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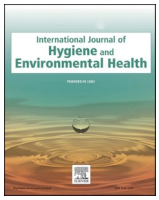

Harmonized human biomonitoring in European children, teenagers and adults: EU-wide exposure data of 11 chemical substance groups from the HBM4EU Aligned Studies (2014–2021)

Eva Govarts [a,*,1], Liese Gilles [a,1], Laura Rodriguez Martin [a], Tiina Santonen [b], Petra Apel [c], Paula Alvito [d,e], Elena Anastasi [f], Helle Raun Andersen [g], Anna-Maria Andersson [h], Lenka Andryskova [i], Jean-Philippe Antignac [j], Brice Appenzeller [k], Fabio Barbone [l], Zohar Barnett-Itzhaki [m], Robert Barouki [n], Tamar Berman [o], Wieneke Bil [p], Teresa Borges [q], Jurgen Buekers [a], Ana Cañas-Portilla [r], Adrian Covaci [s], Zsofia Csako [t], Elly Den Hond [u], Darina Dvorakova [v], Lucia Fabelova [w], Tony Fletcher [x], Hanne Frederiksen [h], Catherine Gabriel [y,z], Catherine Ganzleben [aa], Thomas Göen [ab], Thorhallur I. Halldorsson [ac], Line S. Haug [ad], Milena Horvat [ae], Pasi Huuskonen [b], Medea Imboden [af,ag], Marta Jagodic Hudobivnik [ae], Beata Janasik [ah], Natasa Janev Holcer [ai,aj], Spyros Karakitsios [y,z], Andromachi Katsonouri [f], Jana Klanova [i], Venetia Kokaraki [ak], Tina Kold Jensen [al], Jani Koponen [am], Michelle Laeremans [a], Federica Laguzzi [an], Rosa Lange [c], Nora Lemke [c], Sanna Lignell [ao], Anna Karin Lindroos [ao], Joana Lobo Vicente [aa], Mirjam Luijten [p], Konstantinos C. Makris [ap], Darja Mazej [ae], Lisa Melymuk [i], Matthieu Meslin [aq], Hans Mol [ar], Parisa Montazeri [as,at,au], Aline Murawski [c], Sónia Namorado [av], Lars Niemann [aw], Stefanie Nübler [ab], Baltazar Nunes [av], Kristin Olafsdottir [ax], Lubica Palkovicova Murinova [w], Nafsika Papaioannou [y,z], Susana Pedraza-Diaz [r], Pavel Piler [i], Veronika Plichta [ay], Michael Poteser [az], Nicole Probst-Hensch [af,ag], Loïc Rambaud [ba], Elke Rauscher-Gabernig [ay], Katarina Rausova [w], Sylvie Remy [a], Margaux Riou [ba], Valentina Rosolen [bb], Christophe Rousselle [aq], Maria Rüther [c], Denis Sarigiannis [y,z,bc], Maria J. Silva [bd], Zdenka Šlejkovec [ae], Janja Snoj Tratnik [ae], Anja Stajnko [ae], Tamas Szigeti [t], José V. Tarazona [be], Cathrine Thomsen [ad], Žiga Tkalec [ae], Hanna Tolonen [am], Tomas Trnovec [w], Maria Uhl [bf], An Van Nieuwenhuyse [bg], Elsa Vasco [d], Veerle J. Verheyen [a], Susana Viegas [bh], Anne Marie Vinggaard [bi], Nina Vogel [c], Katrin Vorkamp [bj], Wojciech Wasowicz [ah], Till Weber [c], Sona Wimmerova [w], Marjolijn Woutersen [p], Philipp Zimmermann [c], Martin Zvonar [i], Holger Koch [bk], Marike Kolossa-Gehring [c], Marta Esteban López [r], Argelia Castaño [r], Lorraine Stewart [x], Ovnair Sepai [x], Greet Schoeters [a,s,bl]

[a] *VITO Health, Flemish Institute for Technological Research (VITO), Boeretang 200, 2400, Mol, Belgium*
[b] *Finnish Institute of Occupational Health (FIOH), P.O. Box 40, FI-00032, Työterveyslaitos, Finland*
[c] *German Environment Agency (UBA), Corrensplatz 1, 14195, Dessau-Roßlau, Germany*
[d] *Food and Nutrition Department, National Institute of Health Doctor Ricardo Jorge, Avenida Padre Cruz, 1649-016, Lisbon, Portugal*
[e] *CESAM, Centre for Environmental and Marine Studies, University of Aveiro, Aveiro, Portugal*
[f] *Cyprus State General Laboratory, Ministry of Health, P.O. Box 28648, 2081, Nicosia, Cyprus*
[g] *Department of Public Health, University of Southern Denmark (SDU), J.B. Winsløws Vej 17A, DK-5230, Odense M, Denmark*
[h] *Department of Growth and Reproduction, Copenhagen University Hospital, Rigshospitalet, DK-2100, Copenhagen, Denmark*
[i] *RECETOX, Faculty of Science, Masaryk University, Kotlarska 2, Brno, 611 37, Czech Republic*

* Corresponding author.
E-mail address: eva.govarts@vito.be (E. Govarts).

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Abbreviations

3-PBA 3-phenoxybenzoic acid
4-F-3-PBA 4-fluoro-3-phenoxybenzoic acid
5-cx-MEPP Mono(2-ethyl-5-carboxypentyl) phthalate
5-OH-MEHP Mono(2-ethyl-5-hydroxyhexyl) phthalate
5-oxo-MEHP Mono(2-ethyl-5-oxo-hexyl) phthalate
AAMA N-Acetyl-S-(2-carbamoyl-ethyl) cysteine
As Arsenic
As(III) Arsenite
As(V) Arsenate
AsB Arsenobetaine
BCEP Bis(2-chloroethyl) phosphate
BCIPP Bis(1-chloro-2-propyl) phosphate
BDCIPP Bis(1,3-dichloro-2-propyl) phosphate
BDE-153, -209, −47 Polybrominated diphenyl ethers congener
BE Belgium
BE-value Biomonitoring equivalent value
BP-1, BP-3 Benzophenone
BPA Bisphenol A
BPF Bisphenol F
BPS Bisphenol S
bw Bodyweight
Cd Cadmium
CDC Centers for Disease Control and Prevention
CH Switzerland
CHMS Canadian Health Measures Survey
CIs Confidence Intervals
cis-DBCA Cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid
cis-DCCA Cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid
CNHBM China National Human Biomonitoring survey
COPHES/DEMOCOPHES DEMOnstration of a study to COordinate and Perform Human biomonitoring on a European Scale
Cr VI Chromium VI
crt Creatinine
cx-MINCH Cyclohexane-1,2- dicarboxylate-mono-(7- carboxylate-4-methyl) heptyl ester
cx-MiNP 7-Carboxy-(mono-methylheptyl) phthalate
CY Cyprus
CZ Czech Republic
DE Germany
DEHP Di(2-ethylhexyl) phthalate
DiNCH Diisononyl 1,2-cyclohexanedicarboxylic acid diisononyl ester
DK Denmark
(t)DON (total) Deoxynivalenol
DMA Dimethylarsinic acid
EFSA European Food Safety Authority
EL Greece
ES Spain
EU European Union
FI Finland
FR France
FRs Flame Retardants
GM Geometric mean
HBM Human Biomonitoring
HBM4EU European Human Biomonitoring Initiative
HFRs Halogenated Flame retardants
Hg Mercury
HQ Hazard Quotient
HR Croatia
HU Hungary
IL Israel
IPCHEM Information Platform for Chemical Monitoring
IS Iceland
ISCED International Standard Classification of Education
IT Italy
KoNEHS Korean National Environmental Health Survey
LOD Limit of Detection
LOQ Limit of Quantification
LU Luxembourg
MBzP Mono-benzyl phthalate
MCHP Mono-cyclo-hexyl phthalate
MEHP Mono(2-ethylhexyl) phthalate
MEP Mono-ethyl phthalate
MiBP Mono-isobutyl phthalate
MMA monomethylarsonic acid
MnBP Mono-n-butyl phthalate
MnPeP Mono-n-pentyl phthalate
n/N Sample size
NHANES National Health and Nutrition Examination Survey
NL The Netherlands
NO Norway
OH-MiDP 6-OH-Mono-propyl-heptyl phthalate
OH-MINCH Cyclohexane-1,2- dicarboxylate-mono-(7- hydroxy-4-methyl) octyl ester
OH-MiNP 7-OH-(Mono-methyl-octyl) phthalate
OPFRs Organophosphorus flame retardants
P50 50th Percentile
P95 95th percentile
PAHs Polycyclic aromatic hydrocarbons
Pb Lead
PFASs Per- and polyfluoroalkyl substances
PFHpA Perfluoroheptanoic acid
PFHpS Perfluoroheptane sulfonic acid
PFHxA Perfluorohexanoic acid
PFHxS Perfluorohexane sulfonic acid
PFNA Perfluorononanoic acid
PFOA Perfluorooctanoic acid
PFOS Perfluorooctane sulfonic acid (sum of all isomers)
PFPeA Perfluoropentanoic acid
PL Poland
PT Portugal
QA/QC Quality assurance/Quality control
QAU Quality Assurance Unit
QF Quantification frequency
RfD Reference Dose
SE Sweden
SES Socio-economic status
SG Specific Gravity
SK Slovakia
Sl Slovenia
TCPy 3,5,6-trichloro-2-pyridinol
TDI Tolerable daily intake
TRA Toxicologically relevant arsenic
trans-DCCA Trans-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid
TWI Tolerable weekly intake
VITO Vlaamse Instelling voor Technologisch Onderzoek

[j] Oniris, INRAE, LABERCA, Nantes, France
[k] Luxembourg Institute of Health (LIH), Luxembourg
[l] Department of Medicine - DAME, University of Udine, Udine, Italy
[m] Israeli Ministry of Health, Ruppin Research Group in Environmental and Social Sustainability, Ruppin Academic Center, 4025000, Israel
[n] Université Paris Cité, Inserm T3S, Paris, France
[o] Department of Environmental Health, Ministry of Health, Israel
[p] National Institute for Public Health and the Environment (RIVM), Antonie van Leeuwenhoeklaan 9, 3721 MA, Bilthoven, the Netherlands
[q] Ministry of Health, Lisbon, Portugal
[r] National Centre for Environmental Health, Instituto de Salud Carlos III, Ctra, Majadahonda a Pozuelo km 2,2, 28220, Majadahonda (Madrid), Spain
[s] University of Antwerp, Toxicological Center, Universiteitsplein 1, 2610, Wilrijk, Belgium
[t] National Public Health Center, Budapest, Hungary
[u] Provincial Institute of Hygiene, Antwerp, Belgium
[v] University of Chemistry and Technology (UCT), Prague, Faculty of Food and Biochemical Technology, Department of Food Analysis and Nutrition, Technicka 5, Prague, 166 28, Czech Republic
[w] Slovak Medical University, Faculty of Public Health, Limbová 12, 833 03, Bratislava, Slovak Republic
[x] UKHSA UK Health Security Agency, Harwell Science Park, Chilton, OX11 0RQ, United Kingdom
[y] Environmental Engineering Laboratory, Department of Chemical Engineering, Aristotle University of Thessaloniki, 54124, Thessaloniki, Greece
[z] HERACLES Research Center on the Exposome and Health, Center for Interdisciplinary Research and Innovation, Balkan Center, Bldg. B, 10th km, Thessaloniki, Thermi Road, 57001, Greece
[aa] European Environment Agency (EEA), Kongens Nytorv 6, 1050, Copenhagen K, Denmark
[ab] Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute and Outpatient Clinic of Occupational and Environmental Medicine, Henkestraße 9-11, 91054, Erlangen, Germany
[ac] Faculty of Food Science and Nutrition, University of Iceland, Reykjavik, Iceland
[ad] Norwegian Institute of Public Health, Department of Food Safety, PO Box 222, Skøyen, 0213, Oslo, Norway
[ae] Jožef Stefan Institute, Department of Environmental Sciences, Jamova cesta 39, 1000, Ljubljana, Slovenia
[af] Swiss Tropical and Public Health Institute, Kreuzstrasse 2, 4123, Allschwil, Switzerland
[ag] University of Basel, P.O. Box, CH-4003, Basel, Switzerland
[ah] Nofer Institute of Occupational Medicine (NIOM), Lodz, Poland
[ai] Croatian Institute of Public Health, Department of Environmental Health, Zagreb, Croatia
[aj] Faculty of Medicine of the University of Rijeka, Department of Social Medicine and Epidemiology, Rijeka, Croatia
[ak] School for Advanced Study (IUSS), Science, Technology and Society Department, Pavia, Italy
[al] Department of Clinical Pharmacology, Pharmacy and Environmental Medicine, Italy
[am] Finnish Institute for Health and Welfare (THL), Kuopio, Finland
[an] Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Nobels väg 13, Box 210, 17177, Stockholm, Sweden
[ao] Swedish Food Agency, Risk Benefit Assessment Department, Box 622, SE-751 26, Uppsala, Sweden
[ap] Cyprus International Institute for Environmental and Public Health, Cyprus University of Technology, Limassol, 3041, Cyprus
[aq] French Agency for Food, Environmental and Occupational Health & Safety, Anses, 14 Rue Pierre et Marie Curie, 94701, Maisons-Alfort, France
[ar] Wageningen Food Safety Research - Part of Wageningen University & Research, Akkermaalsbos 2, 6708 WB, Wageningen, the Netherlands
[as] ISGlobal, Barcelona, Spain
[at] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[au] CIBER Epidemiología y Salud Pública (CIBERESP), Spain
[av] Department of Epidemiology, National Institute of Health Doctor Ricardo Jorge, Avenida Padre Cruz, 1649-016, Lisbon, Portugal
[aw] German Federal Institute for Risk Assessment, Dept. Safety of Pesticides, Max-Dohrn-Strasse 8-10, D-10589, Berlin, Germany
[ax] Dept. Pharmacology and Toxicology, University of Iceland, Reykjavik, Iceland
[ay] Austrian Agency for Health and Food Safety, Department Risk assessment, Spargelfeldstraße 191, 1220, Wien, Austria
[az] Medical University of Vienna, ZPH, Dept. of. Environmental Health, Austria
[ba] Department of Environmental and Occupational Health, Santé publique France, 12 rue du Val d'Osne, 94415, Saint-Maurice, France
[bb] Institute for Maternal and Child Health - IRCCS "Burlo Garofolo", Trieste, Italy
[bc] Environmental Health Engineering, Institute of Advanced Study, Palazzo del Broletto, Piazza Della Vittoria 15, 27100, Pavia, Italy
[bd] Department of Human Genetics, National Institute of Health Doctor Ricardo Jorge and Centre of Toxicogenomics and Human Health, NOVA Medical School, Universidade NOVA de Lisboa, Lisbon, Portugal
[be] European Food Safety Authority (EFSA), Methodology and Scientific Support Unit, Via Carlo Magno 1/A, 43126, Parma, Italy
[bf] Environment Agency Austria, 1090, Vienna, Austria
[bg] Department of Health Protection, Laboratoire national de santé (LNS), 1 rue Louis Rech, 3555, Dudelange, Luxembourg
[bh] Escola Superior de Tecnologia da Saúde de Lisboa (ESTeSL), Lisbon, Portugal
[bi] National Food Institute, Technical University of Denmark, Denmark
[bj] Aarhus University, Department of Environmental Science, Frederiksborgvej 399, 4000, Roskilde, Denmark
[bk] Institute for Prevention and Occupational Medicine of the German Social Accident Insurance - Institute of the Ruhr-University Bochum (IPA), Bürkle-de-la-Camp-Platz 1, 44789, Bochum, Germany
[bl] Department of Biomedical Sciences, University of Antwerp, Universiteitsplein 1, 2610, Wilrijk, Belgium

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ABSTRACT

As one of the core elements of the European Human Biomonitoring Initiative (HBM4EU) a human biomonitoring (HBM) survey was conducted in 23 countries to generate EU-wide comparable HBM data. This survey has built on existing HBM capacity in Europe by aligning national or regional HBM studies, referred to as the HBM4EU Aligned Studies. The HBM4EU Aligned Studies included a total of 10,795 participants of three age groups: (i) 3,576 children aged 6–12 years, (ii) 3,117 teenagers aged 12–18 years and (iii) 4,102 young adults aged 20–39 years. The participants were recruited between 2014 and 2021 in 11–12 countries per age group, geographically distributed across Europe. Depending on the age group, internal exposure to phthalates and the substitute DINCH, halogenated and organophosphorus flame retardants, per- and polyfluoroalkyl substances (PFASs), cadmium, bisphenols, polycyclic aromatic hydrocarbons (PAHs), arsenic species, acrylamide, mycotoxins (deoxynivalenol (total DON)), benzophenones and selected pesticides was assessed by measuring substance

[1] Equal contribution of both first authors.

specific biomarkers subjected to stringent quality control programs for chemical analysis. For substance groups analyzed in different age groups higher average exposure levels were observed in the youngest age group, i.e., phthalates/DINCH in children versus teenagers, acrylamide and pesticides in children versus adults, benzophenones in teenagers versus adults. Many biomarkers in teenagers and adults varied significantly according to educational attainment, with higher exposure levels of bisphenols, phthalates, benzophenones, PAHs and acrylamide in participants (from households) with lower educational attainment, while teenagers from households with higher educational attainment have higher exposure levels for PFASs and arsenic. In children, a social gradient was only observed for the non-specific pyrethroid metabolite 3-PBA and di-isodecyl phthalate (DiDP), with higher levels in children from households with higher educational attainment. Geographical variations were seen for all exposure biomarkers. For 15 biomarkers, the available health-based HBM guidance values were exceeded with highest exceedance rates for toxicologically relevant arsenic in teenagers (40%), 3-PBA in children (36%), and between 11 and 14% for total DON, Σ (PFOA + PFNA + PFHxS + PFOS), bisphenol S and cadmium. The infrastructure and harmonized approach succeeded in obtaining comparable European wide internal exposure data for a prioritized set of 11 chemical groups. These data serve as a reference for comparison at the global level, provide a baseline to compare the efficacy of the European Commission's chemical strategy for sustainability and will give leverage to national policy makers for the implementation of targeted measures.

1. Introduction

The European Union (EU)'s zero pollution ambition for a toxic-free environment (2020) aims to better protect citizens and the environment from harmful chemicals. It is part of the Chemicals Strategy for Sustainability in the EU EC (2020). The strategy refers to human biomonitoring (HBM) and its capacity to demonstrate the presence of a growing number of hazardous chemicals in humans. Chemicals are present in air, water, food, but may also enter the human body through the use of consumer products. HBM measures the presence of chemicals and/or their metabolites directly in human fluids or tissues (Angerer et al., 2007). By integrating exposure from various sources and exposure routes, it is the most direct way to quantify the presence of hazardous chemicals in the human body. Lack of harmonized information at the European level concerning the exposure of citizens to chemicals, their interplay with other concurrent environmental exposures and their impact on health has urged the European Commission and European countries to co-fund the European Human Biomonitoring Initiative, HBM4EU (https://www.hbm4eu.eu/), under Horizon 2020. The main aim of the initiative was to coordinate and advance human biomonitoring in Europe and to assess the actual exposure of citizens to environmental chemicals and their possible health effects to support policy making (Ganzleben et al., 2017). HBM4EU followed the successful COPHES/DEMOCOPHES pilot projects, which were the first steps to perform HBM on a European scale (Den Hond et al., 2015). One of the goals of HBM4EU was to generate comparable data on human internal exposure to chemicals and chemical mixtures at the European level as a support to chemicals' regulation in the European Union. To capture policy needs and to prioritize chemical substances to be measured, HBM4EU has created a unique interface between policy makers and scientists both at the European and the national level, with an EU policy board and National Hubs in each of the countries with representatives of risk assessors, policy makers and scientists that are active in the Environment and Health domain. This allowed us to invite policy makers and stakeholders to nominate substances/substance groups of concern and related policy questions. Two such prioritization cycles were organized (Ougier et al., 2021). The first list of high-priority substances for action in HBM4EU included nine substance groups: phthalates and DINCH, bisphenols, per- and polyfluoroalkyl substances (PFASs), flame retardants, cadmium (Cd) and chromium VI (Cr VI), polycyclic aromatic hydrocarbons (PAHs), aromatic amines, chemical mixtures and emerging substances. The second list added acrylamide, aprotic solvents, arsenic (As), diisocyanates, lead (Pb), mercury (Hg), mycotoxins, pesticides (including chlorpyrifos, dimethoate, pyrethroids, glyphosate and polyethoxylated (POE)-tallow amine, and fipronil), and benzophenones, a type of chemical UV-filters. Some policy questions were specific per substance group, whilst others were common to most substance groups. They included: 1) What is the current exposure of the European population?, 2) Does exposure depend on where people live in Europe and why?, 3) Can we detect a significant decrease in internal exposure levels after implementation of EU regulation of the substance such as restriction under REACH?, 4) Are exposure levels above health-based HBM guidance values?, and 5) Should the substance be subject to (further) regulation? To address these questions, the HBM4EU Aligned Studies were designed to collect EU-wide comparable HBM data for some of the HBM4EU prioritized substance groups (Gilles et al., 2021). A quality assurance/quality control (QA/QC) program was designed and implemented to ensure the comparability of the analytical results in the HBM4EU Aligned Studies, which were analyzed in different laboratories (Esteban Lopez et al., 2021).

In this article we present the key findings of the HBM4EU Aligned Studies. The aim is to provide an overview of the internal exposure levels of biomarkers from the different substance groups at the European level, in relation to age groups. We explored whether certain subpopulations in Europe are more exposed than others in relation to geographical region and investigated educational attainment as a proxy marker for socio-economic status (SES). We compared the HBM4EU data with HBM data from large nationally representative HBM studies from Canada, United States and Korea, with similar sampling years and age groups, and to the previous European DEMOCOPHES study (2011–2012). Furthermore, we evaluated the data in relation to health risks by comparing the geometric mean (GM) and ninety fifth percentile (P95), representing an average and reasonable worst-case exposure scenario respectively, with health-based HBM guidance values derived within HBM4EU or established earlier (Apel et al., 2020, 2022a; Santonen et al., 2022). The significance of our results for the chemical policy in Europe is discussed. In other substance specific publications, part of this special issue and/or other journals, more in-depth analysis will be performed looking for example into the identification of determinants of internal exposure, exposure-effect analyses and applying specialized techniques for (mixture) risk assessment.

2. Material and methods

2.1. HBM4EU Aligned Studies' population sample

HBM4EU is the first large scale project in which HBM initiatives in Europe are aligned and data and questionnaire information post-harmonized. The resulting HBM4EU Aligned Studies combined 27 existing national or regional HBM studies from 23 countries that collected urine and/or blood samples. The study design is described in detail in Gilles et al. (2021). In short: the population sample was selected by utilizing a sampling scheme designed to guide the inclusion of eligible studies. The scheme is based on the inclusion of 11–12 primary sampling units (PSUs) per age group, distributed proportionally to the number of inhabitants in the four geographical regions (North, East, South, West) of Europe. The PSUs are HBM studies in European

countries that fulfilled the following inclusion criteria: (i) completed studies with available biobank samples, (ii) studies that were initiated before the start of the HBM4EU project but with sampling within the stipulated timeframe, (iii) new studies, adopting the HBM4EU protocols. Furthermore, samples had to be collected between 2014 and 2021, fall within the aforementioned age groups, analysis had to be performed in laboratories that successfully participated in the HBM4EU QA/QC program and the data must be shared on EU level. Additional criteria were set for PSUs to contribute with a 50:50 ratio of male and female participants, with individuals living in rural areas, towns/suburbs and in cities, and with at least 10% of individuals from low, medium and high educational level. All studies were approved by their local ethical committees as well as sharing of personal data for analysis at European level. All documents have been made available to the European Commission (Knudsen et al., 2022). Further details on ethical committees and funding are available in the Supplemental Material (Table S12). The HBM4EU Aligned Studies collected internal exposure data from 10,795 European citizens and Israel. Biological samples were collected from 3,576 children (6–12 years) from 14 countries (NO, DK, HU, SK, PL, Sl, EL, IT, FR, DE, BE, NL, CY and IL), from 3,117 teenagers (12–18 years) from 11 countries (NO, SE, PL, CZ, SK, Sl, EL, ES, FR, DE, BE) and from 4,102 adults (20–39 years) from 12 countries (DK, IS, FI, PL, CZ, HR, PT, FR, CH, DE, LU and IL). All samples were collected between 2014 and 2021. The characteristics of the HBM4EU Aligned Studies' population in children, teenagers and adults can be found in Table 1. In all three age groups male and female participants are more or less equally represented (Table 1). In general, individuals with low educational attainment (ISCED 0–2) are underrepresented in all three age groups, with only 3.8%, 6.3% and 5.9% of the participants for children, teenagers and adults respectively. 17% of the adults report to be active smokers. A more detailed description of the obtained study populations and contributing HBM studies is addressed in detail in Gilles et al. (2022).

2.2. Quantitative exposure biomarker data

An HBM4EU expert group selected the most appropriate biomarkers for each of the priority substances (Vorkamp et al., 2021). A Quality Assurance/Quality Control (QA/QC) program was established to guarantee the comparability of the biomarker data (Dvorakova et al., 2021; Esteban Lopez et al., 2021; Mol et al., 2022; Nübler et al., 2021, 2022;

Table 1
Characteristics of the study populations of the HBM4EU Aligned Studies.

	Children (N = 3576)			Teenagers (N = 3117)			Adults (N = 4102)		
	N	Median (P25–P75)	Min-max	N	Median (P25–P75)	Min-max	N	Median (P25–P75)	Min-max
Age (years)	3568	9 (7–10)	6–12	3113	14 (13–15)	12–18	4102	29 (25–34)	20–39
BMI (kg/m^2)	3348	16.4 (15.1–18.5)	10.8–39.2	2770	20.1 (18.1–22.6)	12.3–52.0	4010	23.2 (21.2–25.8)	15.8–56.4
Sampling period (years)	3576	2016 (2015–2018)	2014–2021	3117	2017 (2016–2018)	2014–2021	4102	2018 (2016–2019)	2014–2021

	Category	Children (N = 3576)	Teenagers (N = 3117)	Adults (N = 4102)
		N (%)	N (%)	N (%)
Degree of urbanization	Cities	1425 (39.9%)	1155 (37.1%)	2996 (73.0%)
	Towns or suburbs	968 (27.1%)	959 (30.8%)	520 (12.7%)
	Rural areas	922 (25.8%)	977 (31.3%)	481 (11.7%)
	Missing	*261 (7.3%)*	*26 (0.8%)*	*105 (2.6%)*
Educational level[a]	Low education (ISCED 0–2)	136 (3.8%)	196 (6.3%)	243 (5.9%)
	Medium education (ISCED 3–4)	1160 (32.4%)	1150 (36.9%)	943 (23.0%)
	High education (ISCED ≥ 5)	2130 (59.6%)	1702 (54.6%)	2898 (70.7%)
	Missing	*150 (4.2%)*	*69 (2.2%)*	*18 (0.4%)*
Geographical region[b]	North	600 (16.8%)	481 (15.4%)	796 (19.4%)
	South	870 (24.3%)	547 (17.6%)	684 (16.7%)
	East	862 (24.1%)	875 (28.1%)	528 (12.9%)
	West	1244 (34.8%)	1214 (39.0%)	2094 (51.1%)
Sex	Male	1811 (50.6%)	1547 (49.6%)	1944 (47.4%)
	Female	1762 (49.3%)	1570 (50.4%)	2158 (52.6%)
	Missing	*3 (0.1%)*		
Smoking	Non-Smoker	1793 (50.1%)	2096 (67.2%)	3369 (82.1%)
	Smoker	6 (0.2%)	117 (3.8%)	692 (16.9%)
	Missing	*1777 (49.7%)*	*904 (29.0%)*	*41 (1.0%)*

Abbreviations: P25 = 25th percentile; P75 = 75th percentile; ISCED = International Standard Classification of Education.
Contributing studies in children: DK: Odense Child Cohort (OCC), NO: Norwegian Environmental Biobank II (NEBII), HU: Transnational Adaption Actions for Integrated Indoor Air Quality Management (InAirQ), SK: Endocrine disruptors and health in children and teenagers in Slovakia (PCB cohort), PL: Polish Aligned Environmental Study (POLAES), Sl: Exposure of children and adolescents to selected chemicals through their habitat environment (SLO CRP), EL: Cross-Mediterranean Environment and Health Network (CROME), IT: Northern Adriatic cohort II (NACII), FR: Étude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition (ESTEBAN), DE: German Environmental Survey 2014–2017 subsample (GerES V-sub, unweighted), BE: Gezondheid, Gemeenten, Geboorte studie (3xG), NL: Survey on PEstiCide Mixtures in Europe, The Netherlands (SPECIMEn-NL). IL: The National Health and Nutrition Survey 2015 Israel (RAV MABAT), CY: Organic diet and children's health (ORGANIKO). Contributing studies in teenagers: SE: Riksmaten Adolescents 2016–17 (Riksmaten Ungdom), NO: Norwegian Environmental Biobank II (NEBII), CZ: Central European Longitudinal Studies of Parents and Children: Teenagers (CELSPAC: TE), SK: Endocrine disruptors and health in children and teenagers in Slovakia follow-up (PCB cohort follow-up), PL: Polish Aligned Environmental Study (POLAES), Sl: Exposure of children and adolescents to selected chemicals through their habitat environment (SLO CRP), EL: Cross-Mediterranean Environment and Health Network (CROME), ES: Biomonitorización en Adolescentes (BEA), FR: Étude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition (ESTEBAN), DE: German Environmental Survey 2014–2017 subsample (GerES V-sub, unweighted), BE: Flemish Environment and Health Study IV (FLEHS IV). Contributing studies in adults: DK: Copenhagen Minipuberty study (parents)/Danish Young Men Study (CPHMINIPUB/DYMS), IS: Icelandic National Dietary Survey (Diet_HBM), CZ: Central European Longitudinal Studies of Parents and Children: Young Adults ((C)ELSPAC: YA), PL: Polish Aligned Environmental Study (POLAES), HR: Implementation of Human Biomonitoring Survey In Adults in Croatia Using HBM4EU Methodology (HBM in Croatia), PT: Exposure of the Portuguese Population to Environmental Chemicals: a study nested in INSEF 2015 (INSEF-ExpoQuim), CH: Human Biomonitoring for Europe Program for Switzerland (HBM4EU-study Switzerland), FR: Étude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition (ESTEBAN), DE: Environmental Specimen Bank (ESB), LU: Observation des Risques et de la Santé Cardiovasculaire au Luxembourg (Oriscav-Lux2) and IL: The National Health and Nutrition Survey 2015 Israel (RAV MABAT).

[a] For children and teenagers, highest educational attainment of the household is used.

[b] Geographical region based on United Nations Geoscheme.

Vaccher et al., 2022). Due to the available financial resources not all substance groups could be measured in all age groups. Therefore, a selection of substance groups for each age group was performed. This selection was based on i) the potential exposure risk of the age groups, ii) filling knowledge gaps and responding to policy questions, and iii) interest of the participating studies. For the following substance groups comparable HBM data were gathered: phthalates and DINCH in children and teenagers; bisphenols, PAHs, Cd and mycotoxins in adults; organophosphorus FRs (OPFRs) and halogenated FRs (HFRs) in children; PFASs and As species in teenagers; pesticides and acrylamide in children and adults; benzophenones in teenagers and adults.

Supplemental Material Table S1 provides an overview of the parent compounds addressed, the biomarkers measured, the analytical method used and associated limits of detection (LOD) and quantification (LOQ) for each country contributing to the HBM4EU Aligned Studies. Biomarkers were only included in the table if obtained from at least 4 countries within each age group. The LOD and LOQ reported vary among the studies, as well as the methods used for determination of LOD/LOQ. If a laboratory only reported the LOD, this was used as cut-off to report quantifiable data and to calculate the quantification frequency (QF).

The biomarker data for each of the included data collections have a HBM4EU data quality label assigned (Supplemental Material Table S1), defined by the HBM4EU Quality Assurance Unit (QAU). Biomarkers analyzed in laboratories that successfully participated in the HBM4EU QA/QC were labelled as "Biomarker data quality assured by HBM4EU QA/QC program". Specific biomarkers for which the analyzing laboratory did not obtain successful results were labelled as "Biomarker data not quality assured by HBM4EU QA/QC program", so full comparability cannot be guaranteed and those were discarded for the scope of this paper. Some of the contributing studies had already analyzed some of the selected substance groups prior to HBM4EU. If these biomarker data were analyzed in laboratories that participated successfully in the HBM4EU QA/QC program later on and used the same method with continuous internal quality assurance, these data were labelled "Biomarker data generated before HBM4EU QA/QC program but deemed comparable by HBM4EU QAU", and as such these data were included. Data generated before HBM4EU by laboratories that did not participate or did not obtain successful results under the HBM4EU QA/QC program were labelled "Biomarker data generated before HBM4EU QA/QC program but comparability not guaranteed by HBM4EU QAU", so these were excluded from further analyses. As a sensitivity analysis, the data from this latter label were included to verify if interpretations would change.

2.2.1. Data management and analysis

All the HBM4EU Aligned Studies harmonized their data according to the centrally developed codebooks which defined variable names, units, formats and coding rules. The final codebooks with harmonized variables are available online: HBM4EU Harmonized Codebook Children Aligned Studies|Zenodo (https://doi.org/10.5281/zenodo.6598519); HBM4EU Harmonized Codebook Teenagers Aligned Studies|Zenodo (https://doi.org/10.5281/zenodo.6598532). HBM4EU Harmonized Codebook Adults Aligned Studies|Zenodo (https://doi.org/10.5281/zenodo.6598404). The harmonized data of each study was uploaded to the Personal Exposure and Health Data Platform (PEH) at VITO (https://hbm.vito.be/peh-data-platform). Quality control of the data (checking for outliers, coding, inconsistencies, etc.) was performed before integrating the data into the central database. Derived variables (e.g. standardized variables, imputed variables, sum parameters, blood lipids; see further) were calculated centrally and added to the database. Total blood lipid content was calculated using an enzymatic summation method according to the following formula: Total lipids (mg/dL) = 2.27 * (Total cholesterol) + triglycerides + 62.3 mg/dL (Bernert et al., 2007).

Descriptive statistics were calculated for all biomarkers that were obtained from at least 4 countries and with an overall QF >5% in the pooled HBM4EU dataset. The following descriptive statistics were calculated for the HBM4EU population: the geometric mean (GM) (if QF > 60%) and 95th percentile (P95), and their 95% confidence intervals (CIs). Biomarker concentrations are expressed in volume-based (μg/L) and additionally standardized for creatinine (μg/g creatinine) and blood lipids (μg/g lipid) for urinary biomarkers and lipid-soluble markers analyzed in blood respectively. Biomarker concentrations could not be normalized for specific gravity (SG) for the pooled HBM4EU population, as SG was not reported for all data collections included. Summary statistics (P5, P10, P25, P50, P75, P90, P95) are made public via the European HBM dashboard (https://hbm.vito.be/eu-hbm-dashboard) and the HBM module of IPCHEM. In both platforms the summary statistics of urinary biomarker data normalized for specific gravity (SG) (Pearson et al., 2009) can be consulted as well (if available). Measurements below the LOQ or below the LOD, if no quantification limit was given, were imputed by using a truncated lognormal distribution fitted per data collection (Lubin et al., 2004). For each data collection, a truncated lognormal distribution was fitted through the observed values above the limit. Subsequently random values were imputed from the estimated distribution below the limits. Sum parameters of metabolites of the same parent compound were calculated to allow comparison with available health-based HBM guidance values, i.e., metabolites of DINCH, DEHP and TRA. For PFASs, the sum parameter of four PFASs (PFOS, PFOA, PFNA and PFHxS) was calculated for comparison with the health-based HBM guidance value based on the Tolerable Weekly Intake (TWI) from the EFSA opinion (2020) (Table 3). Sum parameters were only calculated if, within a data collection, all the metabolites constituting the sum were measured and if at least one of the metabolites was quantified in at least 60% of the samples. To calculate the sum parameters, values below the LOD/LOQ of the single metabolites were replaced by half the limit (or by LOD + LOQ/2 if both are available). This method was used because in some cases not enough values were quantified for all the metabolites constituting the sum to estimate a truncated lognormal distribution to allow random imputation.

For biomarkers that were quantified for at least 60% in the pooled population, linear regression models were fitted to check the effect of geographical region and socio-economic status on the exposure levels. A p-value <0.05 was taken as significance level. To assess the geographical effect, the participating studies were allocated to four geographical regions i.e., North, East, South, West, according to the United Nations geoscheme (United Nations, 1999). Israel was allocated to the South. Educational attainment was used as a proxy to assess the effect of socio-economic status. For children and teenagers, the highest educational attainment of the household was used, for adults their own educational attainment was used. The exposure biomarkers were used as dependent variables in the models. Urinary biomarkers were standardized for creatinine, lipid soluble blood biomarkers were standardized for blood lipids (i.e., the HFRs). The biomarker data were transformed with the natural logarithm. Basic models were built including the variables of interest, additionally adjusted for some main factors that may influence the exposure levels independently from the variable of interest such as age of the participant (in years), sampling year (in years), sex (male/female), creatinine for urinary markers and blood lipids for lipid-soluble blood markers. For PAHs and cadmium smoking status (yes/no) was included as an additional covariate in the model for adults. To compare the results across biomarkers, a heatmap was generated using the pheatmap function, from package pheatmap in R statistical software. The estimated overall mean and the estimated mean for each stratum of geographical region/educational attainment were obtained from a linear regression model (using the package lm in R) with the z-score of the biomarker ((value - μ)/σ) as dependent variable. The overall mean was subtracted from the estimated mean for each stratum to obtain symmetry around 0. Hierarchical clustering with Euclidean distance metric and average linking was used to generate the hierarchical tree. Statistical analyses were performed in R version 2022.02.0 (R Foundation for Statistical Computing, Vienna, Austria).

Table 2
Overview biomarker levels HBM4EU Aligned Studies (expressed in μg/g crt for urinary biomarkers, μg/g lipid for lipid-soluble blood biomarkers, μg/L for other biomarkers in blood).

Biomarker	Age Group	Countries included	Unit	N	QF (%)	GM (95% CI)	P95 (95% CI)
Pesticides in urine							
TCPy	children	CY; IL; NL; BE	μg/g crt	495	99.8	2.43 (2.24–2.65)	10.8 (9.59–12.2)
	adults	IL; CH; DE; IS	μg/g crt	745	83.6	0.890 (0.821–0.965)	4.25 (3.74–4.73)
AMPA	children	FR; SI; CY; DE; BE	μg/g crt	971	59.4	nc	0.459 (0.431–0.536)[a]
	adults	FR; DE; CH; IS	μg/g crt	912	29.5	nc	0.317 (0.276–0.380)
Pesticides (pyrethroids) in urine							
3-PBA	children	FR; SI; CY; IL; NL; BE	μg/g crt	863	98.0	1.24 (1.15–1.33)	5.38 (4.78–6.47)
	adults	FR; IL; CH; DE; IS	μg/g crt	899	90.9	0.393 (0.366–0.422)	1.98 (1.72–2.41)
cis-DBCA	children	FR; CY; IL; NL; BE	μg/g crt	715	89.2	0.645 (0.589–0.706)	4.34 (3.60–5.20)
	adults	FR; IL; CH; DE; IS	μg/g crt	899	67.2	0.162 (0.147–0.179)	1.72 (1.32–2.16)
cis-DCCA	children	FR; CY; IL; NL; BE	μg/g crt	715	96.2	0.443 (0.414–0.474)	1.99 (1.68–2.34)
	adults	IL; CH; DE; IS	μg/g crt	755	44.5	nc	0.538 (0.441–0.629)
trans-DCCA	children	CY; IL; NL; BE	μg/g crt	493	99.4	0.844 (0.778–0.916)	4.01 (3.27–5.86)
	adults	IL; CH; DE; IS	μg/g crt	755	75.0	0.186 (0.170–0.205)	1.12 (0.86–1.43)
F-3-PBA	children	FR; CY; IL; NL; BE	μg/g crt	715	14.3	nc	0.121 (0.098–0.151)[a]
	adults	FR; IL; CH; DE; IS	μg/g crt	899	6.1	nc	0.109 (0.092–0.152)[a]
CIF3CA	children	CY; IL; NL; BE	μg/g crt	493	45.6	nc	0.679 (0.514–1.02)
	adults	IL; CH; DE; IS	μg/g crt	754	27.1	nc	0.448 (0.386–0.542)
Bisphenols in urine							
BPA total	adults	FR; PL; HR; PT; LU; DK; CZ; CH; FI; DE; IS	μg/g crt	2741	92.3	1.13 (1.08–1.18)	6.67 (6.17–7.57)
BPF total	adults	FR; PL; HR; PT; LU; DK; CZ; CH; DE; IS	μg/g crt	2440	61.7	0.094 (0.085–0.105)	5.00 (3.68–6.62)
BPS total	adults	FR; PL; HR; PT; LU; DK; CZ; CH; DE; IS	μg/g crt	2446	67.0	0.072 (0.065–0.079)	1.83 (1.56–2.20)
Phthalates in urine							
5cx-MEPP	children	FR; EL; IT; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2578	100	15.9 (15.4–16.4)	55.2 (51.3–59.5)
	teenagers	FR; EL; ES; SI; CZ; SE; PL; NO; SK; DE; BE	μg/g crt	2799	99.9	7.97 (7.73–8.20)	28.8 (27.0–30.2)
5OH-MEHP	children	FR; EL; IT; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2578	99.9	12.4 (12.0–12.8)	45.1 (42.2–47.7)
	teenagers	FR; EL; ES; SI; CZ; SE; PL; NO; SK; DE; BE	μg/g crt	2799	99.9	7.82 (7.57–8.07)	32.9 (29.8–37.0)
5oxo-MEHP	children	FR; EL; IT; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2576	99.5	8.21 (7.95–8.47)	29.6 (28.4–33.6)
	teenagers	FR; EL; ES; SI; CZ; SE; PL; NO; SK; DE; BE	μg/g crt	2798	99.9	4.58 (4.45–4.71)	16.6 (15.3–18.0)
cx-MiDP	children	FR; SI; PL; NL; DK; DE; BE	μg/g crt	1556	96.7	0.845 (0.811–0.882)	3.77 (3.23–4.35)
	teenagers	FR; ES; SI; SE; PL; DE; BE	μg/g crt	1881	96.2	0.566 (0.545–0.588)	2.39 (2.11–2.68)
cx-MiNP	children	FR; EL; SI; PL; HU; NL; DK; DE; BE	μg/g crt	1979	97.5	4.87 (4.62–5.12)	26.6 (23.2–31.2)
	teenagers	FR; EL; ES; SI; CZ; SE; PL; SK; DE; BE	μg/g crt	2618	99.8	4.06 (3.91–4.22)	23.2 (20.0–27.3)
MBzP	children	FR; EL; IT; SI; PL; NO; HU; NL; DE; BE	μg/g crt	2278	97.3	3.88 (3.70–4.07)	28.6 (25.2–32.2)
	teenagers	FR; EL; ES; SI; CZ; SE; PL; NO; SK; DE; BE	μg/g crt	2799	96.9	2.07 (1.98–2.17)	18.2 (16.2–21.0)
MEHP	children	FR; EL; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2279	90.3	1.33 (1.26–1.40)	6.99 (6.51–8.17)
	teenagers	FR; EL; ES; SI; CZ; SE; PL; NO; SK; DE; BE	μg/g crt	2799	93.3	1.33 (1.28–1.37)	6.07 (5.56–6.67)
MEP	children	FR; EL; IT; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2579	99.7	27.0 (25.8–28.3)	231 (200–261)
	teenagers	FR; EL; ES; SI; CZ; PL; NO; SK; DE; BE	μg/g crt	2499	100	32.5 (31.1–34.0)	271 (226–321)
MiBP	children	FR; EL; IT; SI; NO; HU; NL; DK; DE; BE	μg/g crt	2278	100	29.1 (28.1–30.0)	117 (104–130)
	teenagers	FR; EL; ES; SI; NO; DE; BE	μg/g crt	1631	99.9	19.5 (18.8–20.3)	76.9 (71.0–89.1)
MnBP	children	FR; EL; IT; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2578	99.8	23.4 (22.7–24.0)	82.5 (76.1–88.4)
	teenagers	FR; EL; ES; SI; CZ; PL; NO; SK; DE; BE	μg/g crt	2499	98.8	18.6 (17.9–19.4)	98.4 (86.7–108)
OH-MiDP	children	FR; IT; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2417	94.6	1.26 (1.21–1.30)	5.91 (5.48–6.72)
	teenagers	FR; ES; SI; SE; PL; NO; DE; BE	μg/g crt	2062	96.6	0.947 (0.910–0.985)	4.66 (4.08–5.24)
OH-MiNP	children	FR; EL; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2279	97.6	4.13 (3.95–4.32)	21.1 (19.2–24.4)
	teenagers	FR; EL; ES; SI; SE; PL; NO; DE; BE	μg/g crt	2212	99.8	3.57 (3.44–3.72)	19.8 (17.0–22.6))
Σ(5cx-MEPP + 5OH-MEHP)	children	FR; EL; IT; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2578		28.7 (27.9–29.6)	97.7 (91.8–108)
	teenagers	FR; EL; ES; SI; CZ; SE; PL; NO; SK; DE; BE	μg/g crt	2799		16.8 (16.3–17.2)	58.3 (54.2–64.9)
Σ(5oxo-MEHP+ 5OH-MEHP)	children	FR; EL; IT; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2576		20.8 (20.1–21.4)	74.6 (70.4–80.9)
	teenagers	FR; EL; ES; SI; CZ; SE; PL; NO; SK; DE; BE	μg/g crt	2798		12.7 (12.3–13.1)	50.3 (45.6–55.2)
Σ(MEHP + 5OH-MEHP + 5oxo-MEHP)	children	FR; EL; SI; PL; NO; HU; NL; DK; DE; BE	μg/g crt	2277		21.4 (20.7–22.1)	78.4 (74.7–83.9)
	teenagers	FR; EL; ES; SI; CZ; SE; PL; NO; SK; DE; BE	μg/g crt	2798		14.3 (13.9–14.7)	55.9 (51.7–61.2)
DINCH in urine							
cx-MINCH	children	FR; EL; IT; SI; PL; HU; NL; DK; SK; DE; BE	μg/g crt	2577	96.2	1.36 (1.30–1.42)	9.64 (8.45–11.4)

(*continued on next page*)

Table 2 (*continued*)

Biomarker	Age Group	Countries included	Unit	N	QF (%)	GM (95% CI)	P95 (95% CI)
	teenagers	FR; EL; ES; SI; SE; PL; SK; DE; BE	μg/g crt	2317	97.8	0.700 (0.670–0.731)	4.32 (3.74–5.07)
OH-MINCH	children	FR; EL; IT; SI; PL; NO; HU; NL; DK; SK; DE; BE	μg/g crt	2877	98.6	2.51 (2.41–2.62)	17.3 (14.4–20.9)
	teenagers	FR; EL; ES; SI; SE; PL; NO; SK; DE; BE	μg/g crt	2499	98.8	1.20 (1.14–1.25)	8.17 (7.22–9.55)
Σ(OH-MINCH + cx-MINCH)	children	FR; EL; IT; SI; PL; HU; NL; DK; SK; DE; BE	μg/g crt	2577		3.89 (3.73–4.05)	26.5 (22.7–32.0)
	teenagers	FR; EL; ES; SI; SE; PL; SK; DE; BE	μg/g crt	2317		1.88 (1.81–1.96)	11.7 (10.0–13.7)
Organophosphorus Flame Retardants (OPFRs) in urine							
BDCIPP	children	FR; SI; NO; DK; SK; DE; BE	μg/g crt	1768	63.9	0.371 (0.349–0.395)	2.61 (2.34–2.97)
DPHP	children	FR; SI; NO; DK; SK; DE; BE	μg/g crt	1768	99.2	1.91 (1.83–1.99)	7.07 (6.33–7.97)
BCIPP	children	FR; SI; DK; SK; DE; BE	μg/g crt	1468	27.3	nc	1.93 (1.56–2.42)
Halogenated Flame Retardants (HFRs) in blood							
BDE-47	children	FR; NO; EL; SI	μg/g lipid	710	62.4	nc[a]	0.002 (0.002–0.003)
BDE-153	children	FR; NO; EL; SI	μg/g lipid	710	40.1	nc	0.001 (0.001–0.002)
Anti-DP	children	FR; NO; EL; SI	μg/g lipid	710	57.2	nc	0.017 (0.013–0.019)
Syn-DP	children	FR; NO; EL; SI	μg/g lipid	710	48.0	nc	0.007 (0.007–0.010)[a]
UV-filters (benzophenones) in urine							
BP-1	teenagers	FR; ES; SE; PL; DE	μg/g crt	1208	96.4	0.898 (0.807–0.999)	19.6 (14.9–24.0)
	adults	FR; LU; DK; DE	μg/g crt	965	82.7	0.330 (0.282–0.385)	12.6 (8.50–18.1)
BP-3	teenagers	FR; ES; SE; PL; NO; DE	μg/g crt	1389	95.6	1.98 (1.79–2.20)	48.9 (39.6–61.3)
	adults	FR; LU; DK; DE	μg/g crt	965	86.4	1.10 (0.946–1.28)	33.0 (25.6–46.2)
Per-/poly-fluorinated compounds (PFASs) in blood							
PFDA	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657	50.2	nc	0.380 (0.350–0.416)
PFHpA	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657	28.2	nc	0.142 (0.132–0.150)[a]
PFHpS	teenagers	FR; ES; EL; SI; SK; NO; BE	μg/L	1357	35.0	nc	0.175 (0.166–0.200)[a]
PFHxA	teenagers	FR; ES; DE; EL; SI; SK	μg/L	1180	30.3	nc	0.249 (0.249–0.249)[a]
PFHxS	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657	80.0	0.341 (0.326–0.356)	1.20 (1.10–1.31)
PFNA	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657	77.7	0.270 (0.260–0.281)	0.786 (0.750–0.867)
PFOA	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657	97.5	0.942 (0.917–0.968)	2.22 (2.10–2.42)
PFOS	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657	100	2.01 (1.95–2.08)	6.06 (5.62–6.77)
PFPeA	teenagers	FR; ES; DE; EL; SI; SK; BE	μg/L	1480	16.0	nc	0.193 (0.193–0.193)[a]
PFUnDA	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657	35.6	nc	0.211 (0.200–0.231)[a]
Σ(PFHxS + PFOS)	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657		2.44 (2.37–2.52)	7.21 (6.71–7.84)
Σ(PFOA + PFNA + PFHxS + PFOS)	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657		3.80 (3.69–3.91)	9.80 (9.09–10.6)
Σ(PFOA + PFNA)	teenagers	FR; ES; DE; EL; SI; SK; NO; BE	μg/L	1657		1.25 (1.22–1.28)	2.96 (2.80–3.14)
Arsenic in urine							
As(III)	teenagers	ES; SI; SE; DE; BE	μg/g crt	1144	91.1	0.205 (0.195–0.216)	0.711 (0.665–0.789)
As(V)	teenagers	ES; SE; DE; BE	μg/g crt	1048	68.3	0.124 (0.116–0.132)	0.646 (0.560–0.737)
AsB	teenagers	ES; SE; DE; BE	μg/g crt	1048	91.9	2.39 (2.050–2.785)	77.3 (63.2–93.4)
DMA	teenagers	ES; SI; SE; DE; BE	μg/g crt	1144	100	2.47 (2.37–2.58)	9.51 (8.51–10.8)
MMA	teenagers	ES; SI; SE; BE	μg/g crt	844	96.2	0.685 (0.642–0.730)	2.18 (2.04–2.40)
Cadmium in urine							
Cd	adults	DE; PL; HR; PT; LU; DK; CZ; IS	μg/g crt	2107	96.0	0.146 (0.141–0.151)	0.534 (0.491–0.580)
Polycyclic Aromatic Hydrocarbons (PAHs) in urine							
1-NAPH	adults	FR; PL; PT; LU; DK; CH; DE	μg/g crt	1798	74.1	0.608 (0.559–0.661)	8.90 (7.93–10.8)
2-NAPH	adults	FR; PL; HR; PT; LU; DK; CZ; CH; DE; IS	μg/g crt	2601	98.9	3.99 (3.83–4.16)	21.9 (20.6–24.6)
1-PHEN	adults	FR; HR; PT; LU; CZ; DE; IS	μg/g crt	1841	93.2	0.093 (0.089–0.098)	0.511 (0.464–0.570)
2-PHEN	adults	FR; PT; DE; IS	μg/g crt	1031	96.9	0.068 (0.064–0.071)	0.317 (0.283–0.397)
3-PHEN	adults	FR; PT; LU; DE	μg/g crt	1038	97.5		0.403 (0.360–0.486)

(*continued on next page*)

Table 2 (*continued*)

Biomarker	Age Group	Countries included	Unit	N	QF (%)	GM (95% CI)	P95 (95% CI)
						0.089 (0.084–0.094)	
4-PHEN	adults	FR; HR; PT; LU; DK; CZ; DE; IS	μg/g crt	2074	70.8	0.025 (0.024–0.026)	0.194 (0.178–0.213)
1-PYR	adults	FR; PL; HR; PT; LU; CZ; CH; DE; IS	μg/g crt	2369	95.9	0.088 (0.084–0.092)	0.487 (0.443–0.561)
2-FLUO	adults	FR; HR; PT; LU; DK; CZ; IS	μg/g crt	1745	95.4	0.206 (0.196–0.216)	1.44 (1.32–1.60)
3-FLUO	adults	FR; HR; LU; CZ; IS	μg/g crt	1203	76.2	0.042 (0.039–0.046)	0.513 (0.413–0.629)
Acrylamide in urine							
AAMA	children	FR; IT; SI; NO; DE	μg/g crt	1198	99.8	69.1 (66.6–71.6)	200 (187–215)
	adults	FR; PT; LU; DE; IS	μg/g crt	1180	98.8	57.8 (55.0–60.9)	272 (239–310)
GAMA	children	FR; IT; SI; NO; DE	μg/g crt	1198	99.8	14.6 (14.0–15.1)	48.1 (43.5–51.9)
	adults	FR; PT; LU; DE; IS	μg/g crt	1164	98.5	11.2 (10.7–11.7)	40.4 (38.9–43.3)
Mycotoxins in urine							
tDON	adults	FR; PL; PT; LU; DE	μg/g crt	1099	96.5	5.09 (4.65–5.58)	31.2 (28.5–34.6)

Abbreviations: QF = quantification frequency; nc = not calculated (proportion of results above limit of detection or limit of quantification was too low (<60%) to provide a valid result).

[a] Data should be interpreted with caution as some of the LOQs in the separate studies exceed the pooled P95.

2.2.2. Selection of biomonitoring data for international comparison and time patterns

To interpret our results in a global context, the internal exposure levels measured in the HBM4EU Aligned Studies were compared (qualitative assessment) to exposure levels reported by national HBM programs outside Europe. Internationally representative HBM programs or HBM studies with similar sampling years (2014–2021) and age groups i.e., children, teenagers or adults, were identified in the US (National Health and Nutrition Examination Survey; NHANES) (CDC, 2017), Canada (Canadian Health Measures Survey; CHMS) (Health Canada, 2021), Korea (Korean National Environmental Health Survey; KoNEHS) (Choi et al., 2017; Jung et al., 2022; Park et al., 2016), China (China National Human Biomonitoring survey; CNHBM) (Cao et al., 2021) and New-Zealand (Li et al., 2022). All these HBM programs or studies provided HBM data (published or upon request) except for CNHBM, for which data were not yet obtained when our manuscript was drafted. Data were available for the following substance groups: As, benzophenones, bisphenols, Cd, PAHs, PFASs, phthalates and DINCH, pesticides and FRs. Because the HBM4EU Aligned Studies collected a mix of first morning, random spot and 24h urine samples, international comparison of urinary biomarker levels was done based on the creatine standardized data to account for urinary dilution of the collected samples. The GM and its 95th confidence interval (95% CI) were used for the comparison.

Furthermore, the HBM4EU Aligned Studies data (GM, 95% CI) were compared (qualitative assessment) with published data from the earlier European COPHES/DEMOCOPHES project (Den Hond et al., 2015) to assess changes in internal exposure over time. The DEMOCPHES project measured biomarker levels in children (5–11 years) and their mothers, therefore the HBM4EU Aligned Studies results in adults were stratified for sex, to allow comparison in similar population groups. Comparison was possible for urinary Cd exposure in women, and for the following urinary phthalates: DEHP (sum of MEHP + 5OH-MEHP + 5oxo-MEHP), DEP (MEP), BBzP (MBzP), DnBP (MnBP), DiBP (MiBP) in children.

2.2.3. Evaluation of population exposure levels in a health risk context

To evaluate HBM data in relation to risks on adverse health effects, the proportion of study participants exceeding available health-based HBM guidance values was calculated. Moreover, GM and P95, representing average and worst-case exposure scenarios at population level, were compared with health-based HBM guidance values for selected phthalates (BBzP (MBzP), DnBP (MnBP), DEP (MEP), DEHP (Σ (5-oxo-MEHP + 5-OH-MEHP); Σ (5-cx-MEPP + 5-OH-MEHP)), DiBP (MiBP)), DINCH (Σ (OH-MINCH + cx-MINCH)), bisphenols (BPA and BPS), Cd, PFASs (PFOS, PFOA and Σ (PFOA + PFNA + PFHxS + PFOS)), acrylamide (AAMA), arsenic (toxicologically relevant arsenic i.e., Σ (As III + As V + MMA + DMA)), cyfluthrin (4-F-3-PBA), deltamethrin (cis-DBCA), pyrethroids (3-PBA, a non-specific biomarker for exposure to most pyrethroids), chlorpyrifos (TCPy), the mycotoxin deoxynivalenol (DON) and its glucuronides (total DON, tDON), and benzophenone-3 (BP-3). Hazard quotients (HQs), or risk characterization ratios, were calculated as the ratio of population level concentrations of a specific chemical at the GM or P95 to the corresponding health-based HBM guidance value. HQ = [level of exposure biomarker]/health-based HBM guidance value. A HQ below one suggests that levels of exposure to the specific chemical in question may not be a concern at the population level. The HQ concept using HBM data was introduced by Aylward et al. (2013) using the NHANES data, followed by St-Amand et al. (2014) and Faure et al. (2020) evaluating the CHMS biomonitoring datasets using a similar approach. For some chemicals, evaluation was conducted using age-specific data, when health-based HBM guidance values were derived for specific age groups (acrylamide, cyfluthrin, deltamethrin, phthalates) or when bioaccumulation with age is expected due to long elimination half-lives of the biomarkers like Cd. Cd evaluations were conducted for the whole adult study population and for smokers and non-smokers separately as evidence shows impact of smoking on urinary concentrations (Berglund et al., 2015). For 4-F-3-PBA only the HQ at the P95 was calculated as the GM was not calculated (QF<60%). The proportion of exceedance is given both for the main output (only including data with quality label A and B; see Table S1) and for the sensitivity analysis (including data with quality label A, B and C; see Table S1). The HQ are calculated based on the main output only.

2.2.4. Selection of health-based HBM guidance values (GVs)

In our analysis, HBM-GVs for the general population (HBM-GV_{GenPop}), derived within the HBM4EU project, were preferred to other health-based HBM guidance values when available, as the HBM-GVs were more recently developed and as such based on current knowledge. The HBM-GV_{GenPop} represents the concentration of a substance or its specific metabolite(s) in human biological matrices (e.g. urine, blood, hair) at and below which, according to current knowledge, there is no risk of health impairment anticipated, and consequently no need for action (Apel et al., 2020). Each HBM-GV underwent a consultation process with national experts to ensure a high degree of both scientific integrity and acceptance. The general methods for deriving HBM-GV, have been described elsewhere (Apel et al., 2020). In addition, also

Table 3
Environmental chemicals, their respective biomarkers and corresponding exposure guidance values, health-based HBM guidance values applied in HBM4EU Aligned Studies.

Chemical Group	Chemical (Biomarker if different)	Exposure marker (Cas No.)	Type health-based HBM guidance value (reference)	value	Unit	Age group	Main output		Sensitivity analysis	
							n	% participants exceeding GV	n	% participants exceeding GV
Pesticides	Chlorpyrifos (TCPy)	3,5,6-trichloro-2-pyridinol (CAS No.: 6515-38-4)	Provisional HBM-GV (Tarazona et al., 2022)	10	µg/L	children	495	7.3%	762	4.7%
				20	µg/L	adults	746	0.3%	889	0.2%
	Cyfluthrin (4-F-3-PBA)	4-fluoro-3-phenoxybenzoic acid (CAS No.: 77279-89-1)	HBM-GV (Apel et al., 2022b)	80	µg/L	children	715	0%	863	0%
				130	µg/L	adults	900	0%	900	0%
	Deltamethrin (cis-DBCA)	cis-3-(2,2-dibromovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (CAS No.: 63597-73-9)	HBM-GV (Apel et al., 2022b)	90	µg/L	children	715	0%	715	0%
				130	µg/L	adults	900	0%	900	0%
	Pyrethroid pesticide (3-PBA)	3-phenoxybenzoic acid (CAS No.: 3739-38-6)	Tier 1 BE-value (Aylward et al., 2018)	1.7	µg/L	children	863	36.0%	863	36.0%
				1.7	µg/L	adults	900	7.6%	900	7.6%
			Tier 2 BE-value (Aylward et al., 2018)	87	µg/L	children	863	0%	863	0%
				87	µg/L	adults	900	0%	900	0%
Bisphenols	BPA	Bisphenol A (CAS No.: 80-05-7)	HBM-GV (Ougier et al., 2021)	230	µg/L	adults	2756	0%	2756	0%
	BPS	Bisphenol S (CAS No.: 80-09-1)	HBM-GV (Meslin et al., 2022)	1.0	µg/L	adults	2456	11.2%	2456	11.2%
Phthalates	DEHP (Σ (5-oxo + 5-OH-MEHP))		HBM-GV (Lange et al., 2021)	340	µg/L	children	2577	0.3%	2873	0.3%
				500	µg/L	teenagers	2798	0.3%	2798	0.3%
	DEHP Σ (5-cx-MEPP + 5-OH-MEHP)			380	µg/L	children	2579	0.5%	2875	0.5%
				570	µg/L	teenagers	2799	0.3%	2799	0.3%
	BBzP (MBzP)	monobenzyl phthalate(CAS No.: 2528-16- 7)		2000	µg/L	children	2279	0.04%	2575	0.04%
				3000	µg/L	teenagers	2799	0%	2799	0%
	DnBP (MnBP)	monobutyl phthalate(CAS No.: 131-70-4);		120	µg/L	children	2579	2%	2875	4.6%
				190	µg/L	teenagers	2499	4.0%	2499	4.0%
	DiBP (MiBP)	monoisobutyl phthalate (CAS No.: 30833-53-5)		160	µg/L	children	2279	3.1%	2575	4.2%
				230	µg/L	teenagers	1631	1.7%	1631	1.7%
	DEP (MEP)	mono-ethyl phthalate(CAS No.: 2306-33-4)	BE-value (Aylward et al., 2009)	18000	µg/L	children	2580	0%	2876	0%
				18000	µg/L	teenagers	2499	0%	2499	0%
	DiNP (cx-MiNP)	7-Carboxy-(mono-methyl-heptyl) phthalate(CAS No.: 936022-02-5)	BE-value (Hays et al., 2011)	490	µg/L	children	1980	0%	1980	0%
				490	µg/L	teenagers	2618	0.2%	2618	0.2%
	DINCH (Σ(OH-MINCH + cx-MINCH))	Di-isononyl cyclohexane-1,2-dicarboxylate (CAS No.: 166412-78-8)	HBM-GV (Lange et al., 2021)	3000	µg/L	children	2579	0%	2579	0%
				4500	µg/L	teenagers	2317	0%	2317	0%
UV-filters	BP-3	Benzophenone 3(CAS No.: 131-57-7)	Provisional HBM-GV (Rousselle et al., 2022)	340	µg/g crt	teenagers adults	1389 965	0.9% 0.6%	1389 965	0.9% 0.6%
Perfluoroalkyl substances	PFOA	Perfluorooctanoic acid(CAS No.: 335-67-1)	HBM-I (Apel et al., 2017)	2	µg/L	teenagers	1657	7.2%	1957	7.7%
	PFOS	Perfluorooctane sulfonate (CAS No.: 1763-23-)	HBM-I (Apel et al., 2017)	5	µg/L	teenagers	1657	8.0%	1957	9.4%
	Σ(PFOA + PFNA + PFHxS + PFOS)		EFSA opinion (EFSA et al., 2020)	6.9	µg/L	teenagers	1657	12.7%	1957	14.3%
				6.4		teenagers	748[d]	40.2%	844	37.4%

(*continued on next page*)

Table 3 (*continued*)

Chemical Group	Chemical (Biomarker if different)	Exposure marker (Cas No.)	Type health-based HBM guidance value (reference)	value	Unit	Age group	Main output		Sensitivity analysis	
							n	% participants exceeding GV	n	% participants exceeding GV
Metals and trace elements	Arsenic (Σ(As III + As V + MMA + DMA))	Toxicologically relevant arsenic	BE-value (Hays et al., 2010)		µg/L					
	U-Cadmium	Cadmium(CAS No.: 7440-43-9)	HBM-GV (Lamkarkach et al., 2021)	0.2–0.5[a]	µg/g crt	adults	2107	11.5%	2500	16.4%
						Adults - smokers	332	11.6%	446	22.0%
						Adults non-smokers	1756	11.5%	2034	15.3%
Acrylamide	AAMA	N-Acetyl-S-(2-carbamoyl-ethyl)cysteine(CAS No.: 81690-92-8)	Provisional HBM-GV (Deliverable 5.11)	321.7[b]	µg/L	children	1199	1.3%	1199	1.3%
				291.4[c]	µg/L	adults	1181	7.0%	1181	7.0%
Mycotoxins	Total DON	Deoxynivalenol(CAS No.: 51481-10-8)	HBM-GV (Apel et al., 2022a)	23	µg/L	adults	1099	13.7%	1099	13.7%

Mono (5-carboxy-2-ethylpentyl) phthalate (CAS No.: 40809-41-4), mono(2-ethyl-5-hydroxyhexyl) phthalate (CAS No.: 40321-99-1), mono(2-ethyl-5-oxohexyl) phthalate (CAS No.: 40321-98-0). PFNA = Perfluorononanoic acid (CAS No.: 375-95-1), PFHXS = Perfluorohexane sulfonic acid (CAS No.: 355-46-4). As(III) = arsenite, As(V) = arsenate, MMA = monomethylarsonic acid, DMA = dimethylarsinic acid. a: age dependent HBM-GV 0.2 µg/g crt for 11–20 years, 0.3 µg/g crt for 21–30 years and 0.5 µg/g crt for 31–40 years, b: calculated for a child of 30 kg, c: calculated for an adult 70 kg, d: exceedance of TRA main output based data from only 3 countries (ES, SE, BE). HBM-GV DON background information available at (https://doi.org/10.5281/zenodo.6622478). Deliverable 5.11: link to be added. Main output is based on the data with the following quality label "Biomarker data quality assured by HBM4EU QA/QC program". Sensitivity analysis is based on data with the following quality label "Biomarker data quality assured by HBM4EU QA/QC program" and "Biomarker data generated before HBM4EU QA/QC program but deemed comparable by HBM4EU Quality assurance unit".

provisional HBM-GVs were derived within HBM4EU for risk assessment purposes according to the approach described by Apel et al., (2020) and using existing toxicological evaluations as starting point (Santonen et al., 2022), but a consultation within HBM4EU was not performed. Provisional HBM-GVs were available for the acrylamide biomarker AAMA, benzophenone-3 (BP-3) (Rousselle et al., 2022), the mycotoxin DON (Apel et al., 2022b) and TCPy (David et al., 2021).

Other health-based HBM guidance values used were Biomonitoring equivalents (BE), Human biomonitoring values (HBM-I) or derived from the EFSA opinion for the sum of four PFASs (EFSA et al., 2020). Biomonitoring equivalents are derived by the team from the Summit Toxicology consulting firm as well as Health Canada (2016) (Faure et al., 2020; St-Amand et al., 2014). The general method for deriving BEs, has been described by (Hays et al., 2008). This method was adopted by the German HBM Commission to derive HBM I values. The general method for deriving HBM-I values, has been described by (Apel et al., 2017).

For 3-PBA, a non-specific marker of several pyrethroid insecticides (cyhalothrin, cypermethrin, deltamethrin, fenpropathrin, permethrin, tralomethrin) with different toxic potency, two BE-values were derived by Aylward et al. for tiered interpretation of HBM exposure levels in risk assessment context. A highly conservative tier one screening value of 1.7 µg/L and a second-tier screening value of 87 µg/L assuming average toxic potency of the parent compounds, to be used when HBM data exceed the Tier one value (Aylward et al., 2018). An overview of all the health-based HBM guidance values used is available in Table 3. All health-based HBM guidance values that were considered refer to threshold endpoints only. This means that genotoxic/carcinogenic effects of e.g., acrylamide, chlorpyriphos and arsenic were not considered. The health-based HBM guidance values can also be consulted in the health-based guidance value (HB2GV) dashboard developed by the international HBM (i-HBM) working group (Nakayama et al., 2022).

3. Results and discussion

3.1. Description of internal exposure levels

Table 2 presents the geometric mean (GM) and the 95th percentile (P95) with their 95% confidence interval (CI) for the exposure biomarkers standardized for creatinine/lipids if applicable, in each of the age groups of the HBM4EU Aligned Studies population; while the volume-based biomarker data is presented in Supplemental Material Table S2. Given that the LOQ within a separate study sometimes exceeds the calculated GM or P95 for the overall HBM4EU study sample, these data (AMPA, 4-F-3-PBA, Syn-DP, BDE-47, PFHpA, PFHpS, PFHxA, PFPeA, PFUnDA) should be interpreted with caution, as flagged in Table 2 and Supplemental Material Table S2.

In the group of **pesticides**, trichloro-2-pyridinol (TCPy) was measured in urine samples as a biomarker of chlorpyrifos and chlorpyrifos-methyl. Quality approved data were obtained from four countries in children (N = 495) and four countries in adults (N = 745), and could be quantified in 99.8% and 84% of the samples of children and adults respectively. Monitoring the exposure levels in the coming years, will inform on the effect of the recent ban on chlorpyrifos and chlorpyrifos-methyl in the EU issued 2020 (EU, 2020). The pyrethroid biomarkers 3-PBA, cis-DBCA and trans-DCCA were quantified with high frequencies both in children and adults (67–99%) (Table 2). Pyrethroids are synthetic short-lived pesticides that are increasingly used as insecticides in public and private places indoors and outdoors and replace some of the banned halogenated pesticides (Saillenfait et al., 2015). The major source for human exposure is residues in food, but also dermal uptake and inhalation of dust are potential exposure routes. GM levels of the pesticide biomarkers were higher in children than in adults. This confirms earlier observations of 3-PBA levels measured in Poland (Wielgomas and Piskunowicz, 2013).

For **bisphenols**, BPA was measured in adults in 11 countries (N = 2,741); only Finland did not measure BPS and BPF (N = 2,446). The GM exposure levels of these substitutes are a factor 10 lower than those observed for BPA (Table 2). The P95 of BPA and PBF are in a similar range, indicating that some participants were highly exposed to BPF as well. Bisphenols are used to make polycarbonate plastics and epoxy resins and are present in food and beverage can liners, reusable beverage bottles and plastic tableware, food, thermal paper, DVDs and CDs, medical devices, toys, automotive parts and some dental sealants (Geens et al., 2012). The major human exposure route is diet as bisphenols can migrate into food from plastic food containers.

Biomarkers of eight different **phthalates and of the substitute DINCH** were measured and well detected in most of the urine samples of

2,877 children and 2,799 teenagers (Table 2). Phthalates are manufactured plasticizers to soften polyvinylchloride plastics, low molecular weight phthalates are used in many applications such as solvents, adhesives, paints and personal care products. Exposure occurs through ingestion, inhalation and dermal uptake (Calafat et al., 2015). Levels in children were higher than those observed in teenagers, except for DEHP (MEHP) and DEP (MEP). The higher concentrations at younger ages may relate to age differences in metabolism, higher food intake per unit body weight, increased inhalation rate, different breathing zone, a larger body-surface-area-to-mass ratio in children, increased hand to mouth contact and specific playing behaviors associated with development (Benedetti et al., 2005). The higher level of DEP (MEP) in teenagers may be attributed to a higher use of cosmetic products, which include diethyl phthalates as one of the principal phthalates (Koch and Calafat, 2009).

All exposure biomarkers of halogenated **flame retardants** (FRs) are moderately quantified (BDE-47 and BDE-153 are quantified in 62% and 40% of the samples respectively; syn-DP and anti-DP for 48% and 57% respectively) in the pooled population of the children in Norway, France, Slovenia and Greece, but strongly depending on the reached LOQ within a study. For BDE-47 only in one data collection the LOQ was low enough to quantify 98% of the data. In the other three studies the QFs were low (15–45%), and the biomarker was not used in further statistical analyses. The halogenated FRs are substituted by organophosphorus FRs, for which metabolites were quantified. BDCIPP, DPHP, BCEP and BCIPP were measured in samples from children from seven countries (N = 1,768), only BDCIPP and DPHP had a QF >60% (64% and 99% respectively) (Table 2).

Benzophenone-1 and -3 (BP-1 and BP-3) are detected in respectively 96% of teenagers and 83–86% of adults, with higher GM in teenagers than in adults (Table 2). This age-related difference in exposure has been reported also in a South-Korean study (Kang et al., 2016) and may relate to a higher body-surface-area-to-mass ratio of children (Manova et al., 2013). Benzophenones are used in personal care products to protect against UV-skin damage and cancer. Dermal absorption is a major uptake route. UV-filters are also used in food packaging to protect against sunlight and prolong shelf life (Crompton, 2007).

All the **PFASs** legacy compounds PFOS, PFOA, PFNA and PFHxS were quantified in more than 60% of the samples from the entire study population of teenagers (N = 1,657 from eight countries). For PFOS, the detected levels could even be an underestimation as in two countries (BE-FLEHS IV, FR-ESTEBAN) only the linear form was measured while in the other studies the branched forms were also included. These branched forms may contribute 30–42% of the total PFOS load in serum (Schulz et al., 2020). The results of the other PFASs should be interpreted with caution as LOQs in some countries were higher than the calculated overall P95 (Table 2). Dietary uptake is a major human exposure route but ingestion of house dust, inhalation and dermal contact may contribute as well (Poothong et al., 2020). These chemicals are used in a wide number of industrial and consumer applications such as food packaging, non-stick cooking pans and utensils, homeware, cleaning products, cosmetics, clothes, coating additives, electronics, firefighting foams because of their resistance to water, oil, grease and stains.

Qualified **arsenic** measurements are obtained from five countries in teenagers. The arsenic species (MMA, DMA, As(III) and Arsenobetaine) are well quantified in 1,144 participants with QFs between 91% and 100%, As(V) is only quantified in 68% of the samples (Table 2). For the general population, consumption of rice, grain-based food, seafood and drinking water are the major exposure sources of inorganic arsenic. Exposure may also come from inhalation of air in polluted areas and from the use of well water with naturally occurring elevated As levels for drinking, cooking, showering, or watering home grown food (Monteiro De Oliveira et al., 2021).

Comparable data on **cadmium** was obtained from eight countries in adults (N = 2,107) with a QF of 96% (Table 2). The major intake route of Cd for the general population is food (cereals and cereal products, leafy green vegetables, organ meat, potatoes, cacao and shellfish) (Vromman et al., 2010), with elevated levels if grown in areas with Cd contaminated soil (EFSA, 2012; Piekut et al., 2017). Cd can be inhaled from cigarette smoke and in polluted areas (ATSDR, 2012; Jarup, 2003).

Biomarkers of **PAHs** were measured in 10 countries (N = 2,601) (Table 2). We have measured biomarkers of the low molecular weight PAHs (naphthalene, fluorene, phenanthrene) and pyrene as a marker of the high molecular weight PAHs. The naphthalene biomarkers were the most abundant biomarkers detected for the PAHs. PAHs are widespread environmental pollutants generated by incomplete combustion of organic materials, such as coal, oil, wood, and gas. They occur as complex mixtures with varying composition. Food is a major uptake route for humans. PAHs occur in food due to food preparation or processing techniques or when crops are grown in contaminated soil. They can also be inhaled from traffic exhaust, industrial emissions, or in the indoor environment from tobacco smoke, from cooking and heating (Lawal, 2017).

AAMA and GAMA as urinary biomarkers for **acrylamide** were quantified in almost all 1,198 children and 1,180 adults gathered from five countries, with AAMA being the most abundant in both age groups. Levels of acrylamide are higher in children than in adults (Table 2). This confirms earlier reports (Spivey, 2010) and identifies children as a high exposure group with specific needs for further protection and advice for healthy diets.

The **mycotoxin** deoxynivalenol (DON) was measured as total DON in urine samples of adults from five countries obtained through HBM4EU QA/QC approved laboratories (N = 1,099), with a total QF of 97% (Table 2). Mycotoxins are fungal metabolites that contaminate up to 25% of food crops, mainly cereals (Eskola et al., 2020).

3.2. *Influence of geographical region and educational attainment on internal exposure*

The heatmaps were used to visualize the geographical (Fig. 4) and social gradient (Fig. 5) observed in the internal exposure levels per biomarker. Colored intensities indicate fold increases (shades of red) and decreases (shades of blue) in the estimated geometric mean biomarker concentrations per geographical region or educational attainment relative to the overall estimated geometric mean, adjusted for age, sampling years, sex, creatinine for urinary markers, smoking status (for PAHs and Cd). Biomarkers with a similar pattern in gradient of exposure across geographical region or educational attainment are clustered.

As shown in Fig. 4, the color gradients indicate that all biomarkers across the different age groups show significant geographical differences in exposure.

Not all geographical regions were represented for the **pesticide** biomarkers. Higher urinary concentrations of cis-DCCA and trans-DCCA, which are metabolites of the pyrethroids cypermethrin, cyfluthrin and permethrin, are observed in children and adults of the South, respectively, while the concentrations of the deltamethrin metabolite cis-DBCA and the common metabolite 3-PBA are higher in urine samples from the West. The levels of the chlorpyrifos metabolite, TCPγ, were higher in Southern countries.

For **bisphenols** higher urinary concentrations of BPA are observed in adults from East and South. The geographic pattern of the other bisphenols is different and may relate to differences in use of consumer goods. The bisphenols are also not clustered together by the heatmap.

Significant differences in exposure biomarkers are observed among the different regions but these differences are not the same for all **phthalates**. The phthalate biomarkers OH-MiDP, MEHP and MEP are high in the South (children and teenagers) as well as DINCH markers in teenagers, while DINCH markers in children are higher in the North. This may reflect differences in use of products and in composition of manufactured products in the different countries. The **OPFR** BDCIPP is in the same cluster as OH-MiNP, with highest levels in the South in

children, while DPHP is in the same cluster with MiBP with higher levels in the East.

Higher urinary concentrations of **benzophenones** (BP-1 and BP-3) are observed in samples from Southern and Eastern Europe where more protection to UV-light may be needed.

The four **PFAS** compounds (PFOS, PFOA, PFNA, PFHxS) measured in blood plasma/serum samples of teenagers, form one cluster with significantly higher biomarker concentrations in blood plasma/serum samples of teenagers from the North and Western sampling sites in Europe without an obvious explanation.

Arsenic levels were significantly higher in teenagers from the North and South versus the West (no data for the East). This geographic difference was observed for all As species measured.

Significantly higher estimated GM **cadmium** levels were observed in the West and East of Europe than in the North and South. This could be related to industrial emissions that resulted in elevated levels of Cd in soil or the use of Cd containing phosphate fertilizers.

PAHs metabolites in adults show biomarker specific gradients, while 1-hydroxypyrene and 4-phenanthrene form one cluster with higher levels in the East and West, the naphthalene and fluorene markers have the lowest levels in the West. Geographic differentiation in exposure may relate to industrial pollution, traffic density and urbanization.

The concentrations of urinary **acrylamide** biomarkers are highest in the South. The reasons for the observed geographic differences are unclear. They may relate to specific dietary habits. Acrylamide is formed in starchy food cooked at high temperature and low moisture including baking, frying, grilling, toasting or roasting as well as in processed foods (Mottram et al., 2002). Also non dietary factors such as smoking habits may explain the differences as acrylamide is present in tobacco smoke (Kenwood et al., 2022). In adult population of the HBM4EU Aligned Studies, the proportion of smokers was the highest for the South.

For **mycotoxins** (total DON) in adults, higher levels were observed in the East and South. Climate change favors the spread of fungi and consequently the production of mycotoxins (Vandicke et al., 2019).

Educational attainment of the adults or of the household where children and teenagers were raised, influenced the biomarker concentrations for some biomarkers (adjusted for age, sampling years, sex, creatinine for urinary markers, smoking status (for PAHs and cadmium)) as visualized by Fig. 5. We use educational attainment as a proxy marker for socio-economic status. It should be noted, however, that low educational attainment was underrepresented (4% in children, 6% in teenagers/adults) (Table 1) and for some of the participating studies even no participants were recruited from this group (NEB II, POLAES, CROME, SPECIMEn-NL, CELSPAC and ESB) (Gilles et al., 2022).

Concentrations of metabolites of all **phthalates**, except for the metabolites of the higher molecular weight DIDP, are higher in teenagers of lower educated households. Due to restrictions, these low molecular weight phthalates are no longer used in newly manufactured products in Europe but they are substituted. Urinary concentrations of the **DINCH** metabolites, which is a phthalate substitute, are more equally distributed across the social gradient, the same holds for **OPFRs** that are not restricted and more equally distributed on the European market. Higher levels of metabolites of **pyrethroid pesticides** are observed in adults with lower educational attainment. Higher **benzophenones**, **PFAS** and **arsenic** levels were observed in teenagers from households with a high educational attainment, similar associations between these biomarkers and the poverty income ratio were observed in NHANES and the authors suggested fish intake as a key mediator for As and PFAS (Tyrrell et al., 2013). This pattern was not observed for benzophenones in adults, for which highest levels were observed in participants with medium educational attainment. In the DEMOCOPHES study an inverse association between **cadmium** and educational attainment was observed which could not be confirmed in our study. This may be explained by adjustment for smoking status of the participants; however, the observed association did not change when not adjusting for smoking status. Lower educational attainment was associated with higher concentrations of **PAH** metabolites in adults. This has been reported before as well and may relate to (environmental tobacco) smoking and living in more polluted areas (Wilhelm et al., 2007). Higher educated adults are more protected from enhanced exposure to **mycotoxins**, **acrylamide**, and **bisphenols** which may relate to more awareness concerning healthy diet and lifestyle choices.

Sensitivity analysis additionally including the biomarker data with label C (Table S1) did not affect the interpretation of the results (data not shown).

3.3. International comparison exposure levels

A qualitative comparison is performed between results from the HBM4EU Aligned Studies and other international HBM data. When comparing our results on **pesticide** levels in children with those reported by US and Canada higher GM levels can be observed for cis-DBCA, cis-DCCA, trans-DCCA. GM levels of the pyrethroid metabolite 3-PBA in the children of the HBM4EU Aligned Studies are similar to levels reported for children from New-Zealand, Korea and the US; Canada reported lower levels. GM 3-PBA levels in European adults (0.39 μg/g crt) are lower than those reported for Korean adults (1.16 μg/g crt). GM levels of chlorpyrifos (TCPγ) in European children (2.44 μg/g crt) are 5-fold lower than those observed in New Zealand in a similar age group (13 μg/g crt) (Supplemental Material Table S3).

The GM levels of **BPA** (1.13 μg/g crt) are in the same range as those found in Canada (0.91, 0.75, 0.69 μg/g crt Cycle IV, V and VI resp.) and the US (1.1 μg/g crt) while highest GM levels are observed in Korea (1.38 μg/g crt). Conversely, GM BPS level observed in the HBM4EU adults study population (0.072 μg/g crt) are lower compared to the US (0.505 μg/g crt; 2015–2016), see Supplemental Material Table S4.

In general, **phthalate** and **DINCH** biomarkers measured in children and teenagers in the HBM4EU Aligned Studies are comparable to those reported by HBM programs in the US and Canada. Internal concentrations (GM) of DEHP metabolites and DnBP (MnBP) in Europe are in line with those reported in the US and Canada but are lower than those reported for Korea. In Europe levels of DiNP metabolites (OH-MiNP, cx-MiNP), DiDP (OH-MiDP), DiBP (MiBP) and DINCH (OH-MINCH) in children are higher compared to those reported by Canada, the US and Korea; for OH-MINCH levels in Europe are even 10-fold higher (2.51 μg/g crt) than those observed in Canada (0.20 μg/g crt (2016–2017), 0.27 μg/g crt (2018–2019)) (Supplemental Material Table S5). BBzP (MBzP) concentrations in HBM4EU children and teenagers are lower than those in US and Canada; lowest levels are reported for Korea see Supplemental Material Table S5. Current concentrations of DEP (MEP), BBzP (MBzP), DiBP (MiBP) and DnBP (MnBP) and DEHP metabolites (Σ (MEHP + 5OH-MEHP + 5oxo-MEHP)) in children are all lower than reported by the DEMOCOPHES project for children 5–11 year (2011–2012) (27.2 μg/g crt vs. 34.4 μg/g crt, 3.4 μg/g crt vs. 7.1 μg/g crt, 30.8 μg/g crt vs. 45.9 μg/g crt and 25.8 μg/g crt vs. 34.6 μg/g crt), indicating a decrease (Den Hond et al., 2015). This may reflect impact of the EU regulation since DnBP, DiBP, BBzP and DEHP are regulated under REACH (ECHA, 2018).

GM levels of the metabolites of the **OPFR** TDCIPP (BDCIPP) are lower than the levels reported in the US. See Supplemental Material Table S6.

Median **BP-3** levels are 10-fold lower in HBM4EU teenagers and adults compared to levels reported by NHANES for similar age groups and time period (2015–2016) (Supplemental Material Table S7), however we should be careful in comparing such short half-life components between studies as differences in the timing of the measurements are very important. The GM levels of **PFOS** (2.01 μg/L) and **PFOA** (0.94 μg/L) in the HBM4EU study participants (teenagers) are below the levels reported by NHANES (PFOS: 2.94/2.68 μg/L, PFOA: 1.25/1.18 μg/L) (CDC) and are similar or higher than levels reported by CHMS (PFOS: 1.9/1.6 μg/L PFOA: 1.1/0.96 μg/L) (Health Canada, 2021). GM levels of **PFNA** and **PFHxS** are below those found in Canada and US

(Supplemental Material Table S8).

GM levels of **TRA** (4.37 μg/g crt) from teenagers of the HBM4EU Aligned Studies are in agreement with levels observed in Canada (3.4/4.5 μg/g crt) and the US (4.0/3.8 μg/g crt) see Supplemental Material Table S9. GM **cadmium** levels (0.15 μg/g crt) are in agreement with GM levels reported for Canada (0.12/0.15 μg/g crt) and the US (0.19 μg/g crt), but highest GM levels are observed in Korea (0.43 μg/g crt) (see Supplemental Material Table S10). GM Cd levels in women from the HBM4EU Aligned Studies (2014–2021) and DEMOCOPHES mothers (2011–2012) are very similar. Although Cd is regulated under REACH in the EU and specific uses are restricted (https://www.hbm4eu.eu/hbm4eu-substances/cadmium-and-chromium/), there is no indication that Cd concentrations in the EU population has decreased over time.

Most **PAH** metabolites measured in adult samples of the HBM4EU Aligned Studies' population, are lower than those reported in the US, Canada and Korea (see Supplemental Material Table S11). International data on **acrylamide** (U-AAMA) exposure is scarce. In NHANES and CHMS, blood biomarkers i.e., hemoglobin adducts were mainly measured instead of the urinary biomarkers for the estimation of the exposure levels. Therefore, a comparison with our urinary AAMA data was not possible.

3.4. Comparison with health-based HBM guidance values

The proportion of the study participants that exceeds the selected health-based HBM guidance values is indicated in Table 3. Figs. 1–3 show the Hazard Quotient's (HQs) at the GM and P95 for exposures in children, teenagers and adults, respectively.

Concerning the **pesticides**, for TCPγ, a specific marker of chlorpyrifos, chlorpyrifos-methyl and triclopyr, the HQ at GM are <1 in both children and adults, but in children the HQ at the P95 exceeds 1. The proportion of exceedances was higher in children (7%) than in adults (<1%) (Tarazona et al., 2022a). It should be noted that the provisional HBM-GV for TCPγ relates to an intake limit that has been recently updated and reduced (EFSA, 2019). Chlorpyrifos was one of the most used organophosphate insecticides, but at EU level it is no longer approved since 2020 due to its suspected genotoxicity and developmental neurotoxicity (EFSA, 2019; EU, 2020). The sample collection period of the HBM4EU Aligned Studies preceded the ban, our results illustrate that this regulatory action was needed.

The HQ at the P95 of 3-PBA, a non-specific metabolite of several co-occurring pyrethroid insecticides, exceeds one in adults. In children the HQ at GM and P95 both exceed one (based on the tier one value of 1.7 μg/L which is conservative as it assumes that all the measured 3-PBA is derived from lambda-cyhalothrin which is the pyrethroid with the highest toxic potency) (Figs. 1 and 3). In children, 36% and in adults 8% of the study participants exceed the tier one value, however, all children and adults have internal exposure levels below 87 μg/L (tier two value which assumes average toxic potency of the pesticide mixture) (Table 3). It should be noted that the BE-value was based on a RfD from USEPA Aylward et al. (2018). Within HBM4EU a provisional HBM-GV close to the tier one BE-value has been derived based on more recent Tolerable Daily Intakes (TDIs) for various pyrethroids from EFSA. Additionally, probabilistic refinement indicated reduced risk (Tarazona et al., 2022b).

No significant health risk is expected in children or adults for cis-DBCA and 4-F-3-PBA, specific markers for deltamethrin and cyfluthrin as both GM and P95 of their respective specific biomarkers were well below health-based HBM guidance values (Figs. 1 and 3) and no individual exceedances are observed (Table 3). Exposure to pyrethroids is associated with neurotoxic and endocrine effects (Saillenfait et al., 2015). Maximum residue levels of pesticides in food and feed of plant and animal origin and in infant formulae are regulated in the EU. There are limits for pesticides in drinking water and import and export of some hazardous pyrethroids is forbidden. Some of the pyrethroids are prohibited as plant protection products but they can be used as biocides with possible indoor applications (https://www.hbm4eu.eu/hbm4eu-substances/pesticides/). The widely used herbicide glyphosate and its degradation product AMPA was quantified in respectively 40% and 59% of the children's urine samples with higher P95 in children than in adults. No health-based HBM guidance values are available for glyphosate, however authorization of glyphosate is controversial. EU (ECHA's RAC) classified glyphosate based on its potential to cause eye damage and aquatic toxicity (https://www.echa.europa.eu/-/glyphosate-no-change-proposed-to-hazard-classification), while IARC classifies glyphosate as probably carcinogenic (Group 2A) (IARC, 2022) and it is a suspected endocrine disruptor (Kalofiri et al., 2021).

For **Bisphenols**, most toxicological information is available on BPA which is a reproductive and developmental toxicant, a suspect obesogen, carcinogen and immunotoxicant (Beausoleil et al., 2018; EFSA, 2015). The health-based HBM-GV of BPA that corresponds to the current t-TDI of 4 μg/kg bw/day is not exceeded in the adult study population and the HQ at the GM and P95 are well below one (0.01, 0.04 respectively) (Fig. 3). Based on this data, no significant health risk of BPA is expected (Meslin et al., 2022). However, EFSA has recently published a draft opinion for the revision of the t-TDI of BPA which suggests lowering the TDI with a factor 10E-5, i.e., from 4 μg/kg bw/day to 0.04 ng BPA/kg bw/day. Based on this revised TDI, a revised provisional HBM-GV of 2.3 ng/L in urine can be derived. As a result, almost all adults exceed the revised provisional HBM-GV (data not shown). Furthermore, the resulting provisional HBM-GV is well below the current LOD and LOQ of BPA in urine samples (LOQ's of the HBM4EU Aligned Studies are: 0.09, 0.20, 0.25, 0.03, 0.07 and 0.29 μg/L). Biomarker concentrations of the substitute BPS exceed the HBM-GV of 1 μg/L in 11% of the participants (adults), therefore risk for adverse health effects cannot be excluded for part of the population (Table 3) (Meslin et al., 2022). The HQ at the P95 also exceeds one (Fig. 3). The HBM-GV of BPS was based on endocrine effects (Meslin et al., 2022). Insufficient toxicity data are available to derive an HBM-GV for BPF which is another substitute for BPA. But several studies confirm the harmful effects of BPA substitutes (Jambor et al., 2021). BPA is the only bisphenol regulated under REACH with

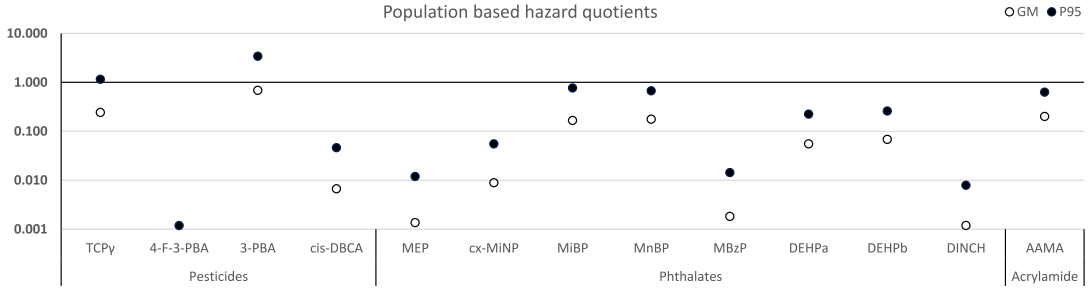

Fig. 1. Chemical specific hazard coefficients based on comparison of internal exposures in children (6–11 years), measured in the HBM4EU Aligned Studies (2014–2021), with corresponding health-based HBM guidance values. DEHPa = Σ (5-oxo + 5-OH-MEHP), DEHPb = Σ (5-cx-MEPP + 5-OH-MEHP), DINCH = Σ (OH-MINCH + cx-MINCH). 4-F-3-PBA HQ at GM not calculated as QF<60%. GM = Geometric mean, P95 = 95th Percentile.

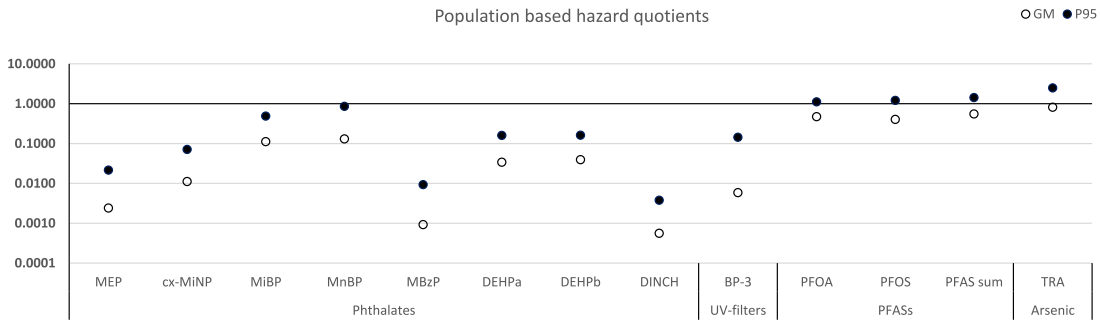

Fig. 2. Chemical specific hazard coefficients based on comparison of internal exposures in teenagers (12–18 years), measured in HBM4EU Aligned Studies (2014–2021), with corresponding health-based HBM guidance values. PFAS sum = Σ (PFOA + PFNA + PFHxS + PFOS), TRA = toxicologically relevant arsenic (Σ (As (III) + As(V) + DMA + MMA)) is based on data from only 3 countries, DEHPa = Σ (5-oxo + 5-OH-MEHP), DEHPb = Σ (5-cx-MEPP + 5-OH-MEHP), DINCH = Σ (OH-MINCH + cx-MINCH). GM = Geometric mean, P95 = 95th Percentile.

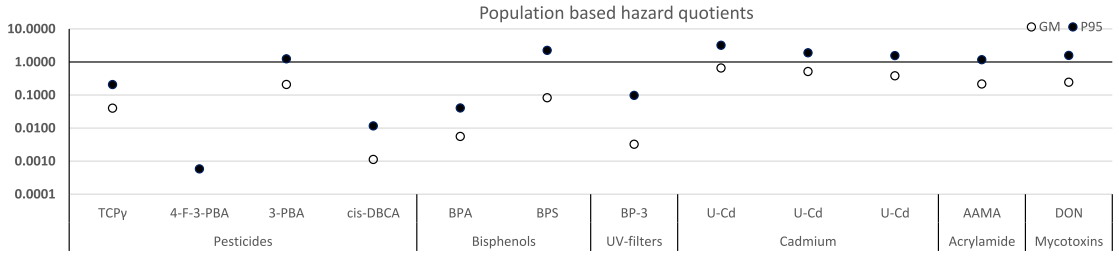

Fig. 3. Chemical specific hazard coefficients based on comparison of internal exposures in adults (20–39 years), measured in HBM4EU Aligned Studies (2014–2021), with corresponding health-based HBM guidance values. BPA HBM-GV of 230 μg/L was used based on t-TDI EFSA (2015). 4-F-3-PBA HQ at GM not calculated as QF<60%. U-cd left to right hazard coefficient for 20-year-old, 21-30-year-old, 31-40-year-old individuals respectively based on age dependent HBM-GV, GM = Geometric mean, P95 = 95th Percentile.

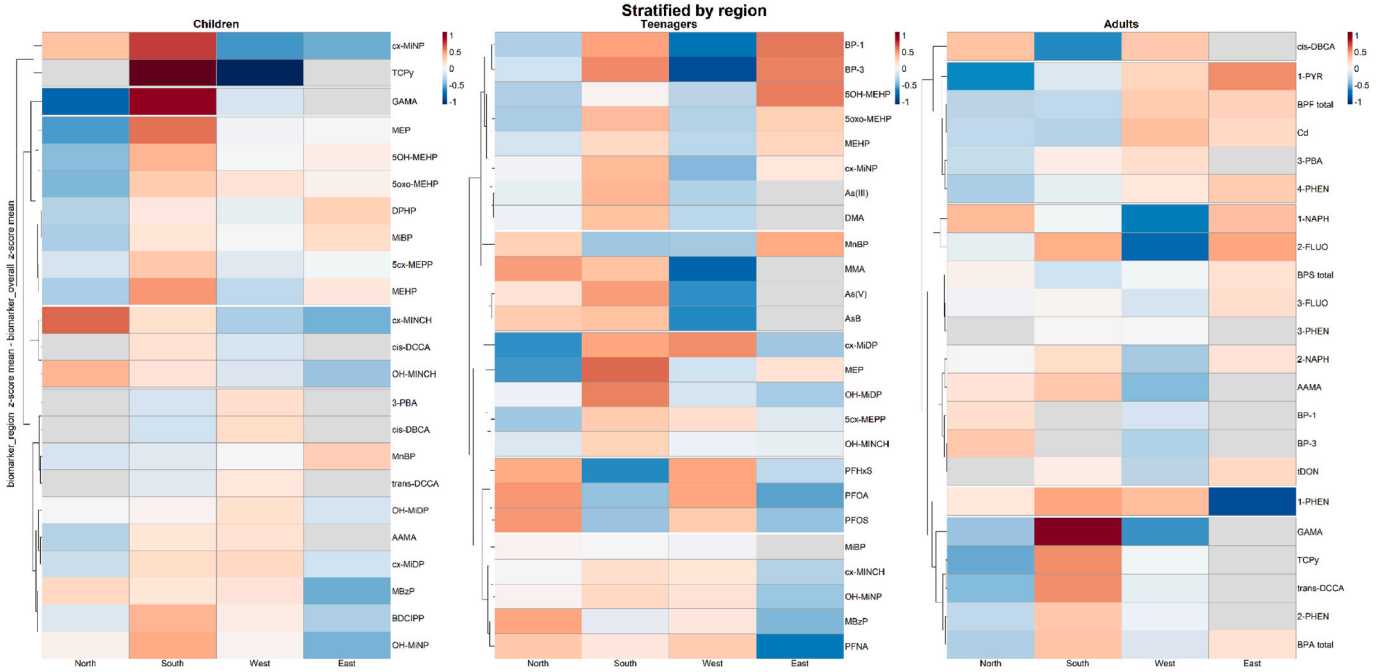

Fig. 4. Heatmap showing clustering of biomarkers (dendrogram to the left side) according to geographical gradient (North, East, South, West) in exposure levels. Red and blue intensities indicate fold increases and decreases, respectively (expressed as $\log_2$) in estimated geometric mean biomarker concentrations for a specific geographical region adjusted for age of the participant, sampling years, sex, creatinine for urinary markers, smoking status (for PAHs and cadmium) relative to the estimated overall geometric mean. Gray rectangles indicate missing data. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

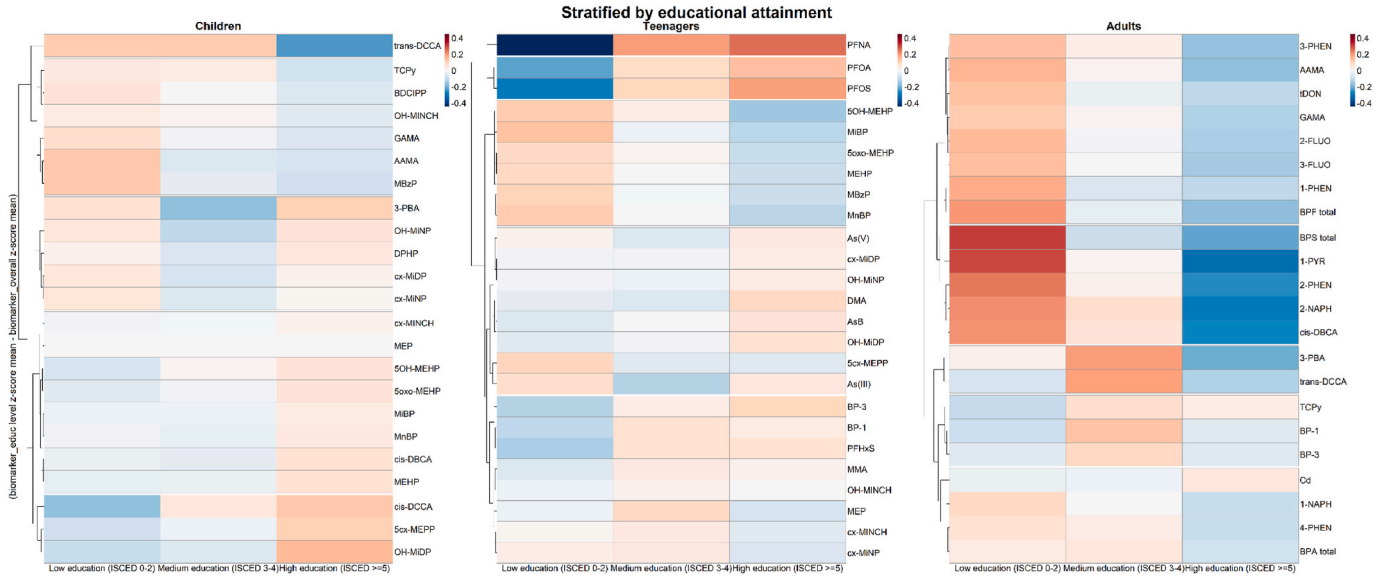

Fig. 5. Heatmap showing clustering of biomarkers (dendrogram to the left side) according to educational attainment (Low, Medium, High) of the participant (adults) or household (children/teenagers) as proxy for the social gradient. Red and blue intensities indicate fold increases and decreases, respectively (expressed as $\log_2$) in estimated geometric mean biomarker concentrations for a specific educational attainment adjusted for age of the participant, sampling years, sex, creatinine for urinary markers, smoking status (for PAHs and cadmium) relative to the estimated overall geometric mean. Gray rectangles indicate missing data. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

restricted use in thermal paper and in materials that come into contact with children's food (https://www.hbm4eu.eu/hbm4eu-substances/bisphenols/); some countries have implemented stricter regulations.

All the **phthalates** (DEHP, BBzP, DnBP, DiBP, DEP, DiNP) and **DINCH** have an HQ value below one at both the GM and P95 concentration (Fig. 1). Yet, in both children and teenagers some individuals have internal exposure levels exceeding the HBM-GVs. Phthalates with the highest number of participants exceeding the health-based HBM guidance values are DnBP and DiBP (<1–4%), both in children and teenagers. It can be noted that fewer teenagers exceed these HBM-GVs as children have generally higher concentrations of phthalate metabolites confirming earlier reports (Nguyen et al., 2019). Biomarkers of the other phthalates show less exceedances, DiNP, BBzP and DEHP HBM-GVs are exceeded in less than 1% of the samples, while no exceedances are measured for DEP and DINCH (Table 3). However, if we sum the biomarker concentrations of different phthalates as they co-occur, and assume similar toxicity, 10% of children and 6% of teenagers exceed the HBM-GVs for the sum of five anti-androgenic phthalates, namely DEHP, DiBP, DnBP, BBzP and DiNP, adverse health risks resulting from co-exposure to different phthalates cannot be excluded (Lange et al., 2022). Phthalates are reprotoxic and have an effect on male fertility (Radke et al., 2018). Some phthalates have also other endocrine disrupting properties or are associated with asthma (Wu et al., 2020). Several phthalates (DEHP, BBZP, DiBP, and DnNBP, DiPeP, DHNUP, DMEP, DnPeP and DnHP) cannot be used in the EU without authorization for specific uses. The European Union has set legal limits for the concentration of DEHP, BBZP and DNBP in food contact materials (https://www.hbm4eu.eu/hbm4eu-substances/phthalates-and-hexamoll-dinch/). DEHP, DnBP, DIBP and BBZP are banned in toys and childcare articles, while DINP, DIDP and DnOP are banned in toys and childcare articles that can be placed in the mouth. The use of phthalates classified as toxic to reproduction is prohibited in cosmetics. Despite obvious decreases in the levels of regulated phthalates further measures are needed to protect against the effects of combined exposures to reprotoxic chemicals.

Benzophenones are suspected endocrine disruptors (Wang et al., 2016), BP-3 is reprotoxic and interferes with thyroid hormones (Krause et al., 2018). BP-3 has a HQ at the GM and P95 below one both in teenagers and adults (Figs. 2 and 3). Less than 1% of the study population of children and adults exceed the provisional HBM-GV of 340 μg/g crt for the UV-filter BP-3. However, other benzophenones co-occur and BP-1 is frequently detected together with BP-3 in the same samples. No HBM-GV is available for BP-1 although available toxicological information confirms the endocrine disrupting potency of BP-1 (Nashev et al., 2010). EU regulation currently restricts use of BP-3 in sunscreens, cosmetics and food contact materials (https://www.hbm4eu.eu/hbm4eu-substances/benzophenones/). This restriction could be expanded to other benzophenones as they co-occur and are equally toxic.

A HQ at the P95 above one is observed for **PFOS** (1.28 μg/L), **PFOA** (1.14 μg/L), and **sum of four PFASs** (1.47 μg/L) (Fig. 2). Respectively 7% and 8% of our study participants (teenagers) exceed the HBM-I value of 2 μg/L (PFOA) and 5 μg/L (PFOS) (Table 3). Up to 13% of the teenager's participants exceeded the guidance value for the sum of PFOS, PFOA, PFNA, PFHxS, which was based on the EFSA derived TWI with impaired immune response to vaccination in one-year old children as the critical endpoint (EFSA et al., 2020) (Abraham et al., 2020) (Table 3). Bil et al. performed mixture risk assessments for PFAS, using three hazard-based approaches: the Hazard Index (HI) approach, the sum value approach as used by EFSA and the Relative Potency Factor (RPF) approach. The mixture assessments further confirm that PFASs exposure may result in a health risk in a considerable fraction of individuals in the HBM4EU teenager study sample (Bil et al., 2022). This data indicates that almost one in seven European teenagers is at risk due to exposure to PFOS, PFOA and the sum of four PFASs (PFOA, PFOS, PFHxS, PFNA). This percentage could even be an underestimation as in two countries only the linear form of PFOS was measured. PFASs are also associated with reduced birth weight, and they are suspected disruptors of thyroid hormone signaling and lipid homeostasis (EFSA, 2020) (Fragki et al., 2021). The four PFASs mentioned are the most abundant long chain PFASs that can be measured in human blood samples but they are members of a large group of thousands of similar chemicals that circulate in the environment as they are persistent and highly mobile (OECD). Despite inclusion of specific PFAS in the Stockholm Convention on Persistent Organic Pollutants and regulations in consumer products and air and water emissions (EEA, 2019), further regulatory actions to reduce exposure are needed. Our data demonstrate exceedances of

health-based HBM guidance values already for the legacy PFAS emphasizing the need for source directed regulations and better control of sources. Additional exposure to other PFAS compounds should be avoided and regulation at substance group level should be considered.

TRA (sum of As III + As V + MMA + DMA) has an HQ exceeding one at the P95 concentration (Fig. 2). Levels of exposure to TRA might be of concern for more than one-third (40%) of the teenagers in Europe, as they have levels exceeding the BE-value of 6.4 μg/L for non-cancer effects which has been derived in 2010 and may need to be updated (Hays et al., 2010). Recently concern is growing about cardiovascular and developmental neurotoxicity at low doses of inorganic arsenic exposure (Rahaman et al., 2021), and As is known to be a human carcinogen (IARC Group I) (IARC, 2012, 2019). As is regulated under REACH in the EU (i.e., specific uses are restricted) (https://www.hbm4eu.eu/hbm4eu-substances/arsenic/).

Of the overall adult study population 12% has urinary **cadmium** levels exceeding the age-dependent HBM-GV, with no difference in the proportion of exceedance between smokers and non-smokers. When including additional data from FR (included in a sensitivity analysis) up to 16.4% of the population has urinary Cd levels exceeding the age dependent HBM-guidance value. For smokers this is even higher i.e., 22% (Table 3). The effect of smoking on urinary Cd levels is observed in many studies, including DEMOCOPHES (Berglund et al., 2015; Den Hond et al., 2015) (Jarup, 2003). Cd accumulates in the kidneys and causes kidney dysfunction, reproductive toxicity and osteoporosis (Jarup and Akesson, 2009); Cd is classified as known human carcinogen by IARC (IARC, 1993; Nordberg, 2022). In the EU, Cd is regulated under REACH, limits for drinking water and specific food items are established, emissions to air are controlled, Cd is banned from cosmetics, concentrations in toys and electronics are limited (https://www.hbm4eu.eu/hbm4eu-substances/cadmium-and-chromium/). Despite these efforts, HBM data from the Aligned Studies demonstrate that current regulations are not protecting the population sufficiently as based on these results adverse health outcomes related to Cd exposure cannot be excluded.

For the **acrylamide marker (AAMA)** a health-based HBM guidance value for non-cancer effects (neurotoxicity) was derived and converted to corresponding AAMA levels in children and adults (Santonen et al., 2022). A HQ at the P95 above one (adults) and below one (children) indicate that especially in adults even non-cancer adverse health effects related to acrylamide exposure cannot be excluded for the highest exposed part of the population (Figs. 1 and 3). A relatively small proportion (7%) of the adult study participants have levels exceeding the provisional HBM-GV for AAMA of 291.4 μg/L. Only 1% of the children's study population has urinary AAMA levels above the provisional HBM-GV for AAMA of 321.7 μg/L (Table 3). Acrylamide has been shown to have neurotoxic, carcinogenic, genotoxic and mutagenic effects (Shipp et al., 2006). Use of acrylamide is restricted under REACH, it is banned in food contact materials, use in cosmetics is regulated, there are drinking water limits and there are bench mark levels for specific foods (https://www.hbm4eu.eu/hbm4eu-substances/acrylamide/).

The **mycotoxin marker (tDON)** exceeds the HQ at the P95 (Fig. 3). Up to 14% of the adult study participants have levels exceeding the recently derived HBM-GV (Table 3) indicating adverse health effects cannot be excluded for part of the population. DON is immunotoxic, reprotoxic and a probable endocrine disruptor (Demaegdt et al., 2016; Pestka, 2010). Climate change constitutes a reason for concern, as its effects favor the spread of fungi and consequently the production of mycotoxins. Regulation in EU requires monitoring in food and feed and sets maximum permissible limits in specific food items.

For the biomarkers of the **flame retardants** no health-based HBM guidance values were available. Therefore, interpretation of these levels in a health-risk context remains uncertain. Plichta et al. calculated an estimated daily intake of OPFRs (TCEP, TCIPP, TDCIPP) based on HBM data from the HBM4EU Aligned Studies in children and compared those to the RfD. They concluded that there is a minimal health risk based on the current knowledge of available exposure, kinetic and toxicity data (Plichta et al., 2022).

Also, for the **PAHs** no health-based HBM guidance values were available. Some PAHs are carcinogens and suspected endocrine disruptors (IARC, 2022; Vondráček et al., 2018). They are associated with a variety of adverse health effects including cancer, inflammation and cardiovascular diseases (Farzan et al., 2016). No threshold is considered for PAHs related carcinogenicity, consequently exposure should be as low as possible.

The lack of available health-based HBM guidance values, for several environmental contaminants and associated biomarkers is a clear limitation of the risk assessment approach performed. Out of the 80 biomarkers that have been measured in the HBM4EU Aligned Studies, only 20 have health-based HBM guidance values available for non-neoplastic endpoints. Legacy compounds such as BPA, PFOS and PFOA, FRs and BP-3 are replaced by substitutes, BPF, PFDA, PFHpA, PFHpS, PFHxA, PFPeA, PFUnDA, BDCIPP, DPHP, BCIPP and BP-1). Al these substitutes were detected in part of the study population (16%–99%) but, no health-based HBM guidance values are available for these substitutes since the toxicological database is incomplete. This hampers the interpretation of the exposure levels of these substitutes that were measured in our study population.

Another limitation of the use of the health-based HBM guidance values is that they are based on current scientific knowledge and regular updating is needed as more scientific knowledge becomes available and analytical capacities become more precise. The values are reviewed by expert panels and very often lower limit values are proposed after review (e.g. recent draft proposal on revised t-TDI for BPA).

For the total of 80 biomarkers investigated in the HBM4EU Aligned Studies, we could identify 20 health-based HBM guidance values. For 15 out of these we observed exceedances in the investigated populations. It should also be noted that we did not consider cancer risks, but several of the substances are classified as known human carcinogens (PAHs, As, Cd, acrylamide, chlorpyrifos).

The current risk assessments address only one substance with the recent exception of the European Food Safety Authority (EFSA) proposed limit value for the sum of four PFASs (EFSA, 2020), the BE-value for 3-PBA, which is a non-specific metabolite for combined exposure to most pyrethroids and TRA, where DMA may not only come from the intake from inorganic As but also from direct intake and metabolization of arsenosugars and –lipids (Luvonga et al., 2020). Risk assessment for individual substances, show that adverse health effects cannot be excluded for a fraction of the European population. However, the biomonitoring data of the HBM4EU Aligned Studies demonstrate clearly that the European population is co-exposed to a number of hazardous chemicals. We notice that several of the hazardous substances are reprotoxic and may act on the same target, hence they may act additively or effects can even be multiplied (Thrupp et al., 2018). Lange et al. have performed a risk assessment based on combined exposure to five anti-androgenic phthalates, namely DEHP, DiBP, DnBP, BBzP and DiNP, indicating that exposures of 17% of children and adolescents resulted in hazard indices (HI) > 1 (Lange et al., 2022).

3.5. Strengths and weaknesses

The strength of the HBM4EU Aligned Studies is the very large sample size obtained for the different substance groups being measured: pesticides (children: six countries, N = 863, adults: five countries, N = 899), bisphenols (adults: 11 countries, N = 2,741), phthalates/DINCH (children: 12 countries, N = 2,877, teenagers: 11 countries, N = 2,799), OPFRs (children: seven countries, N = 1,768), HFRs (children: four countries, N = 710), benzophenones (teenagers: six countries, N = 1,389, adults: four countries, N = 965), PFASs (teenagers: eight countries, N = 1,657), arsenic (teenagers, five countries, N = 1,144), cadmium (adults: eight countries, N = 2,107), PAHs (adults: 10 countries, N = 2,601), acrylamide (children: five countries, N = 1,198; adults: five countries, N = 1,180), and mycotoxins (adults: five countries, N =

1,099). Despite a good overall match for sex and degree of urbanization reached in the HBM4EU Aligned Studies, participants/households with lower educational attainment were underrepresented (as discussed in more detail in (Gilles et al., 2022)). As such, the HBM4EU Aligned Study population cannot be considered representative for Europe. Only 17 out of the 37 participating HBM studies had national geographical coverage. Therefore, the exposure values were calculated for the HBM4EU population sample and should not be labelled as European 'reference' values. In substance specific publications, survey procedures will be used to calculate 'European exposure values' taking into account the complex survey design when calculating variance estimates. This was not done in this overview paper, as for some biomarkers the survey procedure was not able to estimate the variances due to the low number of studies included. Moreover, not for all biomarkers the criterium to have at least one country per region is met, which will be critically evaluated in the substance-specific manuscripts before deriving the European exposure values. Nevertheless, comparable HBM data were obtained by the QA/QC program implemented in the HBM4EU project. However, the alignment of the determination and definition of the LOD/LOQ in the participating studies could still be improved, together with lowering those values which is specifically important for mixture risk assessment. The HBM4EU Aligned Studies were aligned in aspects like age, sampling period, sample collection, and substance groups prioritized. Although all participating studies fitted in the predefined age groups and sampling period, there were still some differences between the participating studies, with some of them covering the whole age range and others only covering a few years. As the participating studies were not obliged to analyze all substance groups/biomarkers selected, there were some data gaps for specific biomarkers of pesticides, FRs, benzophenones, arsenic, acrylamide, and mycotoxins. Within teenagers, specific gravity (SG) was specified as an obligatory measure since especially in this age group creatinine is not the best estimate for urinary dilution due to muscle formation (Barr et al., 2005). The SG analysis was however not performed in the ESTEBAN study. Therefore, the exposure levels for the HBM4EU population are expressed as volume based (μg/L) and standardized for creatinine (μg/g creatinine) only. As the ESB study in adults collected 24 h urine samples (Supplemental Material Table S1), while all other studies collected first morning or random spot urine samples, exposure levels standardized for creatinine are preferred for comparison with data from international studies. Some of the substance groups analyzed in urine (i.e., bisphenols, phthalates, OPFRs, pesticides) represent short-term exposure. For those the timing of sampling is very critical, and therefore, single random spot or first morning urine samples might lead to exposure misclassification (Perrier et al., 2016). However, if we assume that exposure is rather continuous due to stable consumer and nutritional habits, the levels might be stable. We were able to harmonize a large set of variables relevant for further statistical analyses of the exposure data, for example to look into exposure determinants which will be addressed in the substance specific papers. However, as some studies were already ongoing when the HBM4EU Aligned Studies started, post-harmonization was needed, resulting in missing information in some participating studies or not 100% uniform retrieval of information from the participants for very specific variables like food consumption and frequency information. However, for the basic variables reported in this paper, this harmonization aspect was not an issue.

4. Conclusions

This article presents a broad overview of the internal exposure levels assessed in the HBM4EU Aligned Studies (2014–2021). Quality controlled HBM data and auxiliary data were obtained from 10,795 individuals recruited in 22 European countries and Israel. The data serve as a reference for comparison at the global level, provide a baseline to compare the efficacy of the European Commission's chemical strategy for sustainability and will give leverage to national policy makers for the implementation of targeted measures. The results can help to prioritize further needs for development and implementation of protective measures and legislation related to chemicals to safeguard public health.

Our results show that exposure to legacy substances is generalized, but also substitutes of legacy phthalates, flame retardants, BPA, PFASs and benzophenones could be quantified, sometimes with a high detection frequency, showing that the study participants are co-exposed to several of the prioritized substances. In general, exposure levels observed in Europe are in line with those reported internationally (the US, Canada and Korea) except for BP-3, bisphenol S, TDCIPP whose levels are higher in the US, and biomarkers of pyrethroids, chlorpyrifos and metabolites of some high molecular weight phthalates which are lower in Canada. Furthermore, our data illustrate that phthalates, which are regulated under REACH (ECHA, 2018), show decreasing concentrations in European children when compared to the DEMOCOPHES results (2011–2012) (Den Hond et al., 2015). Cd levels in European women from the HBM4EU Aligned Studies and DEMOCOPHES did not change noticeably over the last decade, this suggests that additional measures are needed to lower exposure to Cd since 12% of adults still have exposures exceeding HBM-GV.

Social and Geographical gradients in exposure could be identified. Social gradients were observed for PFAS, As, phthalate metabolites, pyrethroid pesticides, bisphenols, UV-filters, PAHs and acrylamide. Significant differences between geographical regions across Europe are observed for almost all biomarkers. The geographical differences may relate to environmental differences, to differences in lifestyle and dietary habits, to differences in policy implementation and the efficiency to check compliance with regulation. Although regulation of chemicals occurs at EU level, surveillance and targeted measures are needed at national or regional level. Substance specific analysis of questionnaire data in connection with biomarker data will further explore associations to link the biomarker data with possible exposure pathways and sources.

The assessment of this recent internal exposure data in a health risk-based context at the population level is a rapid screening approach to identify environmental chemicals to which the general population may be exposed at levels near or exceeding existing health-based HBM guidance values. Our results demonstrate that for 15 biomarkers for which health-based HBM guidance values for non-cancer effects are available, exceedances are observed. The fraction of the population that exceeds these values and for which adverse health effects cannot be excluded varies depending on the biomarker. Highest exceedance rates are observed for toxicologically relevant arsenic in teenagers (40%), and for 3-PBA in children (36%), and 11–14% for total DON, Σ (PFOA + PFNA + PFHxS + PFOS), BPS and Cd.

These results provide exposure-based input for prioritization. The ongoing collection and evaluation of HBM data from the European population will help to track exposures and support the ongoing work to mitigate exposures and reduce health risks.

Declarations of competing interest

The authors declare no conflict of interest. José V. Tarazona is employed by the European Food Safety Authority (EFSA). The views expressed in this publication are those of the authors and should not be interpreted as representing the official position of EFSA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2023.114119.

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