (Schoeny & Poirier, 1993), United States EPA recommends using toxicity equivalency factors (TEFs) to convert concentrations of 19 carcinogenic PAHs (cPAHs) to an equivalent concentration of benzo(a)pyrene (B[a]P). In this scheme (Fig. 13), the TEF for B[a]P is set equal to one.

Fig. 13. TEFs for 19 polycyclic aromatic hydrocarbons (PAHs)



Source: adapted from Schoeny & Poirier (1993).

Similar to VOCs, urinary levels of PAHs and their respective metabolites (Table 25) are associated with proximity to combustion sources such as municipal solid waste incinerators (Ranzi et al., 2013). Levels of 1-hydroxypyrene (1-OH-P) (a major urinary PAH metabolite) were found to be higher for smokers (0.14 µg/g creatinine) than for non-smokers (0.08 µg/g creatinine) in the study by Lafontaine et al. (2006), but not in the study by Leroyer et al. (2010). Proximity to hot spot industrial sites in Germany was found to significantly affect PAH exposure levels with the mean urinary 1-OH-P level of 0.31 µg/g creatinine in the children living close to hot spots compared to 0.15 µg/g creatinine compared to children living far from hot spots (Wilhelm et al., 2007). In all cases, the 1-OH-P levels were lower than the RV of 0.5 ng/L.

Studies in the Czech Republic (Rossner et al., 2011 and 2013) found that levels of B[a]P-like DNA adducts were similar in the Ostrava and Prague regions, although B[a]P levels in the Ostrava region were more than eight times higher. This was attributed to the more efficient DNA repair capacity in the highly exposed population. The nonlinear association between exposure levels and the formation of DNA-adducts, or the occurrence of oxidative stress, highlights the need to use advanced multiomics approaches that can help to explain the observed pattern and reveal the mechanisms of interaction between environmental toxicants and human systems, which are modified by genetic make up and other intrinsic factors.

Exposure to PAHs is affected by proximity to intense combustion sources, such as heavily trafficked roads, municipal waste incinerators and industrial sites. An additional source of PAHs is combustion of solid fuel for space heating. In this regard, special attention ought to be paid to the use of biomass in large urban and metropolitan areas, which, if not controlled, may contribute substantially to the overall PAH exposure of the urban population. Biomass combustion for heating is expected to contribute to indoor exposure as well.

Table 25. 1-OH-P, a major PAH metabolite, ∑1-, 2-, 3-, 4- and 9-hydroxyphenanthrenes (∑ OH-Ph) and anthracene in urine: arithmetic means (min-max) of country-level GM or median values

Subregion (countries)	1-OH-P (µg/g Creat.) – Non smokers	1-OH-P (µg/g Creat.) – Smokers	1-OH-P (µg/g Creat.) – Non industrial	1-OH-P (µg/g Creat.) – Industrial	1-OH-P ReV	∑ OH-Ph (µg/g Creat.)	Anthracene (µg/L)
Western Europe (Belgium, France, Germany)	0.14 (0.08–0.2)	0.14 (France)	0.15 (Germany)	0.31 (Germany)	0.5 µg/L or 0.3 µg/g creatinine RV95 for Germany (Wilhelm et al., 2008)		
Southern Europe (Italy)							0.6 – general population 0.9 – residence near municipal waste incinerators
Southern Europe (Spain)	0.08 GM	0.18 GM	0.12 GM			Smokers: 3.17 Non smokers: 0.09 Non industrial: 1.30	

Source: compiled from Lafontaine et al. (2006); Wilhelm et al. (2007); Leroyer et al. (2010); Morrens et al. (2012); Bartolomé et al. (2015).

There is no sufficient evidence that exposure to PAHs has declined during the last ten years in Europe. In terms of spatial differentiation, exposure to PAHs is expected to be higher in areas with intense traffic and industrial activity. Personal lifestyle factors, such as smoking and the use of indoor biomass combustion for heating and cooking, are also important determinants of exposure. Indoor combustion sources, while uncommon in affluent countries, can be important sources of exposure in some Member States in central and western Asia, where HBM data on PAHs are currently not available.

5. Application of HBM data: opportunities and challenges

Human biological monitoring can be an important supplement to the conventional sources of information for regulatory risk assessments and for supporting public health protection policies. As the analyses of temporal trends and spatial patterns in biomarker values in the European Region demonstrate, HBM data can identify subpopulations with elevated exposures and provide independent metrics of the success of exposure mitigation measures at regional, national and international levels. Examples include country-to-country variability in the levels of DDT, phthalates and mercury in human biological samples, as well as temporal trends in exposures to POPs showing the beneficial effects of the Stockholm convention (UNEP, 2011), and an increase in exposures to plasticizers which were introduced as substitutes of DEHP.

HBM data can also be used to support public health protection policies that focus on exposure prevention and early identification of homeostatic perturbations that may lead to adverse health outcomes. There may be challenges with the poor compatibility of data arising from the use of different study designs, recruitment and sampling protocols, data gaps (especially in countries with limited research capacity) and the lack of supplemental information on the characteristics of the study population, environmental levels of pollutants and exposure sources. Time trend analysis of HBM data can also identify emerging environmental pollutants and define new policy priorities. A key benefit of using HBM data is the possibility to identify public health threats before they cause substantial adverse effects at the population level.

This review is primarily focused on biomarkers of exposure to xenobiotics. While biomarkers of health effects and vulnerability are discussed in introductory sections, comparison of countries or assessment of temporal trends based on such biomarkers was beyond the scope of this report, mainly due to the lack of universally accepted standardized methods for collecting and interpreting these types of data. Broader application of biomarkers of effect and vulnerability in public health assessments would require harmonization of assessment methods and development of standardized approaches to data interpretation, including reference values and system-level effects. For example, further support of research aimed at developing and validating new biomarkers of health effect of EDCs is necessary to link the exposure to EDCs with the pre-clinical manifestations of subtle biological effects that can disrupt endocrine homeostasis and cause adverse health outcomes.

Further research is also needed to develop and validate biomarkers of subclinical health effect reflecting combined exposures to multiple health stressors that are chemical, physical and biological in nature. Other development areas include the application of sophisticated statistical methods to link multiple exposure biomarkers to a single health outcome. These statistical methods will enable analysis of health effects of chemical mixtures. Methods for analysis of HBM data from longitudinal studies and methods for linking biomarkers of pre-clinical effects with overt diseases in epidemiological investigations also need to be further developed.

HBM data can help to identify population subgroups with increased risk of adverse health effects from environmental pollutants, such as subgroups with increased exposure to xenobiotics due to certain lifestyle factors, dietary habits or SES. For example, analysis of existing HBM data reveals a clear association between country-level socioeconomic characteristics, such as GDP per capita, and levels of certain environmental pollutants (DDT, plasticisers, etc.). Further analysis of HBM data may reveal similar associations within specific countries, where exposure levels may vary among sub-national geographic areas or among defined subpopulations living within the same area. Combining HBM data with information on lifestyle factors, consumer behaviour and sources of exposure can help to design targeted interventions aimed at reducing exposures in disadvantaged groups. HBM can also serve as an important tool for evaluating exposures, assessing health risks and raising awareness of health hazards associated with industrial contaminated sites.

6. Status of the implementation of Parma commitments

Analysis of the available HBM data has demonstrated that exposures to some pollutants, such as POPs, lead and regulated phthalates, are declining. At the same time, exposures to other important pollutants, such as mercury, cadmium and arsenic, remain steady. Exposure to diisononyl phthalate (DiNP), which replaced DEHP as a plasticizer, may be increasing. There is substantial variability in exposure levels among Member States of the WHO European Region related to differences in diet, regulatory environment, consumer behaviour and other factors. Levels of some pollutants, such as DDT and phthalates, show a clear inverse association with per capita GDP. Exposures to other pollutants, such as methylmercury, are associated with nutrition and lifestyle factors, which can be particularly common in specific geographic areas. More progress needs to be made in order to better promote health and prevent disease arising from chemical, biological and physical environments. These are two goals which reflect specific targets set in the Parma Declaration (WHO Regional Office for Europe, 2010).

In section A on "Protecting children's health", the Regional Priority Goal (RPG) 4, commitment (i) states:

> *We will take advantage of the approach and provisions of relevant international agreements[2]. We will contribute to the Strategic Approach to International Chemical Management (SAICM) and to the development of the global legal instrument on mercury.*

Recent international and national surveys demonstrated that exposure to mercury remains an important public health concern in a number of Member States with high seafood consumption. The global instrument on mercury (Minamata Convention) was adopted in 2013. As of November 2014, more than half of the Member States of the WHO European Region have signed the Minamata Convention (UNEP, 2014). HBM will be an important tool for characterizing baseline conditions and monitoring the effects of the Convention on reducing actual human exposures. WHO is collaborating with UNEP to develop an international plan for applying HBM as a global tool for monitoring population exposure to mercury. This initiative builds upon the experience and expertise in the WHO European Region, as demonstrated in the COPHES, DEMOCOPHES and CROME projects and various national surveys, as well as ongoing efforts to facilitate the use of a harmonized HBM methodology for assessing pre-natal exposures to mercury in the Region.

Coordinated policy measures at the global scale were implemented under the Stockholm Convention in order to reduce exposures to POPs. The observed declining trends in POPs in human samples reflect successes in the implementation of the Stockholm Convention and relevant national measures aimed at eliminating emissions of PCBs, dioxins, DDT and other organochlorine pesticides. However, early life exposures to POPs via contaminated

2 Such as the Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal, the Rotterdam Convention on the Prior Informed Consent Procedure for Certain Hazardous Chemicals and Pesticides in International Trade, and the Stockholm Convention on Persistent Organic Pollutants, as well as the protocols on heavy metals and on persistent organic pollutants to the 1979 Convention on Long-Range Transboundary Air Pollution.

breast milk remain an issue of concern. Infant intake of dioxins through contaminated breast milk remains above levels considered to be safe. Recent data showing a high level of DDT in breast milk in Tajikistan demonstrate the need for more active measures aiming at completely eliminating the use of this pesticide.

The overall objective of the Strategic Approach to International Chemicals Management (SAICM) is to achieve the sound management of chemicals throughout their life-cycle, so that, by 2020, chemicals are used and produced in ways that lead to the minimization of significant adverse effects on human health and the environment. The objective will be achieved, among other ways, through the implementation of activities set out in the Global Plan of Action. The observed associations between GDP per capita and levels of exposure to some chemical pollutants in Member States point out where further efforts are needed to improve the management of chemicals and reduce exposures in countries with limited internal resources.

The RPG4, commitment (ii) states:

> *We aim to protect each child from the risks posed by exposure to harmful substances and preparations, focusing on pregnant and breast-feeding women and places where children live, learn and play. We will identify those risks and eliminate them as far as possible, by 2015.*

National and international HBM programmes have helped to identify and assess the risks for pregnant and breast-feeding women and children. In response to evidence coming from these programmes and other relevant information sources, regulatory actions have been undertaken in the EU and individual Member States. Examples include the EU BPA directive (EC, 2011b) and the organochlorine pesticides regulation (EU, 2004).

More research is needed in order to fully characterize the risks to children, at the in-utero stage of development and in infancy, from low-level exposures to EDCs and to chemical mixtures. Further development and application of biomarkers, including early effect biomarkers, can facilitate progress in these areas.

While risks associated with exposures to classic pollutants, such as mercury, are relatively well characterized, eliminating these risks will require substantial investments and coordinated efforts within the Region and globally.

The biggest remaining challenge is to fully characterize exposures to xenobiotics, especially organic compounds, in Member States with limited internal resources, such as those in the eastern and south-eastern parts of the European Region. Some sources of emission and exposure, such as the indoor combustion of biofuels for heating and cooking, have declined or completely disappeared in many countries in the western part of the Region. However, these sources of exposure may still be prevalent in the resource-limited Member States.

The RPG 4, commitment (iii) states:

> *We will act on the identified risks of exposure to carcinogens, mutagens and reproductive toxicants […] and endocrine disruptors, and urge other stakeholders to do the same. […]*

Several carcinogens and mutagens have been banned in the EU as prescribed by the Restriction of Hazardous Substances Directive 2002/95/EC (EU, 2003) and the Cosmetics Directive 76/768/EEC (EU, 1976). Examples of banned substances include: lead, mercury, cadmium, hexavalent chromium, polybrominated biphenyls (PBB) and PBDE. Significant efforts have been undertaken to reduce inadvertent population exposure to these substances via environmental matrices such as ambient air, soil, drinking-water and food.

The RPG 4, commitment (iv) states:

> *We call for more research into the potentially adverse effects of persistent, endocrine-disrupting and*

bio-accumulating chemicals and their combination, as well as for the identification of safer alternatives. […] We will develop and use improved health risk assessment and benefit assessment methods.

New research on reproductive toxicants and EDCs has been fostered in the framework of national and international programmes, such as those funded by the European Commission in the EU.

Key hurdles to improving capacity for effective risk management of reproductive toxicants and EDCs are: the complexity of the respective biological mechanisms, the widespread use of many of these chemicals and the lack of international consensus on their toxicological characteristics. BPA is a typical example. Although the observed levels in human samples (a few µg/L) are far below the respective BE of 2 300 µg/L, some epidemiological studies have demonstrated associations between (low-level) BPA exposure and adverse health outcomes related to endocrine disruption. In this context, knowledge transfer and the harmonization of analytical, sampling and assessment procedures is essential for supporting policies aimed at improving the protection of the European population.

Further development of appropriate computational tools and models for thorough interpretation of HBM data are necessary in order to enhance the use of HBM data in health risk and health impact assessments.

While many Member States in the western part of the Region have national HBM programmes or other projects involving the use of HBM, there are glaring data gaps and in the eastern part of the Region. More efforts are necessary in order to characterize temporal trends and identify sub-populations that are at an increased risk of adverse health effects due to elevated levels of exposure.

In Section D on "Knowledge and tools for policy-making and implementation", item no. 11 states:

We will contribute to develop a consistent and rational approach to human biomonitoring as a complementary tool to assist evidence-based public health and environmental measures, including awareness-raising for preventive actions.

Efforts toward the development of a consistent and rational approach to HBM for use in environmental health risk assessment have been undertaken in the last few years, as demonstrated by the COPHES/DEMOCOPHES and CROME projects funded by the EC.

The WHO Regional Office for Europe has organized international workshops on the application of HBM in exposure assessment, and has taken initial steps to promote and facilitate the use of a harmonized HBM methodology in the eastern part of the Region.

More capacity building and international QA and QC schemes, as well as the harmonization of sampling, laboratory analysis, exposure data analysis, and data reporting and interpretation approaches are needed in order to fulfil the potential of HBM in informing and enhancing human health risk assessment in relation to chemicals. This is especially true in the eastern part of the Region. Harmonized procedures for sampling, sample storage, analytical processing and collection of ancillary information (e.g. time-activity and dietary data) will significantly enhance the usefulness of HBM data in supporting the decision- and policy-making processes related to the protection of public health.

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