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Review article

Biomarkers of exposure in environment-wide association studies – Opportunities to decode the exposome using human biomonitoring data

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Abbreviations: β-HCH, β-hexachlorocyclohexane; μg/l, microgram per liter; μM/l, micromolar per liter; Σ, total; 1-HP, 1-hydroxypyrene; 2, 3-DHBA, 2,3-dihydroxybenzoic Acid; 2cx-MMHP, mono-(2-carboxymethylhexyl) phthalate; 3PBA, 3-phenoxybenzoic acid; 4F3PBA, 4-fluoro-3-phenoxybenzoic acid; 5cx-MEPP, mono-(5-carboxy-2-ethylpentyl) phthalate; 5OH-MEHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; 5oxo-MEHP, Mono-(2-ethyl-5-oxo-hexyl) phthalate; AAMA, N-acetyl-S-(2-carbamoylethyl)-L-cysteine; AAs, alkylating agents; ADI, acceptable daily intake; ALARP, as low as reasonably practicable; AM, arithmetic mean; APGAR, adaptation, partnership, growth, affection, resolve; As, arsenic; AUDIT, alcohol use disorders identification Test; BAC, blood alcohol content; BAT, biological tolerance value; BDCM, bromodichloromethane; BDE 99, 2,2′,4,4′,5-pentabromodiphenyl ether; BE, biomonitoring equivalents; BEI, biological exposure indices; BFRs, brominated flame retardants; BMD-L, benchmark dose lower confidence limit; BoE, biomarker of exposure; BPA, bisphenol A; BPA-glu, glucuronidated metabolite of BPA; BPAD, biological pathway altering dose; BPF, bisphenol F; BPS, bisphenol S; BPP, butylbenzyl phthalate; Br_2CA, 2,2-dibromovinyl-2,2-dimethylcyclopropanecarboxylic acid; BzBP, benzylbutyl phthalate; CAL REL, California acute reference exposure levels; CC, critical concentration; Cd, cadmium; cis-Cl_2CA, cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid; cis-DCCA, 2,2-dichloro-2-dimethylvinyl-cyclopropane carboxylic acid; CYP, cytochrome P450; CYP1A1, cytochrome P450 1A1; CIT, citrinin; CPK, creatine phosphokinase; Cr, chromium; CRP, C-reactive protein; crea., creatinine; Cu, copper; dBA, decibel; DAP, dialkylphosphate; DBCA, 2,2-Dibromo-2-Dimethylvinyl-Cyclo-Propane Carboxylic Acid; DBCM, dibromochloromethane; DBP, di-n-butyl phthalate; DBPs, disinfection by-products; DCCA, 2,2-Dichloro-2-Dimethylvinyl-Cyclopropane Carboxylic Acid; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; DEDTP, diethyl dithiophosphate; DEHP, di-2(ethylhexyl) phthalate; DEHT, di(2-ethylhexyl) terephthalate; DEP, diethyl phthalate; DETP, diethyl thiophosphate; DiBP, di-iso-butyl phthalate; DINCH, diisononyl 1,2-cyclohexanedicarboxylic acid; DiNP, diisononyl phthalate; DMP, dimethyl phosphate; DMDTP, dimethyl dithiophosphate; DMTP, dimethyl thiophosphate; DNA, deoxyribonucleic acid; DnBP, Di-n-butyl Phthalate; DON, deoxynivalenol; ECO, expired carbon-monoxide; EMF, electromagnetic field; EU's FP7, European Union's 7th Framework Programme; EWAS, environment-wide association studies; FAO, food and agriculture organization; FAS, family affluence scale; Fe, iron; FFQ, food frequency questionnaires; GAMA, N-acetyl-S-(2-carbamoyl-2-hydroxyethyl)-L-cysteine; GGT, γ-glutamyl transferase; GM, geometric mean; GPAQ, global physical activity questionnaires; GWAS, genetic-wide association studies; h, hours; HBCDD, hexabromocyclododecane; HBM, human biomonitoring; HCB, hexachlorbenzene; HEALS, health and environment-wide associations based on large population surveys; Hg, mercury; ICC, intraclass correlation coefficient; IL-6, interleukin-6; IMD, index of multiple deprivation; IPAQ, international physical activity questionnaires; JEM, job-exposure-matrix; LDH, lactate dehydrogenase; LOAEL, lowest observed adverse effect level; m7Gua, 7-methylguanine; MAA, 2-methoxy acetic acid; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; MCT, measure of central tendency; MEHP, mono-(2-ethylhexyl) phthalate; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, mono-ethyl phthalate; MHA, methylhippuric acid; MiNP, mono-isononyl phthalate; Mn, manganese; mg/kg/day, milligram per kilogram per day; mg/m^3, milligram per cubic meter; MnBP, mono-n-butyl phthalate; MOA, mode of action; MRL, minimal risk level; MVOC, microbial volatile organic compounds; n, sample size; NDMA, N-nitrosodimethylamine; NMTCA, N-nitroso-2-methylthiazolidine-4-carboxylic acid; NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; No., number; NOAEL, no observed adverse effect level; NOC, N-nitroso compounds; NOx, nitrogen oxides; NPRO, N-nitrosoproline; NPs, nanoparticles; NSAR, N-nitrososarcosine; NTCA, N-nitrosothiazolidine-4-carboxylic acid; O_3, Ozone; OH-MiNP, 7OH-mono-methyloctyl phthalate; OCPs, organochlorine pesticides; OPPs, organophosphate pesticides; OTA, ochratoxin A; oxo-MiNP, 7oxo-mono-methyloctyl phthalate; P_{90}, 90th percentile; P_{95}, 95th percentile; PAH, polycyclic aromatic hydrocarbon; Pb, lead; PBB, polybrominated biphenyls; PBBK, physiology-based biokinetic; PBDE, polybromodiphenyl ether; PCB, polychlorinated biphenyl; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated dibenzofurans; PCP, pentachlorphenol; PER, perchlorethylene; PFC, perfluorinated compounds; PFOA, perfluorooctanoic acid; PFOS, perfluorooctanesulfonic acid; pg/ml, pictogram per milliliter; PGA, phenylglyoxylic acid; PK, pharmacokinetic; PM, particulate matter; POD, point of departure; POPs, persistent organic pollutants; PSS, perceived stress scale; PTWI, provisional tolerable weekly intake; PYR, pyrene; RfC, reference concentration; RfD, reference dose; RI, reference interval for clinical guidance; Rn, radon; RV_{95}, reference value; S-PMA, S-phenyl mercapturic acid; SC, stachybotrys chartarum; SD, standard deviation; Se, selenium; SED, systemic exposure dose; SES, socioeconomic status; SG, satratoxin G; SHS, second-hand smoke; STA, state-trait anxiety inventory; TBBPA, Tetrabromobisphenol A; TCAA, trichloroacetic acid; TCEQ ReV, reference value of the Texas commission on environmental quality; TCDD, tetrachlorodibenzo-p-dioxin; TDI, tolerable daily intake; THMs, trihalomethanes; THS, third-hand smoke; TLV, threshold limit values; trans-Cl2CA, trans-2-dichlorovinyl-2,2-dimethylcyclopropane-1-carboxylic acid; trans-DCCA, 2,2-dichloro-2-dimethylvinyl-cyclopropane carboxylic acid; U/L, units per litre; UFPs, ultrafines particles; UK, United Kingdom; US, United States; UVR, ultraviolet radiation; Zn, Zinc

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ABSTRACT

Background: The European Union's 7th Framework Programme (EU's FP7) project HEALS – Health and Environment-wide Associations based on Large Population Surveys – aims a refinement of the methodology to elucidate the human exposome. Human biomonitoring (HBM) provides a valuable tool for understanding the magnitude of human exposure from all pathways and sources. However, availability of specific biomarkers of exposure (BoE) is limited.

Objectives: The objective was to summarize the availability of BoEs for a broad range of environmental stressors and exposure determinants and corresponding reference and exposure limit values and biomonitoring equivalents useful for unraveling the exposome using the framework of environment-wide association studies (EWAS).

Methods: In a face-to-face group discussion, scope, content, and structure of the HEALS deliverable "Guidelines for appropriate BoE selection for EWAS studies" were determined. An expert-driven, distributed, narrative review process involving around 30 individuals of the HEALS consortium made it possible to include extensive information targeted towards the specific characteristics of various environmental stressors and exposure determinants. From the resulting 265 page report, targeted information about BoE, corresponding reference values (e.g., 95th percentile or measures of central tendency), exposure limit values (e.g., the German HBM I and II values) and biomonitoring equivalents (BEs) were summarized and updated.

Results: 64 individual biological, chemical, physical, psychological and social environmental stressors or exposure determinants were included to fulfil the requirements of EWAS. The list of available BoEs is extensive with a number of 135; however, 12 of the stressors and exposure determinants considered do not leave any measurable specific substance in accessible body specimens. Opportunities to estimate the internal exposure stressors not (yet) detectable in human specimens were discussed.

Conclusions: Data about internal exposures are useful to decode the exposome. The paper provides extensive information for EWAS. Information included serves as a guideline – snapshot in time without any claim to comprehensiveness – to interpret HBM data and offers opportunities to collect information about the internal exposure of stressors if no specific BoE is available.

1. Introduction

The European Union's 7th Framework Programme (EU's FP7) project HEALS – Health and Environment-wide Associations based on Large Population Surveys – started in 2013 with a term of 5 years. The objective of HEALS is the refinement of an integrated methodology and the application of analytical and computational tools for elucidating human exposome through the integrated use of advanced statistical tools for environment-wide association studies (EWAS) in support of EU-wide environment and health assessments (www.heals-eu.eu).

Important determinants for the development of diseases are genetic influences and the interaction of environmental stressors (Schwartz and Collins, 2007). Described with the complementary approach of nature and nurture, the term "environment" includes everything that is not genetic (Smith et al., 1999). Consequently, the genome needs to be complemented by the exposome (Wild, 2005, 2012). While the human "genome is fixed at conception" (but changed by mutagenic influences) (Rappaport, 2011), "the exposome encompasses life-course environmental exposures […], from the prenatal period onwards" (Wild, 2005). Based on the above, genome-wide association studies (GWAS) attempt to describe the influence of genetic factors for the development of diseases (Hirschhorn and Daly, 2005), while EWAS investigate the associations between a wide range of environmental factors and diseases (Patel et al., 2010). In this context, human biomonitoring (HBM) –procedures to determine substances or biological markers in human specimens (Angerer et al., 2007) – provides a valuable tool for understanding the magnitude of exposure from all pathways and sources. A biomarker of exposure (BoE) "may be the identification of an exogenous substance within the system, the interactive product between a xenobiotic compound and endogenous components, or other event in the biological system related to the exposure"(NRC, 1987). BoEs include either stressors themselves (e.g. the parent compounds), or their metabolites (reaction products), identified in a variety of human specimens such as blood, urine, deciduous teeth or hair (CDC, 2005).

HEALS encompasses a more integrative approach for associating environmental exposures and disease mechanisms and outcomes. Data from the external environment, e.g., measurements of chemicals in different media (e.g. air, water, soil and food), are combined with data regarding internal exposure, e.g., measurements of chemicals in urine or blood, to build the exposome and to derive environment-wide associations between exposure and disease. Starting from HBM samples, quantification of exposure biomarkers, together with identification of markers of effect and susceptibility (mainly-omics), builds the analytical exposure biology framework for unraveling the human exposome using multi-omics technologies according to the HEALS paradigm.

To evaluate HBM data, reference and exposure limit values as well as biomonitoring equivalents are useful and receive particular attention in the HEALS project. Reference values describe the upper level of the populations' background concentration (Angerer et al., 2007; Schulz et al., 2011). The HBM Commission of the German Environment Agency defines the reference value RV_{95} as "the 95 population percentile […] rounded off within the 95% confidence interval" of the respective parameter in the matrix obtained from the reference population (Schulz et al., 2011). Reference values contain no information about health-related biological exposure limits (Angerer et al., 2007).

Popular health-related biological exposure limit values are the German HBM I and II values. There is no health risk assumable if the concentration of a substance in urine or blood is below the HBM I level.

A health risk cannot be excluded if the concentration of a substance in urine or blood is between HBM I and HBM II. An increased risk for adverse health effects is given if the concentration is above HBM II (Schulz et al., 2011). Additional exposure limit values are used in the literature. Mocarelli et al. (1986) defined a cut-off limit for pathological results set at "eight times the SD [standard deviation] value above the mean". Critical concentrations (CC) define the concentration below which the probability of health effects is negligible as was it observed in children at birth (ANSES, 2013). Specific exposure limit values are also mentioned. For example, the copper concentration indicating probable depletion resulting in health effects (Burtis et al., 2012), the early morning cortisol concentration suggesting adrenal insufficiency, and cut-off points which distinguish tobacco use vs. no tobacco use (Kim, 2016) have been determined. The BAT (biological tolerance value) and BEI (biological exposure indices) values are occupational exposure limit values. BAT is the "concentration for a substance […] in the corresponding biological material at which the health of an employee generally is not adversely affected even when the person is repeatedly exposed during long periods" (DFG, 2016). The BEI is the "level of the determinant most likely to be observed in specimens collected from a worker with an internal dose equivalent to that arising solely from inhalation exposure at the TLV [threshold limit value] concentration". The TLV represents a safe concentration in air in occupational contexts (Morgan, 1997).

Besides reference values and exposure limit values, biomonitoring equivalents (BEs) are of importance, because they are a first screening method to evaluate potential risk from exposure to environmental stressors using HBM data. BEs are defined as the concentration of a chemical or metabolite in a biological matrix (blood, urine, human milk, etc.), consistent with defined exposure guidance values or toxicity criteria. These include reference doses (RfD) and reference concentrations (RfC), minimal risk levels (MRL) and tolerable daily intakes (TDI), which have been defined using the knowledge available regarding the toxicokinetic properties of the chemical (Boogaard et al., 2011). The application of BEs is based on the assumption that intake and excretion are at equilibrium. This ensures coherence between the guidance values for chronic exposure and the estimated BE (Angerer et al., 2011). Use of reliable physiology-based biokinetic (PBBK) models is the most convenient way to translate external exposure reference values into BEs. Details on the methodology and the specific assumptions for the derivation of BEs for each compound can be found in the references given in Table 4. In general, the main steps for deriving a BE are summarized below:

(I) The identification of the point of departure (POD) that was used for deriving the external exposure reference value (e.g., TDI or RfD).
(II) If the POD has been derived from an animal study (which is the most common case), then the respective uncertainty factors that account for interspecies extrapolation and, if needed, the lowest observed adverse effect level (LOAEL) to no observed adverse effect level (NOAEL) extrapolation, are used to calculate the human-equivalent POD.
(III) By using either a simple pharmacokinetic (PK) or more sophisticated PBBK model, we estimate the expected concentration at the matrix of interest, assuming an intake equal to the human-equivalent POD. For rapidly metabolized compounds, when a urinary metabolite is identified the daily urinary excretion of the compound normalized by average urine volume and average creatinine excretion at the daily exposure rate equal to the human-equivalent POD has to be estimated. For this we have to make an assumption on the percentage of intake that is eliminated via the urinary tract. In both cases, the result of the toxicokinetic calculation helps us to derive the biological matrix-related BE_{POD}.
(IV) Finally, to end up with a BE value that is relevant to humans, uncertainty factors related to intraspecies differences have to be applied on the BE_{POD}. When a detailed PBTK model is available, intraspecies variability can be directly incorporated in the relevant anthropometric (i.e. bodyweight, body mass index) and biochemical (e.g. metabolic rates based on the genetic polymorphisms of the cytochrome P450 [CYP] isozymes) parameters.

For non-persistent compounds, such as phthalates and bisphenol A, BEs refer usually to levels of metabolite(s) measured in urine; for persistent compounds the biological matrix of reference is either milk (e.g. for POPs) or blood (e.g. heavy metals like Cd and Pb).

In the framework of HEALS, BoEs of a large number of environmental stressors were reviewed and used for supporting environment-wide associations. The main objective of this work was to summarize the availability of BoEs for the broad range of environmental stressors and exposure determinants of interest in HEALS (including heavy metals, persistent and non-persistent organic compounds, particulate matter and biologicals) and corresponding reference and exposure limit values and biomonitoring equivalents useful for unraveling the exposome using the EWAS framework. Additionally, environmental stressors and exposure determinants without known BoEs were discussed.

2. Methodology

This review was based on an expert panel discussion to determine scope, content, and structure of the HEALS guidelines for appropriate BoE selection for EWAS studies. An extensive list of the most important environmental stressor categories as well as selected stressors relevant to human health of the population in the EU was created based on expert opinion. An expert-driven, distributed, narrative review process involving around 30 scientists of the HEALS consortium made it possible to include extensive information targeted towards the specific characteristics of the individual stressor. A narrative/qualitative review design was preferred in contrast to a systematic one, because the intention was to give a broad comprehensive overview of the great number of topics included (Callcut and Branson, 2009; Cook et al., 1997).

The review process was organized on the basis of stressor-specific fact sheets. Every author summarized the latest information about chemical properties, effects on biological systems, exposure routes, absorption, elimination, specimens for analysis, and eventually reference and exposure limit values for at least one (mostly more than one) fact sheet(s). There was no common systematic strategy for literature searches because of the diversity of topics. However, an internal review process (see below) reduced possible researcher bias during the literature search. While most fact sheets were created for specific environmental stressors (e.g., mercury), in some cases it was necessary to summarize a group of stressors in one fact sheet (e.g., psychological occupational hazards). This was an essential, yet feasible approach in some cases, so as to represent a wide range of stressors important to determine the exposome of the EU population.

Information was obtained from comprehensive reports of international organizations (e.g., WHO's Environmental Health Criteria) and other mainstream scientific literature supplemented by the latest research results published in PubMed listed journal papers. Overall, more than 800 references were reviewed.

For quality assurance, all contributors were involved in an internal review process. Each fact sheet was reviewed by at least two project partners, while one of them was the project coordinator, co-coordinator, or leader of the HEALS HBM work package. The leading question for the review process was: "Is the quality, content, and extent of the fact sheet as well as the literature selection suitable and is the information included up to date?" The literature review process described above resulted in a dedicated technical report available for download on the HEALS website: http://www.heals-eu.eu/wp-content/uploads/2013/08/HEALS_D4.2.pdf. A concise selection of information was extracted, updated, and key conclusions are summarized in this

Table 1
Summarizing table, comprising a list of stressor categories, individual stressors and biomarkers of exposure considered and availability (√: available, X: not available) of reference values (R), exposure limit values (E) and biomonitoring equivalents (BE).

Stressor categories		Individual stressors		Biomarker of Exposure			Availability		
No.		No.	(alphabetically by stressor category)	No.	(alphabetically by individual stressor)		R	E	BE
1	persistent organic pollutants (POPs)	1	BFRs	1	BDE-99		√	X	√
				2	HBCDD		X	X	√
				3	PBDE		√	X	X
		2	dioxins and furans	4	dioxin-like compounds	CYP1A1	X	X	X
				5	GGT		√	√	X
				6	PCDD		√	X	X
				7	PCDF		√	X	X
				8	TCDD	bile acids	X	X	X
				9		steroids	X	X	X
		3	OCPs	10	β-HCH		√	X	X
				11	DDE		√	X	√
				12	DDT		√	X	√
				13	HCB		√	X	√
		4	PCBs	14	ΣPCB		√	√	X
				15	dioxin-like PCBs		√	X	X
				16	indicator PCBs		√	X	X
				17	PCB 28		√	X	X
				18	PCB 52		√	X	X
				19	PCB 101		√	X	X
		5	PFC	20	PFOA		√	√	X
				21	PFOS		√	√	X
2	other organic contaminants	6	bisphenols	22	BPA		√	√	X
				23	BPA-glu		X	X	√
		7	OPPs	24	DAP	DEDTP	√	X	X
				25		DETP	√	X	X
				26		diethyl phosphate	√	X	X
				27		DMDTP	√	X	X
				28		DMP	√	X	X
				29		DMTP	√	X	X
		8	PAHs	30	1-hydroxypyrene		√	X	X
				31	fluoranthene	3-hydroxy-fluoranthene	√	X	X
				32	fluorene	2-hydro-xyfluorene	√	X	X
				33		3-hydro-xyfluorene	√	X	X
				34	naphthalene	1-naphthol	√	X	X
				35		2-naphthol	√	X	X
				36	phenanthrene	1-hydroxy-phenanthrene	√	X	X
				37		2-hydroxy-phenanthrene	√	X	X
				38		3-hydroxy-phenanthrene	√	X	X
		9	parabens	39	butyl parabens		√	X	X
				40	ethyl parabens		√	X	X
				41	methyl parabens		√	X	X
				42	propyl parabens		√	X	X
		10	phthalates	43	BzBP	MBzP	X	X	√
				44	DBP	MBP	X	X	√
				45	DEHP	2cx-MMHP	X	X	√
				46		5cx-MEPP	X	X	√
				47		MEHHP	X	X	√
				48		MEHP	5OH-MEHP	√ √	√
				49			5oxo-MEHP	√ √	√
				50		MEOHP		X X	√
				51	DEP	MEP		X X	√
				52	DiBP			X X	X
				53	DiNP	MiNP		X X	√
				54		oxidative metabolites	carboxy-MiNP	X X	√
				55			OH-MiNP	X X	√
				56			oxo-MiNP	X X	√
				57	DnBP			X X	X
				58	MnBP			X X	X

(*continued on next page*)

Table 1 (*continued*)

Stressor categories		Individual stressors		Biomarker of Exposure				Availability		
No.		No.	(alphabetically by stressor category)	No.	(alphabetically by individual stressor)			R	E	BE
		11	PYR	59	ΣPYR			√	X	X
				60	3PBA			√	X	X
				61	cyfluthrin	4F3PBA		X	X	√
				62		cis-Cl_2CA		√	X	X
				63		cis-DCCA		X	X	√
				64		DCCA		X	X	√
				65		trans-Cl_2CA		√	X	X
				66		trans-DCCA		X	X	√
				63*	cypermethrin	cis-DCCA		X	X	√
				66*		trans-DCCA		X	X	√
				67	deltamethrin	Br_2CA		√	X	X
				62*		cis-Cl_2CA		√	X	X
				68		DBCA		X	X	√
				65*		trans-Cl_2CA		√	X	X
				63*	permethrin	cis-DCCA		X	X	√
				66*		trans-DCCA		X	X	√
3	toxic and potential toxic elements	12	As	69	As			√	√	X
				70	dimethylated As			X	X	√
				71	inorganic As			X	X	√
				72	monomethylated As			X	X	√
		13	Cd	73	Cd			√	√	√
		14	Cr	74	Cr			√	X	X
		15	Cu	75	Cu			√	√	X
		16	Fe	76	Fe			X	X	X
		17	Hg	77	Hg			√	√	X
		18	Mn	78	Mn			√	X	X
		19	Pb	79	Pb			√	X	X
		20	Se	80	Se			√	X	X
		21	Zn	81	Zn			√	√	X
4	volatile organic compounds (VOCs)	22	acrylamide	82	AAMA			√	X	X
				83	GAMA			√	X	X
		23	benzene	84	benzene			√	X	√
				85	S-PMA			√	X	X
		24	cyanide	86	2-Aminothiazoline-4-carboxylic acid			√	X	X
		25	ethylbenzene	87	ethylbenzene			√	X	√
				88	PGA			√	X	X
		26	glycol ethers	89	MAA			√	√	X
		27	PCP	90	PCP			√	√	X
		28	PER	91	PER			√	X	X
		29	styrene	92	mandelic acid			√	X	X
				93	N-Acetyl-S-(phenyl-2-hydroxyethyl)-L-cysteine			√	X	X
				88*	PGA			√	X	X
				94	styrene			√	X	√
		30	toluene	95	hippuric acid			√	X	X
				96	N-Acetyl-S-(benzyl)-L-cysteine			√	X	X
				97	toluene			√	X	√
		31	triclosan	98	triclosan			√	X	√
		32	xylene	99	2-MHA			√	X	X
				100	3-MHA			√	X	X
				101	4-MHA			√	X	X
				102	*m, p*-xylene			√	X	X
				103	MHA			√	X	X
				104	*o*-, *m*-, *p*-xylene			√	X	X
				105	*o*-xylene			√	X	√
				106	xylene			√	X	X
5	pharmaceuticals	33	antibiotics	→	*see substance of interest*			→	→	→
		34	chemotherapy	→	*see substance of interest*			→	→	→
6	smoking	35	smokeless tobacco	X	*no BoE available*			X	X	X
		36	tobacco smoke	107	nicotine	cotinine		√	√	X
7	air pollution	37	bioaerosols	108	mold	SC	SG	X	X	X
				109	MVOC			X	X	X
				110	mycotoxins			X	X	X
		38	diesel exhaust	111	1-HP			√	X	X
		39	NO_x	112	NO_x			√	X	X
		40	NPs	X	*no BoE available*			X	X	X
		41	O_3	113	2,3-DHBA			X	X	X
		42	PM	X	*no BoE available*			X	X	X
		43	UFPs	X	*no BoE available*			X	X	X
8	food contamination	44	biological agents	114	mycotoxins	CIT		√	X	X
				115		DON	DON15GlcA	√	X	X
				116		OTA		√	X	X
		45	chemical agents	→	*see substance of interest*			→	→	→

(*continued on next page*)

Table 1 (*continued*)

Stressor categories		Individual stressors		Biomarker of Exposure			Availability		
No.		No.	(alphabetically by stressor category)	No.	(alphabetically by individual stressor)		R	E	BE
9	water contamination	46	DBPs	117	TCAA		√	X	X
		47	THMs	118	BDCM		√	X	√
				119	bromoform		√	X	√
				120	chloroform		√	X	√
				121	DBCM		√	X	√
10	noise	48	noise	X	*no BoE available*		X	X	X
11	DNA-damaging agents	49	AAs	122	m^7Gua		√	X	X
				123	nitrosamines	Σnitrosamines	√	X	X
				124		NSAR	X	X	X
				125	NNAL		√	X	X
				126	NNK		√	X	X
				127	NOC		√	X	X
		50	EMF	X	*no BoE available*		X	X	X
		51	Rn	X	*no BoE available*		X	X	X
		52	UVR	128	thymine dimers		√	X	X
12	occupational hazards	53	biological	→	*see substance of interest*		→	→	→
		54	chemical	→	*see substance of interest*		→	→	→
		55	mechanical	X	*no BoE available*		X	X	X
		56	physical	X	*no BoE available*		X	X	X
		57	psychological	X	*no BoE available*		X	X	X
13	cultural factors	58	alcohol consumption	129	ethanol		X	X	X
		59	consumer products	X	*no BoE available*		X	X	X
		60	drug consumption	→	*see substance of interest*		→	→	→
		61	nutritional status	→	*see substance of interest*		→	→	→
				130	folate		√	X	X
				131	vitamin C		√	X	X
		62	physical activity	132	ammonia		√	X	X
				133	creatinine		√	X	X
				134	lactate		√	X	X
		63	SES	X	*no BoE available*		X	X	X
		64	stress	135	cortisol		√	√	X

Abbreviations: √, available; X, not available; →, see substance of interest. * same BoE for more than one stressor; No., number (*used to count the number of stressor categories, individual stressors, and biomarkers included in this manuscript*), R, reference values; E, exposure limit values; BE, biomonitoring equivalent. *Abbreviations of stressor groups and biomarkers are explained in the list of abbreviations at the end of the manuscript.*

paper. The paper focuses on the availability of BoE in body fluids (blood/serum/plasma, breast milk, urine) as well as hair. Presented are reference values, exposure limit values and biomonitoring equivalents (BEs). If available, the reference value (RV_{95}) as defined by the Human Biomonitoring Commission of the German Environment Agency (Schulz et al., 2007) on the basis of a guideline from the International Union of Pure and Applied Chemistry (IUPAC) (Poulsen et al., 1997) is presented. If not available, the 95th percentile (P_{95}) was included as reference value. Otherwise, the third choice was the 90th percentile and the fourth choice was (the range of) measures of central tendency (MCT) like mean or median presented in combination with the maximum value, if available. Condensed values for a population (distinguished in children and adults) were preferred (e.g., P_{95} for adults aged 18–69 years) instead of values separated by subgroup (e.g., P_{95} for 18–19 years old, P_{95} for 20–29 years old, etc.). If a condensed value is not given in the original publication, the range of youngest to oldest is presented in this paper. Values based on the general population are preferred instead of subgroups with special exposures (e.g. like smokers, people with amalgam fillings or high fish consumption). Latest values are presented. Non-creatinine-corrected values are preferred, if available. For reference values, the main – but not exclusive – focus lay on populations in the EU.

The first choice of exposure limit values was the German HBM values (HBM I and II). Otherwise, critical concentrations, cut-offs or other values are included. Some examples of occupational exposure limit values (e.g., BAT) were included. Completeness was not intended. Stressors without measurable BoE are explicitly discussed. All content was updated to at least January 2017 or later as appropriate.

3. Results

A total of 64 chemical, biological, physical, social, or psychological stressors organized in 13 broad stressor categories were selected (Table 1) to fulfil the requirements of EWAS, although the BoEs for some exposure determinants/modifiers (e.g., socioeconomic status) were not expected to be available. In total, information of 135 BoE is summarized. If available, reference values (Table 2), exposure limit values (Table 3), and biomonitoring equivalents (Table 4) are presented. From the complete list of individual stressors (Table 1), 12 were identified without a BoE. These stressors (and some summarized groups of stressors like psychological occupational hazards) are included in Table 5 to discuss opportunities other than HBM to collect information about their internal exposure.

Table 1 includes the stressor categories and stressors with available BoEs as well as – if available – an incomplete selection of corresponding reference values. Reference values were found for 104 of the 135 considered BoEs. Table 3 contains exposure limit values and Table 4 BEs by stressor, when available. Exposure limit values are available for 16 of the 130 considered BoEs. BEs are available for not more than 42 of the 130 BoEs considered.

4. Discussion

Specific BoEs are available for several environmental stressors but not for others. While chemicals and their primary metabolites may be measureable in human specimens, it is not possible at this time to identify BoEs for stressors such as electromagnetic fields or for exposure determinants/modifiers such as socioeconomic status using

Table 2
Biomarkers of exposure and reference values.

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
POPs						
BFRs	ΣPBDEs	serum	MCT (median): 2.1-15.4 ng/g lipid	Population (*age not specified*; n: 1667), several EU countries (Belgium, France, Greece, Norway, Spain, Sweden, United Kingdom)	1994-2004	(Gari and Grimalt, 2013)
			P_{90}: 34.6 ng/g lipid	Adults (18-74 years; n: 731), Catalonia/Spain	2002	(Gari and Grimalt, 2013)
	BDE-99	serum	MCT (median): 0.08-2.4 ng/g lipid	Population (*age not specified*; n: 1667), several EU countries (Belgium, France, Greece, Norway, Spain, Sweden, United Kingdom)	1994-2004	(Gari and Grimalt, 2013)
			P_{90}: 5.2 ng/g lipid	Adults (18-74 years; n: 731), Catalonia/Spain	2002	(Gari and Grimalt, 2013)
dioxins and furans	dioxin-like compounds					
	CYP1A1	peripheral blood lymphocytes	/	/	/	(Päpke et al., 2011; Saurat et al., 2012; Van Duursen et al., 2010)
	GGT	serum	Reference limit (#): 4-27 U/L	Children (6-10 years; n: about 1000), Italy	1976-1982	(Mocarelli et al., 1986)
	PCDD and PCDF	breast milk	MCT (mean): 3.3-22.3 pg/g fat WHO-TEQ	*Subgroup not specified* (*age not specified*; *sample size not specified*), 27 countries (among others: Fiji [lower value], Egypt [upper value])	*Survey year not specified*	(Costopoulou et al., 2006)
		serum	MCT (mean): 6.8-37 pg/g fat WHO-TEQ	*Subgroup not specified* (*age not specified*; *sample size not specified*), 10 countries (among others: Greece [lower value], Finland [upper level])	*Survey year not specified*	(Costopoulou et al., 2006)
			AM: 6.9-28.6 pg WHO-TEQ g^{-1} lipid (##) (Max: 88.1 pg WHO-TEQ g^{-1} lipid)	Adults (24-76 years; n: 126), Slovak Republic	2006-2007	(Chovancova et al., 2012)
	TCDD					
	Bile acids	24-h urine	/	/	/	(Jeanneret et al., 2014)
	steroids	24-h urine	/	/	/	(Jeanneret et al., 2014)
OCPs	β-HCH	serum	P_{95}: 190 ng/g	Adults (18-74 years; n: 386), France	2006-2007	(InVS, 2010)
		whole blood	P_{95}: 0.1 µg/l	Children (7-14 years; 1,063), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009)
			MCT (median): 12-860 ng/g lipid	Adults (*age not specified*; n: 47-2824), several EU countries (Belgium, Czech Republic, Germany, Italy, Romania, Slowakia, Spain, Sweden, UK)	1992-2009	(Gari et al., 2014)
		whole blood	P_{95}: 0.1-0.3 µg/l (§)	Children (7-14 years; n: 1063), Germany	2003-2006	(Schulz et al., 2009; Schulz et al., 2011)
			P_{95}: 0.3-0.9 µg/l (##)	Adults (18-69 years; n: 2749), Germany	1997-1999	(Schulz et al., 2011; Wilhelm et al., 2003)
		breast milk	P_{95}: 0.07 mg/kg fat	Breast-feeding women (*age not specified; sample size not specified*), Germany	2004-2005	(Schulz et al., 2011)
	ΣDDTs	breast milk	RV_{95}: 0.5 mg/kg fat	Breast-feeding women (*age not specified; sample size not specified*), West Germany	2003-2005	(HBM-UBA, 2008; Schulz et al., 2011)
	DDE	blood	RV_{95}: 0.7 µg/l	Children (7-14 years; n: 942), West Germany	2003-2006	(Schulz et al., 2009)
			RV_{95}: 1.5-11 µg/l (##)	Adults (18-69 years; n: 2290), West Germany	1997-1999	(Schulz et al., 2012; Wilhelm et al., 2003)
			RV_{95}: 1.4 µg/l	Children (7-14 years; n: 137), East Germany	2003-2006	(Schulz et al., 2009)
			RV_{95}: 3.0-31.0 µg/l (##)	Adults (18-69 years; n: 535), East Germany	1997-1999	(Schulz et al., 2012; Wilhelm et al., 2003)
		serum	P_{95}: 730 ng/g lipid	Adults (18-74 years; n: 386), France	2006-2007	(InVS, 2010)
			MCT (median): 100-2500 ng/g lipid	Adults (*age not specified*; n: 47-2824), several EU countries (Belgium, Czech Republic, Germany, Italy, Romania, Slowakia, Spain, Sweden, UK)	1992-2009	(Gari et al., 2014)
	DDT + DDE	serum	/	/	/	/
	HCB	breast milk	P_{95}: 0.06 mg/kg fat	Breast-feeding women (*age not specified; sample size not specified*), Germany	2004-2005	(HBM-UBA, 2008; Schulz et al., 2011)
		plasma	P_{95}: 0.13 µg/l	Students (*age not specified*; n: 116), Germany (Ulm)	2010	(UBA, 2017)
			P_{95}: 0.14 µg/l	Students (*age not specified*; n: 111), Germany (Münster)	2010	(UBA, 2017)
			P_{95}: 0.32 µg/l	Students (*age not specified*; n: 113), Germany (Greifswald)	2010	(UBA, 2017)

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
			P_{95}: 0.18 µg/l	Students (*age not specified*; n: 104), Germany (Halle/Saale)	2010	(UBA, 2017)
		serum	P_{95}: 73 ng/g lipid	Adults (18-74 years; n: 386), France	2006-2007	(InVS, 2010)
			MCT (median): 11-2400 ng/g lipid	Population (*age not specified*; n: 47-2824), several EU countries (Belgium, Czech Republic, Germany, Italy, Romania, Slowakia, Spain, Sweden, UK)	1992-2009	(Gari et al., 2014)
		whole blood	P_{95}: 0.1, 0.2 or 0.3 µg/l (***)	Children (7-14 years; n: 1,079), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009; Schulz et al., 2011; Schulz et al., 2012)
			P_{95}: 0.4-5.8 µg/l (##)	Adults (18-69 years; n: 2824), Germany	1997–1999	(Schulz et al., 2011; Schulz et al., 2012; Wilhelm et al., 2003)
PCBs	ΣPCB 138, 153, 180	whole blood	P_{95}: 1 µg/l	Children (7-14 years; n: 1079), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009)
			RV_{95}: 1.1-7.8 µg/l (##)	Adults (18-69 years; n: 2816), Germany	1997-1999	(Schulz et al., 2011; Wilhelm et al., 2003)
		breast milk	RV_{95}: 0.5 mg/kg fat	Breast-feeding women (*age not specified; sample size not specified*), West Germany	2003-2005	(HBM-UBA, 2008; Schulz et al., 2011)
		plasma	P_{95}: 0.73-0.82 µg/l (##)	Children (6-17 years; n: 601), Germany	2010-2014	(Schettgen et al., 2015)
			P_{95}: 0.88-4.82 µg/l (##)	Adults (18-65 years; n: 2317), Germany	2010-2014	(Schettgen et al., 2015)
		serum	P_{95}: 720 ng/g lipid	Adults (18-74 years; n: 386), France	2006-2007	(InVS, 2010)
	dioxin-like PCBs	breast milk	MCT (mean): 1.8-20.0 pg/g fat WHO-TEQ	*Subgroup not specified* (*age not specified*; *sample size not specified*), 27 countries (among others: Fiji [lower value], Ukraine [upper value])	*Survey year not specified*	(Costopoulou et al., 2006)
		serum	MCT (mean): 1.2-6.4 pg/g fat WHO-TEQ	*Subgroup not specified* (*age not specified*; *sample size not specified*), 10 countries (among others: Greece [lower value], New Zealand [upper value],	*Survey year not specified*	(Costopoulou et al., 2006)
			AM: 13.6-47.5 pg WHO-TEQ g^{-1} lipid (#) (Max: 220 pg WHO-TEQ g^{-1} lipid)	Adults (24-74 years; n: 126), Slovak Republic	2006-2007	(Chovancova et al., 2012)
	indicator PCBs	breast milk	MCT (mean): 17-502 ng/g fat	*Subgroup not specified* (*age not specified*; *sample size not specified*), 27 countries (among others: Fiji [lower value], Czech Republic [upper value]	*Survey year not specified*	(Costopoulou et al., 2006)
	PCB 28	whole blood	P_{95}: < 0.1 µg/l (*)	Children (7-14 years; n: 1079), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009)
	PCB 52	whole blood	P_{95}: < 0.1 µg/l (*)	Children (7-14 years; n: 1079), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009)
	PCB 101	whole blood	P_{95}: < 0.1 µg/l (*)	Children (7-14 years; n: 1079), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009)
PFC	PFOA	plasma	Preliminary P_{95}: 10 µg/l	Children (6 years; n: 80), Germany	2003-2006	(Wilhelm et al., 2009)
			Preliminary P_{95}: 10 µg/l	Males (5-77 years; n: 342), Germany	2003-2006	(Wilhelm et al., 2009)
			Preliminary P_{95}: 10 µg/l	Females (5-84; n: 317), Germany	2003-2006	(Wilhelm et al., 2009)
		serum	MCT (mean): 4-20 µg/l	Population (*age not specified*; *sample size not specified*), several European countries	*Survey year not specified*	(Stahl et al., 2011)
			GM: 0.716 ng/ml (Max: 8.97 ng/ml)	Adults (18-65 years; n: 300) Czech Republic	2015	(Sochorova et al., 2017)
			Mean:1.92-3.88 ng/ml^{-1} (###) (Max:10.21 ng/ml)	Adults (15-89 years; n: 142), Greece	2009	(Vassiliadou et al., 2010)
		cord blood serum	GM: 1.19 µg/l	Children (newborns; n: 269), Belgium	2012-2015	(Schoeters et al., 2016)

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
	PFOS	plasma	Preliminary P_{95}: 10 µg/l	Children (6 years old; n: 170), Germany	2003-2006	(Wilhelm et al., 2009)
			Preliminary P_{95}: 25 µg/l	Males (5-77 years; n: 443), Germany	2003-2006	(Wilhelm et al., 2009)
			Preliminary P_{95}: 15 µg/l	Females (5-84 years; n: 539), Germany	2003-2006	(Wilhelm et al., 2009)
		serum	MCT (mean): 4-55 µg/l	Population (*age not specified*; *sample size not specified*), several European countries (e.g., Italy [lower value], Poland [upper value])	*Survey year not specified*	(Stahl et al., 2011)
			GM: 2.29 ng/ml (Max: 51.1 ng/ml)	Adults (18-65 years; n: 300), Czech Republic	2015	(Sochorova et al., 2017)
			Mean: 7.49-14.93 ng/ml (###) (Max: 40.36 ng/ml)	Adults (24-87 years; n: 142), Greece	2009	(Vassiliadou et al., 2010)
		cord blood serum	GM: 1.10 µg/l	Children (newborns; n: 269), Belgium	2012-2015	(Schoeters et al., 2016)
other organic contaminants						
bisphenols	ΣBPA	24-h urine	Average concentration: 1-3 µg/l	Population (*age not specified*; *sample size not specified*), several cohorts from Japan, USA	*Survey year not specified*	(Dekant and Volkel, 2008)
		spot urine	Median: 1.51 µg/l	General adults (51 ± 12 years, n: 122), Cyprus	*2013-2014*	(Andrianou et al., 2016)
			Median: 3.78 µg/l	General adults (47 ± 13 years, n: 90), Romania	*2014-2015*	(Andrianou et al., 2016)
		24-h urine	P_{95}: 7.07 µg/l	Students (*age not specified*; n: 60), Germany (Münster)	2009	(UBA, 2017)
		first morning urine	P_{95}: 30 µg/l	Children (3-5 years; n: 137), Germany	2003-2006	(HBM-UBA, 2012)
			P_{95}: 15 µg/l	Children (6-14 years; n: 462), Germany	2003-2006	(HBM-UBA, 2012)
			P_{95}: 7 µg/l	Adults (20-29 years; n: 600), Germany	1995-2009	(HBM-UBA, 2012)
			P_{95}: 13.1 µg/l	Children (5-12 years, n: 653), several European countries (Belgium, Denmark, Luxembourg, Slovenia, Spain, Sweden)	2011-2012	(Covaci et al., 2015)
			P_{95}: 11.1 µg/l	Mothers (*age not specified*; n: 639), several European countries (Belgium, Denmark, Luxembourg, Slovenia, Spain, Sweden)	2011-2012	(Covaci et al., 2015)
OPPs	DAP					
	DEDTP	first morning urine	RV_{95}: < 0.3 µg/l (§§)	Children (3-14 years, n: 599), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009)
	DETP	first morning urine	RV_{95}: 10 µg/l	Children (3-14 years, n: 599), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009; Schulz et al., 2011)
		urine (*not further specified*)	P_{95}: 6.53 µg/g crea.	Adults (18-74 years; n: 392), France	2006-2007	(InVS, 2010)
	Diethyl phosphate	first morning urine	RV_{95}: 30 µg/l	Children (3-14 years, n: 599), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009; Schulz et al., 2011)
			RV_{95}: 16 µg/l	General population (children and adults; *age not specified*; n: 1149), Germany	1998	(HBM-UBA, 2003; Heudorf et al., 2006; Schulz et al., 2011)
		urine (*not further specified*)	P_{95}: 15.91 µg/g crea.	Adults (18-74 years; n: 392), France	2006-2007	(InVS, 2010)
	DMDTP	first morning urine	RV_{95}: 10 µg/l	Children (3-14 years, n: 599), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009)
	DMP	first morning urine	P_{95}: 75 µg/l	Children (3-14 years; n: 599), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009; Schulz et al., 2011)
		spot urine	P_{95}: 135 µg/l	General population (children and adults; *age not specified*; n: 1149), Germany (Frankfurt/Main)	1998	(HBM-UBA, 2003; Heudorf and Angerer, 2001; Heudorf et al., 2006; Schulz et al., 2011)
	DMTP	first morning urine	RV_{95}: 100 µg/l	Children (3-14 years; n: 599), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009; Schulz et al., 2011)

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
		spot urine	RV_{95}: 160 µg/l	General population (children and adults; *age not specified*; n: 1149), Germany	1998	(HBM-UBA, 2003; Heudorf and Angerer, 2001; Heudorf et al., 2006; Schulz et al., 2011)
			P_{95}: 37 µg/l	General population (6-79 years; n: 2559), Canada	2009-2011	(Health Canada, 2013)
		urine (*not further specified*)	P_{95}: 48.74 µg/g crea.	Adults (18-74 years; n: 392), France	2006-2007	(InVS, 2010)
		morning urine *(not specified if first morning urine)*	P_{95}: 124 µg/l	Children (2-17 years; n: 363), Germany	2001-2002	(Becker et al., 2006)
		first morning urine	P_{95}: 23.83 µg/g crea.	Children (6-11 years; n: 125), Spain (Valencia)	2010	(Roca et al., 2014)
		spot urine	P_{95}: 210.9 µg/l	Children (3-7 years; n: 89), Canada (Quebec)	2003	(Health Canada, 2013; Valcke et al., 2006)
			Median: 99.3 nmol/g crea. (Max: 1526.0 nmol/g crea.)	Children (6-7 years; n: 195), Italy (Siena)	1995	(Aprea et al., 2000)
			P_{95}: 62.0 µg/l	Children (6-11 years, n: 471), USA	1999-2000	(Barr et al., 2004)
			P_{95}: 69.0 µg/l	Adolescents (12-19 years, n: 664), USA	1999-2000	(Barr et al., 2004)
			P_{95}: 38.0 µg/l	Adults (20-59 years, n: 814), USA	1999-2000	(Barr et al., 2004)
PAHs	1-hydroxypyrene	morning urine	RV_{95}: 0.5 µg/l	Non-smoking adults (18-69 years; n: 389), Germany	1997-1999	(Wilhelm et al., 2008)
			RV_{95}: 0.5 µg/l	Non-smoking children (3-14 years; n: 571), Germany	2003-2004	(Wilhelm et al., 2008)
		urine (*not further specified*)	P_{95}: 730 ng/l	Population (≥6 years; n: 2312), USA	1999-2000	(Grainger et al., 2006)
	fluoranthene 3-hydroxyfluoranthene	urine (*not further specified*)	P_{95}: 98.8 ng/l	Population (≥6 years; n: 2236), USA	1999-2000	(Grainger et al., 2006)
	fluorene					
	2-hydroxyfluorene	urine (*not further specified*)	P_{95}: 6450 ng/l	Population (≥6 years; n: 2315), USA	1999-2000	(Grainger et al., 2006)
	3-hydroxyfluorene	urine (*not further specified*)	P_{95}: 3390 ng/l	Population (≥6 years; n: 2312), USA	1999-2000	(Grainger et al., 2006)
	naphthalene	spot urine (sampled three times during a week)	P_{95} (geometric mean of three determinations): 266 ng/l	General population (19 to 75 years; n: 100), Italy (Milan)	2007-2008	(Fustinoni et al., 2010)
	1-naphthol	spot urine	P_{95}: 108.0 nmol/l	General adults (> 18 years; n: 298), UK	2006	(IEH, 2008)
		morning urine	P_{95}: 10.7-29.9 µg/l	Non-smoking general population (2.5-51 years; n = 259), 4 cohorts from Germany	*Survey year not specified*	(Preuss et al., 2004; Wilhelm et al., 2008)
	2-naphthol	spot urine	P_{95}: 81.0 nmol/l	General adults (> 18 years; n: 298), UK	2006	(IEH, 2008)
		morning urine	P_{95}: 6.5-17.1 µg/l	Non-smoking general population (2.5-51 years; n = 259), 4 cohorts from Germany	*Survey year not specified*	(Preuss et al., 2004; Wilhelm et al., 2008)
	phenanthrene					
	1-hydroxyphenanthrene	urine (*not further specified*)	P_{95}: 1070 ng/l	Population (≥6 years; n: 2246), USA	1999-2000	(Grainger et al., 2006)
	2-hydroxyphenanthrene	urine (*not further specified*)	P_{95}: 828 ng/l	Population (≥6 years; n: 2179), USA	1999-2000	(Grainger et al., 2006)
	3-hydroxyphenanthrene	urine (*not further specified*)	P_{95}: 657 ng/l	Population (≥6 years; n: 2299), USA	1999-2000	(Grainger et al., 2006)
Parabens	Methyl parabens	spot urine	P_{95}: 974 µg/l	General population (≥6 years; n: 2548), USA	2005-2006	(Calafat et al., 2010)
	Propyl parabens	spot urine	P_{95}: 299 µg/l	General population (≥6 years; n: 2548), USA	2005-2006	(Calafat et al., 2010)
	Butyl parabens	spot urine	P_{95}: 19.6 µg/l	General population (≥6 years; n: 2548), USA	2005-2006	(Calafat et al., 2010)
	Ethyl parabens	spot urine	P_{95}: 57.2 µg/l	General population (≥6 years; n: 2548), USA	2005-2006	(Calafat et al., 2010)
Phthalates	DEHP					

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
	5OH-MEHP	spot urine	P_{95}: 146.0 nmol/l	General adults (> 18 years; n: 337), UK	2006	(IEH, 2008)
	5oxo-MEHP	spot urine	P_{95}: 230.0 nmol/l	General adults (> 18 years; n: 337), UK	2006	(IEH, 2008)
	DEP	urine	/	/	/	(Koch and Angerer, 2012)
	MEP	urine	/	/	/	(Koch and Angerer, 2012)
	DiBP	urine	/	/	/	(Koch and Angerer, 2012)
	DiNP	urine	/	/	/	(Koch and Angerer, 2012)
	DnBP	urine	/	/	/	(Koch and Angerer, 2012)
	MnBP	urine	/	/	/	(Koch and Angerer, 2012)
PYR						
	ΣPYR ([§§§])	breast milk	Mean: 4.89 ng/g^{-1} lipid weight (Max: 7.79 ng/g^{-1} lipid weight)	Mothers (*age not specified*; n: 6), Spain	2009	(Corcellas et al., 2012)
	3PBA	spot urine	P_{95}: 28.3 nmol/l	General adults (> 18 years; n: 336), UK	2006	(IEH, 2008)
		urine (*not further specified*)	P_{95}: 3.48 µg/g crea.	Adults (18-74 years; n: 396), France	2006-2007	(InVS, 2010)
		first morning urine	RV_{95}: 2 µg/l	General population (children and adults; *age not specified*; n: 1149), Germany	1998	(HBM-UBA, 2003; Heudorf et al., 2006; Schulz et al., 2011)
		first morning urine	RV_{95}: 2 µg/l	Children (3-14 years; n: 598), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2011)
		spot urine	P_{95}: 28.3 nmol/l	General adults (> 18 years; n: 336), UK	2006	(IEH, 2008)
	cyfluthrin					
	cis-Cl_2CA [*also a biomarker for* deltamethrin]	spot urine	P_{95}: 3.8 nmol/l	General adults (> 18 years; n: 336), UK	2006	(IEH, 2008)
		urine (*not further specified*)	P_{95}: 1.24 µg/g crea.	Adults (18-74 years; n: 396), France	2006-2007	(InVS, 2010)
	cis-Cl2CA & trans-Cl_2CA [*also a biomarker for* deltamethrin]	spot urine	P_{95}: 10.4 nmol/l	General adults (> 18 years; n: 92), UK	2006	(IEH, 2008)
	trans-Cl_2CA [*also a biomarker for* deltamethrin]	spot urine	P_{95}: 7.7 nmol/l	General adults (> 18 years; n: 335), UK	2006	(IEH, 2008)
		urine (*not further specified*)	P_{95}: 2.64 µg/g crea.	Adults (18-74 years; n: 396), France	2006-2007	(InVS, 2010)
deltamethrin						
	Br_2CA	spot urine	P_{95}: 5.3 nmol/l	General adults (> 18 years; n: 336), UK	2006	(IEH, 2008)
		urine (*not further specified*)	P_{95}: 2.18 µg/g crea.	Adults (18-74 years; n: 396), France	2006-2007	(InVS, 2010)
	cis-Cl_2CA [*also a biomarker for* cyfluthrin]	spot urine	P_{95}: 3.8 nmol/l	General adults (> 18 years; n: 336), UK	2006	(IEH, 2008)
		urine (*not further specified*)	P_{95}: 1.24 µg/g crea.	Adults (18-74 years; n: 396), France	2006-2007	(InVS, 2010)
	cis-Cl2CA & trans-Cl_2CA [*also a biomarker for* cyfluthrin]	spot urine	P_{95}: 10.4 nmol/l	General adults (> 18 years; n: 92), UK	2006	(IEH, 2008)
	trans-Cl_2CA [*also a biomarker for* cyfluthrin]	spot urine	P_{95}: 7.7 nmol/l	General adults (> 18 years; n: 335), UK	2006	(IEH, 2008)
		urine (*not further specified*)	P_{95}: 2.64 µg/g crea.	Adults (18-74 years; n: 396), France	2006-2007	(InVS, 2010)
toxic and potential toxic elements						
As	As	24-h urine	P_{95}: 41.9 µg/l	Students (*age not specified*; n: 126), Germany (Münster)	2016	(UBA, 2017)
			P_{95}: 46.4 µg/l	Students (*age not specified*; n: 132), Germany (Greifswald)	2016	(UBA, 2017)
			P_{95}: 57.7 µg/l	Students (*age not specified*; n: 118), Germany (Halle/Saale)	2016	(UBA, 2017)
			P_{95}: 32.6 µg/l	Students (*age not specified*; n: 131), Germany (Ulm)	2016	(UBA, 2017)

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
		first morning urine	P_{95}: 18.9 µg/l	General adults (18-96 years, n: 4741), Germany	1997-1999	(Wilhelm et al., 2004)
			RV_{95}: 15.0 µg/l	Adults who did not eato fish 48 h before sample collection (18-69 years; n: 3924), Germany	1997-1999	(Schulz et al., 2011; Wilhelm et al., 2004)
			P_{95}: 14.0 µg/l	Children (3-14 years; n: 1734), Germany	2003-2006	(Becker et al., 2008)
			RV_{95}: 15.0 µg/l	Children who did not eat fish 48 h before sample collection (3-14 years; n: 1487), Germany	2003-2006	(Schulz et al., 2009; Schulz et al., 2011)
		urine (*not further specified*)	P_{95}: 61.3 µg/g crea.	Adults (18-74 years; n: 1515), France	2006-2007	(InVS, 2010)
Cd	Cd	24-h urine	P_{95}: 0.23 µg/l	Students (*age not specified*; n: 126), Germany (Münster)	2016	(UBA, 2017)
			P_{95}: 0.28 µg/l	Students (*age not specified*; n: 132), Germany (Greifswald)	2016	(UBA, 2017)
			P_{95}: 0.29 µg/l	Students (*age not specified*; n: 118), Germany (Halle/Saale)	2016	(UBA, 2017)
			P_{95}: 0.25 µg/l	Students (*age not specified*; n: 131), Germany (Ulm)	2016	(UBA, 2017)
		first morning urine	RV_{95}: 0.2 µg/l	Non-smoking children (3-14 years; n: 1667), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009; Schulz et al., 2011)
			RV_{95}: 0.8 µg/l	Non-smoking adults (18-69 years; n: 3128), Germany	1997-1999	(Schulz et al., 2011; Wilhelm et al., 2004)
		spot urine	P_{95}: 7.9 nmol/l	General adults (> 18 years; n: 362), UK	2006	(IEH, 2008)
		blood	RV_{95}: < 0.3 µg/l	Non-smoking children (3-14 years; n: 1498), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2009; Schulz et al., 2011)
			RV_{95}: 1.0 µg/l	Non-smoking adults (18-69 years; n: 3061), Germany	1997-1999	(Wilhelm et al., 2004)
Cr	Cr	blood	RI: 0.7-28.0 µg/l	Population (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
		24-h urine	Reference value(**): < 0.2 µg/l	Population (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
		serum	RI: 0.1-0.2 µg/l	Population (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
Cu	Cu	24-h urine	P_5-P_{95}: 3.63-13.9 µg/l	Students (*age not specified*; n: 126), Germany (Münster)	2016	(UBA, 2017)
			P_5-P_{95}: 4.01-14.9 µg/l	Students (*age not specified*; n: 132), Germany (Greifswald)	2016	(UBA, 2017)
			P_5-P_{95}: 3.22-13.4 µg/l	Students (*age not specified*; n: 118), Germany (Halle/Saale)	2016	(UBA, 2017)
			P_5-P_{95}: 2.72-13.4 µg/l	Students (*age not specified*; n: 131), Germany (Ulm)	2016	(UBA, 2017)
		plasma	P_5-P_{95}: 0.70-1.84 µg/l	Students (*age not specified*; n: 125), Germany (Münster)	2016	(UBA, 2017)
			P_5-P_{95}: 0.75-2.12 mg/l	Students (*age not specified*; n: 131), Germany (Greifswald)	2016	(UBA, 2017)
			P_5-P_{95}: 0.70-1.89 mg/l	Students (*age not specified*; n: 118), Germany (Halle/Saale)	2016	(UBA, 2017)
			P_5-P_{95}: 0.70-1.89 mg/l	Students (*age not specified*; n: 132), Germany (Ulm)	2016	(UBA, 2017)
		serum	RI: 70-140 µg/dl	Men (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
			RI: 80-155 µg/dl	Women (*age not specified*; *sample size not specified*), *country not specified*		

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
Hg	Hg	24-h urine	P_{95}: 0.23 µg/l	Students (*age not specified*; n: 126), Germany (Münster)	2016	(UBA, 2017)
			P_{95}: 0.37 µg/l	Students (*age not specified*; n: 132), Germany (Greifswald)	2016	(UBA, 2017)
			P_{95}: 0.36 µg/l	Students (*age not specified*; n: 118), Germany (Halle/Saale)	2016	(UBA, 2017)
			P_{95}: 0.22 µg/l	Students (*age not specified*; n: 132), Germany (Ulm)	2016	(UBA, 2017)
		hair	P_{95}: 1.9 µg/g	Mothers (< 45 years; n: 1839), Europe (Belgium, Switzerland, Cyprus, Czech Republic, Germany, Denmark, Spain, Hungary, Ireland, Luxemburg, Poland, Portugal, Romania, Sweden, Slovenia, Slovac Republic, UK)	2011-2012	(Den Hond et al., 2015)
			P_{95}: 1.3 µg/g	Children (5-11 years; n: 1836), Europe (Belgium, Switzerland, Cyprus, Czech Republic, Germany, Denmark, Spain, Hungary, Ireland, Luxemburg, Poland, Portugal, Romania, Sweden, Slovenia, Slovac Republic, UK)	2011-2012	(Den Hond et al., 2015)
			P_{95}: 1.8 µg/g	Adults (18-74 years; n: 365), France	2006-2007	(InVS, 2010)
			P_{95}: 1.2 µg/g	Children (3-17 years; n: 1364), France	2006-2007	(InVS, 2010)
		blood	RV_{95}: 0.8 µg/l	Children who ate fish ≤ 3 times per month (3-14 years; n: 891), Germany	2003-2006	(Schulz et al., 2009; Schulz et al., 2011)
			RV_{95}: 2.0 µg/l	Adults who ate fish ≤ 3 times per month (18-69 years; n: 2310), Germany	1997-1999	(Wilhelm et al., 2004)
		first morning urine	RV_{95}: 0.4 µg/l	Children without amalgam fillings (3-14 years; n: 1612), Germany	2003-2006	(Schulz et al., 2009; Schulz et al., 2011)
			RV_{95}: 1.0 µg/l	Adults without amalgam fillings (18-69 years; n: 1560), Germany	1997-1999	(Wilhelm et al., 2004)
			P_{95}: 15 nmol/l	General adults (> 18 years; n: 362), UK	2006	(IEH, 2008)
Mn	Mn	blood	RI: 5-15 µg/l	(*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
		serum	RI: 0.5-1.3 µg/l	(*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
		urine (*not further specified*)	RI: 0.5-9.8 µg/l	(*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
Pb	Pb	blood	RV_{95}: 35 µg/l	Children (3-14 years; n: 1560), Germany	2003-2006	(Schulz et al., 2009; Schulz et al., 2011)
			RV_{95}: 70 µg/l	Women (18-69 years; n: 2303), Germany	1997-1999	(Schulz et al., 2011; Wilhelm et al., 2004)
			RV_{95}: 90 µg/l	Men (18-69 years; n: 2342), Germany	1997-1999	(Schulz et al., 2011; Wilhelm et al., 2004)
			P_{95}:18.5 µg/l	Students (*age not specified*; n: 126), Germany (Münster)	2016	(UBA, 2017)
			P_{95}: 26.4 µg/l	Students (*age not specified*; n: 132), Germany (Greifswald)	2016	(UBA, 2017)
			P_{95}: 22.5 µg/l	Students (*age not specified*; n: 116), Germany (Halle/Saale)	2016	(UBA, 2017)
			P_{95}: 21.8 µg/l	Students (*age not specified*; n: 130), Germany (Ulm)	2016	(UBA, 2017)
Se	Se	blood	RI: 60-120 µg/l (females); 79-130 µg/l (males)	General population (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Wilhelm et al., 2004)
		plasma	P_5-P_{95}: 68.2-109 µg/l	Students (*age not specified*; n: 125), Germany (Münster)	2016	(UBA, 2017)
			P_5-P_{95}: 69.6-111 µg/l	Students (*age not specified*; n: 131), Germany (Greifswald)	2016	(UBA, 2017)
			P_5-P_{95}: 64.6-109 µg/l	Students (*age not specified*; n: 118), Germany (Halle/Saale)	2016	(UBA, 2017)
			P_5-P_{95}: 70.8-114 µg/l	Students (*age not specified*; n: 132), Germany (Ulm)	2016	(UBA, 2017)
		serum	RI: 16-71 µg/l	Children (< 2 years;; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
			RI: 40-103 µg/l	Children (2-4 years; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
			RI: 55-134 µg/l	Children (4-16 years; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
			RI: 63-160 µg/l	Adults (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
Zn	Zn	24-h urine	P_5-P_{95}: 48.8-529 µg/l	Students (*age not specified*; n: 126), Germany (Münster, Ulm)	2016	(UBA, 2017)

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
			P_5-P_{95}: 55.8-527 µg/l	Students (*age not specified*; n: 132), Germany (Greifswald)	2016	(UBA, 2017)
			P_5-P_{95}: 54.2-559 µg/l	Students (*age not specified*; n: 118), Germany (Halle/Saale)	2016	(UBA, 2017)
			P_5-P_{95}: 50.0-603 µg/l	Students (*age not specified*; n: 131), Germany (Ulm)	2016	(UBA, 2017)
		plasma	P_5-P_{95}: 0.56-0.94 mg/l	Students (*age not specified*; n: 125), Germany (Münster)	2016	(UBA, 2017)
			P_5-P_{95}: 0.55-1.07 mg/l	Students (*age not specified*; n: 131), Germany (Greifswald)	2016	(UBA, 2017)
			P_5-P_{95}: 0.55-0.88 mg/l	Students (*age not specified*; n: 118), Germany (Halle/Saale)	2016	(UBA, 2017)
			P_5-P_{95}: 0.55-0.93 mg/l	Students (*age not specified*; n: 132), Germany (Ulm)	2016	(UBA, 2017)
		serum	RI: 80-120 µg/dl	Adults (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Burtis et al., 2012)
volatile organic compounds						
acrylamide	AAMA	urine (*not further specified*)	P_{95}: 139 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
			P_{95}: 279 µg/l	Children (12-19 years; n: 384), USA	2011-2012	(CDC, 2017)
			P_{95}: 285 µg/l	Adults (≥20 years; n: 1688), USA	2011-2012	(CDC, 2017)
	GAMA	urine (*not further specified*)	P_{95}: 50.9 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
			P_{95}: 68.0 µg/l	Children (12-19 years; n: 384), USA	2011-2012	(CDC, 2017)
			P_{95}: 64.5 µg/l	Adults (≥20 years; n: 1688), USA	2011-2012	(CDC, 2017)
benzene	benzene	blood	MCT (mean, median, or GM): 50-200 ng/l	Non-smoking general population (*age not specified*; *sample size not specified*), *countries not specified* (several cohorts)	*Survey year not specified*	(Arnold et al., 2013)
			P_{95}: 0.120 ng/ml	Children (12-19 years; n: 912), USA	2007-2008	(CDC, 2017)
			P_{95}: 0.328 ng/ml	Adults (20-59 years; n: 1445), USA	2007-2008	(CDC, 2017)
			P_{95}: 0.213 ng/ml	Adults (≥60 years; n: 814), USA	2007-2008	(CDC, 2017)
		spot urine	P_{95}: 311.5 ng/l	Non-smoking and non-occupationally exposed general population (27-78 years; n: 86), Italy	2006-2007	(Campagna et al., 2014)
		urine (*not further specified*)	MCT (mean, median, or GM): 0.10-0.25 µg/l	Non-smoking general population (*age not specified*; *sample size not specified*), *countries not specified* (several cohorts)	*Survey year not specified*	(Arnold et al., 2013)
		spot urine (sampled three times during a week)	P_{95} (geometric mean of three determinations): 1598 ng/l	General population (19 to 75 years; n: 100), Italy (Milan)	2007-2008	(Fustinoni et al., 2010)
		first morning urine	Median: 118 ng l^{-1}	General population (18-83 years; n: 48), Cyprus (Nicosia)	2013	(Tsangari et al., 2017)
	S-PMA	spot urine	P_{95}: 38.0 nmol/l	Adults (> 18 years; n: 355), UK	2006	(IEH, 2008)
		urine (*not further specified*)	MCT (mean, median, or GM): 0.5-9 µg/l	Non-smoking general population (*age not specified*; *sample size not specified*), *countries not specified* (several cohorts)	*Survey year not specified*	(Arnold et al., 2013)
cyanide	2-Aminothiazoline-4-carboxylic acid	urine (*not further specified*)	P_{95}: 911 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
			P_{95}: 583 µg/l	Children (12-19 years; n: 384), USA	2011-2012	(CDC, 2017)
			P_{95}: 483 µg/l	Adults (≥20 years; n: 1688), USA	2011-2012	(CDC, 2017)
ethylbenzene	ethylbenzene	blood	P_{95}: 0.068 ng/ml	Children (12-19 years; n: 448), USA	2007-2008	(CDC, 2017)
			P_{95}: 0.131 ng/ml	Adults (20-59 years; n: 1473), USA	2007-2008	(CDC, 2017)
			P_{95}: 0.100 ng/ml	Adults (≥60 years; n: 829), USA	2007-2008	(CDC, 2017)
		spot urine	P_{95}: 289 ng/l^{-1}	Primary school children (*age not specified*; n: 151)Italy (Treviglio)	1995	(Minoia et al., 1996)
			P_{95}: 75 ng/l^{-1}	Primary school children (*age not specified*; n: 107), Italy (Poggibonsi)	1995	(Minoia et al., 1996)
			P_{95}: 98 ng/l^{-1}	Primary school children (*age not specified*; n: 139), Italy (Valenza)	1995	(Minoia et al., 1996)
		spot urine (sampled three times during a week)	P_{95} (geometric mean of three determinations): 130 ng/l	General population (19 to 75 years; n: 100), Italy (Milan)	2007-2008	(Fustinoni et al., 2010)
		First morning urine	Median: 9.2 ng l^{-1}	General population (18-83 years; n: 48), Cyprus (Nicosia)	2013	(Tsangari et al., 2017)

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
	PGA [*also a biomarker for styrene*]	urine (*not further specified*)	P_{95}: 508 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
			P_{95}: 662 µg/l	Children (12-19 years; n: 384), USA	2011-2012	(CDC, 2017)
			P_{95}: 732 µg/l	Adults (≥20 years; n: 2466), USA	2011-2012	(CDC, 2017)
glycol ethers	MAA	24-h urine	P_{95}: 0.3 mg/l	General population (19-52 years; n: 44), Germany (Bavaria)	2007-2008	(Fromme et al., 2013; HBM-UBA, 2014)
PCP	PCP	Blood	P_{95}: 2.2 µg/l	Students (*age not specified*; n: 116,), Germany (Ulm)	2010	(UBA, 2017)
			P_{95}: 1.13 µg/l	Students (*age not specified*; n: 111), Germany (Münster)	2010	(UBA, 2017)
			P_{95}: 1.15 µg/l	Students (*age not specified*; n: 128), Germany (Greifswald)	2010	(UBA, 2017)
			P_{95}: 1.14 µg/l	Students (*age not specified*; n: 104), Germany (Halle/Saale)	2010	(UBA, 2017)
		first morning urine	RV_{95}: 5 µg/l	Adults (18-69 years; n: 691; living in homes without wood preservatives), Germany	1997-1999	(Schulz and Butte, 2007; Schulz et al., 2011)
		plasma	Mean: < 5 µg/l	Not exposed population (*age not specified*; *sample size not specified*), *Germany*	*Survey year not specified*	(Scholz 2001a)
		serum	P_{95}: 25 µg/l	Population (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Scholz 2001a)
			RV_{95}: 12 µg/l	Adults (41-65 years; n: 251), Germany	1995-1996	(HBM-UBA, 1999; Schulz et al., 2011)
		first morning urine	RV_{95}: 2.0 µg/l (*)	Children (3-14 years; n: 599), Germany	2003-2006	(Becker et al., 2008; Schulz et al., 2011)
		urine (*not further specified*)	P_{95}: < 10 µg/l	Population (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Scholz 2001a)
		24-h urine	P_{95}: 0.30 µg/l	Students (*age not specified*; n: 116), Germany (Ulm)	2010	(UBA, 2017)
			P_{95}: 0.18 µg/l	Students (*age not specified*; n: 112), Germany (Münster)	2010	(UBA, 2017)
			P_{95}: 0.16 µg/l	Students (*age not specified*; n: 128), Germany (Greifswald)	2010	(UBA, 2017)
			P_{95}: 0.17 µg/l	Students (*age not specified*; n: 105), Germany (Halle/Saale)	2010	(UBA, 2017)
PER	PER	Blood	P_{95}: < 1 µg/l	Population (*age not specified*; *sample size not specified*), *country not specified*	*Survey year not specified*	(Gratza and Kevekordes, 2001)
styrene	mandelic acid	urine (*not further specified*)	P_{95}: 384 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
			P_{95}: 421 µg/l	Children (12-19 years; n: 384), USA	2011-2012	(CDC, 2017)
			P_{95}: 638 µg/l	Adults (≥20 years; n: 1688), USA	2011-2012	(CDC, 2017)
	N-Acetyl-S-(phenyl-2-hydroxyethyl)-L-cysteine	urine (*not further specified*)	P_{95}: 3.21 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
			P_{95}: 3.50 µg/l	Children (12-19 years; n: 384), USA	2011-2012	(CDC, 2017)
			P_{95}: 3.26 µg/l	Adults (≥20 years; n: 1688), USA	2011-2012	(CDC, 2017)
	PGA [*also a biomarker for ethylbenzene*]	urine (*not further specified*)	P_{95}: 508 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
	styrene	blood	P_{95}: 0.200 ng/ml	Population (≥12 years; n: 950), USA	2001-2008	(CDC, 2017)
			P_{95}: 512 ng/l	Not occupationally exposed hospital staff and blood donors (20-58 years; n= 81), *country not specified (author team from Italy and China)*	*Survey year not specified*	(Brugnone et al., 1993)
toluene	hippuric acid	spot urine	P_{95}: 0.36 g/g crea.	Non-occupational exposed population (18-60 years; n: 115), Brazil	*Survey year not specified*	(Siqueira and Paiva, 2002)
	N-Acetyl-S-(benzyl)-L-cysteine	urine (*not further specified*)	P_{95}: 29.7 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
			P_{95}: 36.5 µg/l	Children (12-19 years; n: 384), USA	2011-2012	(CDC, 2017)
			P_{95}: 38.7 µg/l	Adults (≥20 years; n: 1688), USA	2011-2012	(CDC, 2017)
	toluene	blood	P_{95}: 0.318 ng/ml	Children (12-19 years; n: 439) USA	2007-2008	(CDC, 2017)
			P_{95}: 0.839 ng/ml	Adults (20-59 years; n: 1483) USA	2007-2008	(CDC, 2017)
			P_{95}: 0.610 ng/ml	Adults (≥60 years; n: 809) USA	2007-2008	(CDC, 2017)
			Reference value: < 1 µg/l (**)	Non-smoker (*age not specified; sample size not specified*), *country not specified*	*Survey year not specified*	(Scholz, 2001b)
		spot urine	P_{95}: 481-1361 ng/l^{-1}, depending on the city	Primary school children (age not specified; n: 107-147, depending on the city), Italy (Poggibonsi, Treviglio, Valenza)	1995	(Minoia et al., 1996)

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
		spot urine (sampled three times during a week)	P_{95} (geometric mean of three determinations): 618 ng/l	General population (19 to 75 years; n: 100), Italy (Milan)	2007-2008	(Fustinoni et al., 2010)
		First morning urine	Median: 124 ng l^{-1}	General population (18-83 years; n: 48), Cyprus (Nicosia)	2013	(Tsangari et al., 2017)
triclosan		urine (*not further specified*)	P_{95}: 124 µg/l	Children (6-11 years; n: 409), USA	2013-2014	(CDC, 2017)
			P_{95}: 224 µg/l	Children (12-19 years; n: 462), USA	2013-2014	(CDC, 2017)
			P_{95}: 420 µg/l	Adults (≥20 years; n: 1815), USA	2013-2014	(CDC, 2017)
xylene	2-MHA	urine (*not further specified*)	P_{95}: 122 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
			P_{95}: 173 µg/l	Children (12-19 years; n: 384), USA	2011-2012	(CDC, 2017)
			P_{95}: 232 µg/l	Adults (≥20 years; n: 1688), USA	2011-2012	(CDC, 2017)
	3- and 4-MHA	urine (*not further specified*)	P_{95}: 889 µg/l	Children (6-11 years; n: 394), USA	2011-2012	(CDC, 2017)
			P_{95}: 1680 µg/l	Children (12-19 years; n: 384), USA	2011-2012	(CDC, 2017)
			P_{95}: 1740 µg/l	Adults (≥20 years; n: 1688), USA	2011-2012	(CDC, 2017)
	m-, p-xylene	blood	P_{95}: 0.216 ng/ml	Children (12-19 years; n: 447), USA	2007-2008	(CDC, 2017)
			P_{95}: 0.379 ng/ml	Adults (20-59 years; n: 1520), USA	2007-2008	(CDC, 2017)
			P_{95}: 0.308 ng/ml	Adults (≥60 years; n: 854), USA	2007-2008	(CDC, 2017)
		spot urine (sampled three times during a week)	P_{95} (geometric mean of three determinations): 178 ng/l	General population (19 to 75 years; n: 100), Italy (Milan)	2007-2008	(Fustinoni et al., 2010)
		first morning urine	Median: 29 ng l^{-1}	General population (18-83 years; n: 48), Cyprus (Nicosia)	2013	(Tsangari et al., 2017)
	MHA	spot urine	P_{95}: 440.0 µmol/l	Adults (> 18 years; n: 360), UK	2006	(IEH, 2008)
			P_{95}: 94.7 mg/g crea.	Adults (> 18 years; n: 360), UK	2006	(IEH, 2008)
	o-, m-, p-xylene	spot urine	P_{95}: 230-909 ng/l^{-1}, depending on the city	Primary school children (*age not specified*; n: 96-144, depending on the city), Italy (Poggibonsi, Treviglio, Valenza)	1995	(Minoia et al., 1996)
	o-xylene	Blood	P_{95}: 0.066 ng/ml	Children (12-19 years; n: 457), USA	2007-2008	(CDC, 2017)
			P_{95}: 0.086 ng/ml	Adults (20-59 years; n: 1524), USA	2007-2008	(CDC, 2017)
			P_{95}: 0.091 ng/ml	Adults (≥60 years; n: 854), USA	2007-2008	(CDC, 2017)
		spot urine (sampled three times during a week)	P_{95} (geometric mean of three determinations): 64 ng/l	General population (19 to 75 years; n: 100), Italy (Milan)	2007-2008	(Fustinoni et al., 2010)
		first morning urine	Median: 28 ng l^{-1}	General population (18-83 years; n: 48), Cyprus (Nicosia)	2013	(Tsangari et al., 2017)
	xylene	blood	Reference value: < 1 µg/l (**)	Non-smoker (*age not specified; sample size not specified*), *country not specified*	*Survey year not specified*	(Scholz, 2001c)
pharmaceuticals						
antibiotics	*the substance of interest*	blood	/	/	/	
		urine	/	/	/	
chemotherapy	*the substance of interest*	urine	/	/	/	
smoking						
tobacco smoke	Nicotine Cotinine					
		spot urine	P_{95}: 3230 µg/l	General adults (> 18 years; n: 356), UK	2006	(IEH, 2008)
			P_{95}: 233.73 µg/g crea.	Ex-smoker (> 18 years; n: 129), UK	2006	(IEH, 2008)
			P_{95}: 43.45 µg/g crea.	Never smoker (> 18 years; n: 175), UK	2006	(IEH, 2008)
			P_{95}: 7243.47 µg/g crea.	Current smoker (> 18 years; n: 46), UK	2006	(IEH, 2008)
			P_{95}: 9162.68 µg/g crea.	Second-hand smoke exposed who shares home with smoker (> 18 years; n: 40), UK	2006	(IEH, 2008)

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
			P_{95}: 2454.59 µg/g crea.	Second-hand smoke exposed who not shares home with smoker (> 18 years; n: 313), UK	2006	(IEH, 2008)
air pollution						
bioaerosols	Mold	blood	/	/	/	(Beirao and Araujo, 2013)
	SC					
	SG	serum	/	/	/	(Yike et al., 2006)
diesel exhaust	1-HP	spot urine	P_{75}: 0.74 pmol/ml (Max.: 1.40 pmol/ml)	African American students (12-14 years; n: 24), USA (Harlem/New York City)	1997	(Northridge et al., 1999)
NO_x	NO_x	plasma	Mean: 47.5 µM/l	Healthy subjects (20-69 years; n: 738), *country not specified* (*author team from Japan)*	*Survey year not specified*	(Kawakatsu et al., 2002)
O_3	2,3-DHBA	plasma	/	/	/	(Liu et al., 1999)
food contamination	Mycotoxins					
	CIT	morning urine *(not specified if first morning urine)*	Mean: 31.4 pg/ml (Max.: 392.8 pg/ml)	Children (3-12 years; n: 155), Belgian	2013-2014	(Heyndrickx et al., 2015)
			Mean: 56.7 pg/ml (Max.: 1398.0 pg/ml)	Adults (19-65 years; n: 239), Belgian	2013-2014	(Heyndrickx et al., 2015)
	DON	24-h urine	Mean: 11.89 ng/ml (Max.: 67.36 ng/ml)	General population 3-85 years; n: 50) Italy	2011	(Solfrizzo et al., 2014)
	DON15GlcA	morning urine *(not specified if first morning urine)*	Mean: 58.4 ng/ml (Max.: 343.0 ng/ml)	Children (3-12 years; n: 155), Belgian	2013-2014	(Heyndrickx et al., 2015)
			Mean: 53.8 ng/ml (Max.: 460.8 ng/ml)	Adults (19-65 years; n: 239), Belgian	2013-2014	(Heyndrickx et al., 2015)
	OTA	morning urine *(not specified if first morning urine)*	Mean: 79.5 pg/ml (Max.: 3683.0 pg/ml)	Children (3-12 years; n: 155), Belgian	2013-2014	(Heyndrickx et al., 2015)
			Mean: 27.8 pg/ml (Max.: 368.1 pg/ml)	Adults (19-65 years; n: 239), Belgian	2013-2014	(Heyndrickx et al., 2015)
		24-h urine	Mean: 0.144 ng/ml (Max.: 2.129 ng/ml)	General population 3-85 years; n: 52) Italy	2011	(Solfrizzo et al., 2014)
Water contamination						
DBPs	TCAA	spot urine	P_{95}: 49.6 nmol/l	General adults (> 18 years; n: 330), UK	2006	(IEH, 2008)
THMs	BDCM	blood	P_{95}: 9.5 pg/ml	General population (≥20 years; n: 1322), USA	2003-2004	(LaKind et al., 2010)
		first morning urine	AM: 131 ng g^{-1} (summer), 61 ng g^{-1} (winter)	General population (18-87 years; n: 310) Cyprus (Nicosia)	2012-2013	(Andrianou et al., 2014)
	bromoform	blood	P_{95}: 7.2 pg/ml	General population (≥20 years; n: 1310), USA	2003-2004	(LaKind et al., 2010)
		first morning urine	AM: 32 ng g^{-1} (summer), 147 ng g^{-1} (winter)	General population (18-87 years; n: 310) Cyprus (Nicosia)	2012-2013	(Andrianou et al., 2014)
	chloroform	blood	P_{95}: 50.0 pg/ml	General population (≥20 years; n: 1238), USA	2003-2004	(LaKind et al., 2010)
		first morning urine	AM: 608 ng g^{-1} (summer), 243 ng g^{-1} (winter)	General population (18-87 years; n: 310) Cyprus (Nicosia)	2012-2013	(Andrianou et al., 2014)
	DBCM	blood	P_{95}: 9.5 pg/ml	General population (≥20 years; n: 1333), USA	2003-2004	(LaKind et al., 2010)
		first morning urine	AM: 77 ng g^{-1} (summer), 119 ng g^{-1} (winter)	General population (18-87 years; n: 310) Cyprus (Nicosia)	2012-2013	(Andrianou et al., 2014)
DNA-damaging agents						
AAs	m^7Gua	spot urine	P_{95}: 105 mol/mol crea.	Population-based matched control group without lung cancer (50-64 years; n: 261), Denmark	1993-1997	(Loft et al., 2007)
	Σnitrosamines ($)	24-h urine	Mean: 57.33 nmol/l (Max.: 178.4 nmol/l)	Control group without urinary diversion (*age not specified*; n: 20), Germany	1989	(Tricker et al., 1989)
	NNAL	spot urine	P_{95}: 11.7 pg/ml	Non-tobacco users in general population (≥6 years; n: 4831); USA	2011-2012	(Wei et al., 2016)
	NNK	hair	Mean: 1.1 pg/mg	Non-smokers not exposed at home (*age not specified*; n: 24) Spain (Barcelona)	*Survey year not specified*	(Perez-Ortuno et al., 2016)
	NOC	12-h overnight urine	Mean 1.12 µmol/l (Max:3.8 µmol/l)	Non-smoking healthy adults (*age not specified*; n: 12), France (Lyon)	*Survey year not specified*	(Pignatelli et al., 1989)

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Table 2 (*continued*)

Stressor group Stressor	Biomarker of exposure	Matrix	Reference value RV_{95} (otherwise P_{95} or measure of central tendency)	Subgroup (years of age; n: sample size), country	Survey year	Reference
UVR	thymine dimers	morning urine	Mean: 189 fmol/mol crea. (Max.: 519 fmol/mol crea.)	Adult lifeguards/farm workers (18-54 years; n: 22), Sweden	2006	(Liljendahl et al., 2013)
occupational Hazards						
biological	*see substance of interest*					
chemical	*see substance of interest*					
cultural factors						
drug consumption	*see substance of interest*					
nutritional status	*see substance of interest (two examples below)*					
	folate	serum	P_{95}: 28.5 ng/ml	General population (≥1 years; n: 16411); USA	2003-2006	(CDC, 2012)
		serum	Adequacy level: ≥10 nmol/L	Adults	*Survey year not specified*	(EFSA, 2014)
		red cells	Adequacy level: ≥340 nmol/L	Adults	*Survey year not specified*	(EFSA, 2014)
	vitamin C / ascorbate	serum	P_{95}: 103 µmol/l	General population (≥6 years; n: 14579); USA	2003-2006	(CDC, 2012)
		plasma	Reduction in the risk of chronic disease: ≥50 µmol/L	Healthy adults	*Survey year not specified*	(EFSA, 2013)
physical activity	ammonia	serum	Normal range: 15-45 µg/dl	General population, no sprinters and no medium or long distance runners (*age not specified, sample size not specified*); *country not specified*	*Survey year not specified*	(Palacios et al., 2015)
	creatinine	serum	Concentration > 1.3 mg/dl	Adult male athletes (*age not specified, sample size not specified*), *country not specified*	*Survey year not specified*	(Palacios et al., 2015)
	lactate	blood	Threshold at which lactate increases exponentially due to exercises: 4.0 mmol/L	General population (*age not specified, sample size not specified*); *country not specified*	*Survey year not specified*	(Palacios et al., 2015)
stress	cortisol	plasma	Reference range: 138-690 nmol/l	Adults (*age not specified, sample size not specified*); *country not specified*	*Survey year not specified*	(Zografos et al., 2010)
		saliva (early morning)	MCT (mean): 3.6-8.3 nmol/l	Healthy laboratory worker (*age not specified; sample size not specified*); Hungary, UK	*Survey year not specified*	(El-Farhan et al., 2017)
		serum	/	/	/	(Hellhammer et al., 2009)
	free cortisol	24-h urine	Reference range: 20-90 µg/24-h	Adults (*age not specified, sample size not specified*); *country not specified*	*Survey year not specified*	(Zografos et al., 2010)

Abbreviations: /, there was no reference value found for the biomarker of exposure in the mentioned matrix; Σ, total; cr., creatinine; GM, geometric mean; MCT, range of measures of central tendency; e.g. mean, median, etc. (Arnold et al., 2013); n, sample size; P_{90}: 90th percentile; RI: reference interval for clinical guidance; RV_{95}, reference value; U/L, units per litre.
Abbreviations of stressor groups and biomarkers are explained in the list of abbreviations at the end of the manuscript.
(#): Reference limit was "chosen to represent a "healthy" fraction of the general population" (Mocarelli et al., 1986).
(##): range of youngest to oldest age group.
(###): range of two cohorts (Athens, Argolida).
(*): "no reference value, but should there be analytically reliable and confirmed concentrations above the mentioned value a special exposure must be expected" (Schulz et al., 2009).
(**): definition of reference value is not given.
(***): There is ambiguity about the reference value of HCB derived in the GerES IV study on children. Schulz et al. (2011) and Schulz et al. (2012) present P_{95}: 0.3 µg/l; Becker et al. (2008) present P_{95}: 0.21 µg/l; Schulz et al. (2009) present P_{95}: 0.1 µg/l and P_{95}: 0.2 µg/l.
(§) There is ambiguity about the reference value of β-HCH derived in the GerES IV study on children. Schulz et al. (2011). Schulz et al. (2009): 0.3 µg/l for children 9-11 years; 0.1 µg/l fir children 7-14 years. Schulz et al. (2011): 0.3 µg/l for children 7-14 years.
(§§):"no reference value, but should there be analytically reliable and confirmed concentrations of DEDTP in urine above 0.3 mg/l, a special exposure must be expected" (Schulz et al., 2009).
(§§§): ΣPYR includes tetramethrin, bifenthrin, λ-cyhalothrin, deltamethrin/ tralomethrin, esfenvalerate/fenvalerate, permethrin and cypermethrin).
($):ΣNitrosamines includes NDMA, NSAR, NPRO, NTCA, NMTCA).

Table 3
Exposure limit values.

Stressor group Stressor	Biomarker	Matrix	Exposure limit values (BAT, BEI, HBM, CC, etc.)	Subgroup (years of age), country	Reference
POPs					
dioxins and furans	GGT	serum	Cut-off limit (*): 80 U/L	Children (6–10 years), Italy	(Mocarelli et al., 1986)
PCBs	ΣPCBs	plasma	CC: 700 ng/g serum lipid	Children (< 3 years), women in childbearing age, pregnant women, breastfeeding women, USA	(Aylward et al., 2013)
			CC: 1800 ng/g serum lipid	Adults (excluded: women in childbearing age, pregnant women, breastfeeding women), USA	(Aylward et al., 2013)
PFC	PFOA	plasma	HBM I: 2 ng/ml	Adults (*age not specified*), Germany	(HBM-UBA, 2009)
	PFOS		HBM I: 5 ng/ml	Adults (*age not specified*), Germany	(HBM-UBA, 2009)
other organic contaminants					
BPA	ΣBPA	urine *(not further specified)* (**)	HBM I: 1.5 mg/l	Children (*age not specified*), Germany	(HBM-UBA, 2012)
			HBM I: 2.5 mg/l	Adults (*age not specified*), Germany	(HBM-UBA, 2012)
phthalates	5oxo -and 5OH-MEHP	urine *(not further specified)* (**)	HBM I: 500 µg/l	Children (6–13 years), Germany	(Schulz et al., 2011)
			HBM I: 300 µg/l	Women in child-bearing age, Germany	(Schulz et al., 2011)
			HBM I: 750 µg/l	Adult men and women of the general population (≥14 years) except women in child-bearing age, Germany	(Schulz et al., 2011)
toxic and potential toxic elements					
As	As	/	ALARP	/	(EFSA, 2009)
Cd	Cd	urine *(not further specified)* (**)	HBM I: 1 µg/g crea.	Adults (*age not specified*), Germany	(Schulz et al., 2011)
			HBM II: 4 µg/g crea.	Adults (*age not specified*), Germany	(Schulz et al., 2011)
			HBM I: 0.5 µg/g crea	Children (*age not specified*), Germany	(Schulz et al., 2011)
			HBM II: 2 µg/g crea.	Children (*age not specified*), Germany	(Schulz et al., 2011)
Cu	Cu	plasma	Concentration indicates probable depletion: < 50 µg/dl	Adults (*age not specified*)	(Burtis et al., 2012)
			Concentration indicates probable depletion: < 30 µg/dl	Infants (*age not specified*)	(Burtis et al., 2012)
Hg	Hg	blood	HBM I: 5 µg/l	Children and adults (*age not specified*), Germany	(Schulz et al., 2011)
			HBM II: 15 µg/l	Children and adults (*age not specified*), Germany	(Schulz et al., 2011)
		urine *(not further specified* (**)	HBM I: 7 µg/l	Children and adults (*age not specified*), Germany	(Schulz et al., 2011)
			HBM II: 25 µg/l	Children and adults (*age not specified*), Germany	(Schulz et al., 2011)
Pb	Pb	Blood	*suspended (***)*	/	(Schulz et al., 2011)
Zn	Zn	Serum	Concentration suggests likely deficiency: < 30 µg/dl	Adults (*age not specified*)	(Burtis et al., 2012)
Volatile organic compounds					
glycol ethers	MAA	urine *(not further specified)* (**)	HBM I: 0.4 mg MAA/g crea.	General population (*age not specified*), Germany	(HBM-UBA 2014)
			HBM II: 1.6 mg MAA/g crea.	General population (*age not specified*), Germany	(HBM-UBA 2014)
PCP	PCP	urine *(not further specified)* (**)	HBM I: 25 µg/l	General population (*age not specified*), Germany	(Schulz et al., 2007, 2011)
			HBM I: 20 µg/g crea.	General population (*age not specified*), Germany	(Schulz et al., 2007, 2011)
			HBM II 40 µg/l	General population (*age not specified*), Germany	(Schulz et al., 2007, 2011)
			HBM II: 30 µg/g crea.	General population (*age not specified*), Germany	(Schulz et al., 2007, 2011)
		serum	HBM I: 40 µg/l	General population (*age not specified*), Germany	(Schulz et al., 2007, 2011)
			HBM II: 70 µg/l	General population (*age not specified*), Germany	(Schulz et al., 2007, 2011)
smoking					
active tobacco smoke	nicotine				
	cotinine	serum	Cut-off points to distinguish tobacco use vs. no tobacco use: 3–20 ng/ml	Range of 14 studies (≥4 years, depending on study), Germany, India, Italy, Norway, Spain, USA	(Kim, 2016)
			Cut-off points to distinguish smokers from nonsmokers: 3 ng/ml	Overall population (≥12 years and older), USA	(Benowitz et al., 2009)
		urine (sample collection differ depending on the study)	Cut-off points to distinguish tobacco use vs. no tobacco use: 31.5–330 ng/ml	Range of 5 studies (≥18 years, depending on study), several countries (e.g., Poland, USA)	(Kim, 2016)
second-hand smoke (SHS)	nicotine				
	cotinine	first morning urine	Cut-off points to distinguish SHS exposed from non-exposed: 3.2 ng/g crea.;	Children (5–11 years), Poland	(Lupsa et al., 2015)

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Table 3 (*continued*)

Stressor group Stressor	Biomarker	Matrix	Exposure limit values (BAT, BEI, HBM, CC, etc.)	Subgroup (years of age), country	Reference
			Cut-off points to distinguish SHS exposed from non-exposed: 2.2 ng/g crea.;	Children (5–11 years), Portugal	
			Cut-off points to distinguish SHS exposed from non-exposed 2.5 ng/g crea.	Children (5–11 years), Romania	
			Cut-off points to distinguish SHS exposed from non-exposed: 1.2 ng/g crea.	Non-smoking mothers (27–45 years), Poland	
			Cut-off points to distinguish SHS exposed from non-exposed: 2.1 ng/g crea.	Non-smoking mothers (26–45 years), Portugal	
			Cut-off points to distinguish SHS exposed from non-exposed 1.5 ng/g crea.	Non-smoking mothers (25–45 years), Romania	
Occupational Hazards					
chemical occupational hazards					
VOCs					
2-Butoxy-ethanol	Butoxyacetic acid	spot urine	BAT: 100 mg/l	Employee (*age not specified*), Germany	(DFG, 2016)
			BAT: 200 mg/l (after hydrolysis)	Employee (*age not specified*), Germany	(DFG, 2016)
2-Ethoxy-ethanol	Ethoxyacetic acid	spot urine	BAT: 50 mg/l	Employee (*age not specified*), Germany	(DFG, 2016)
benzene	S-PMA	spot urine	BEI: 25 µg/g crea.	Employee (*age not specified*), USA	(ACGIH) cited in (Arnold et al. 2013)
styrene	Styrene	spot urine	BAT: 600 mg/g crea.	Employee (*age not specified*), Germany	(DFG, 2016)
toluene	Toluene	blood	BEI: 0.05 mg/l	Employee (*age not specified*), USA	(ACGIH) cited in (ATSDR 2000)
			BAT: 600 µg/l	Employee (*age not specified*), Germany	(DFG, 2016)
	Hippuric acid	urine *(not further specified)*	BEI: 1.6 g/g crea.	Employee (*age not specified*), USA	(ACGIH) cited in (ATSDR 2000)
xylene	*o*-xylene	blood	BAT: 1.5 mg/l	Employee (*age not specified*), Germany	(DFG, 2016)
	MHA (all isomers)	spot urine	BAT: 2000 mg/l	Employee (*age not specified*), Germany	(DFG, 2016)
cultural factors					
stress	cortisol	serum	Early morning concentrations below 140 nmol/L suggests adrenal insufficiency	General population (*age not specified*), 12 countries (e.g., UK)	(Kazlauskaite et al., 2008) cited in (El-Farhan et al., 2017)

Abbreviations: ALARP, as low as is reasonably practicable; CC, critical concentration (ANSES, 2013; Aylward et al., 2013); OCPs, organochlorine pesticides; PCP, pentachlorophenol.
Abbreviations of stressor groups and biomarkers are explained in the list of abbreviations at the end of the manuscript.
(*) The cut-off limit is defined as “eight times the SD [standard deviation] value above the mean” (Mocarelli et al., 1986).
(**) In the corresponding publications, it is not further specified into first morning urine, spot urine, or 24-h urine. However, the commission “Human Biomonitoring” of the German Environment Agency published a statement with the opinion, that 24-h urine is favorable but less feasible (HBM-UBA, 2007).
(***) In 2009 the HBM Commission of the German Environment Agency suspended the HBM values for lead in blood of children and adults, because several findings consistently show no threshold levels especially for developmental toxicity in children. The HBM Commission concluded that establishing an effect threshold for blood lead levels would be arbitrary and therefore not justified (Schulz et al., 2011).

Table 4
Biomonitoring equivalent (BE) values for selected stressors (based on WHO, 2015 and supplemented).

Stressor group	Biomarker	Matrix	BE value	Subgroup	Intake-based reference value publishing institute, type of value, (value and unit)	Reference
POPs						
BFRs	BDE 99	blood	520 ng/g lipid	/	US EPA, RfD (0.1 μg/kg/day)	(Krishnan et al., 2011)
	HBCDD	blood	190,000 ng/g lipid	/	EU Draft, BMD-L (2 mg/kg/day)	(Aylward and Hays, 2011)
		breast milk	190,000 ng/g lipid	/	EU Draft, BMD-L (2 mg/kg/day)	(Aylward and Hays, 2011)
OCPs	DDT + DDE	serum	5,000 ng/g lipid	/	US EPA, RfD; RIVM, TDI; ATSDR, Intermediate oral MRL (0.0005 mg/kg/day)	(Kirman et al., 2011)
	HCB	serum	47 ng/g lipid	/	ATSDR, MRL (5×10^{-4} mg/kg/day)	(Aylward et al. 2013)
other organic contaminants						
bisphenols	BPA-glu	24-h urine	2,000 μg/l		EFSA, TDI (50 μg/kg/day)	(Krishnan et al., 2010a)
phthalates	BzBP					
	MBzP	24-h urine	12 μg/l	/	EFSA, TDI (500 μg/kg/day)	(Aylward et al., 2009a)
	DBP					
	MBP	24-h urine	0.2 μg/l	/	EFSA, TDI (10 μg/kg/day)	(Aylward et al., 2009a)
	DEHP					
	MEHP, MEHHP, and MEOHP	24-h urine	660 μg/l	/	EFSA, TDI (50 μg/kg/day)	(Aylward et al., 2009b)
	MEHP, MEHHP, MEOHP, and 5cx-MEPP	24-h urine	1000 μg/l	/	EFSA, TDI (50 μg/kg/day)	(Aylward et al., 2009b)
	MEHP, MEHHP, MEOHP, 5cx-MEPP, and 2cx-MMHP	24-h urine	1100 μg/l	/	EFSA, TDI (50 μg/kg/day)	(Aylward et al., 2009b)
	DEP					
	MEP	24-h urine	18 μg/l	/	USEPA, RfD (800 μg/kg/day)	(Aylward et al., 2009a)
	DiNP					
	oxidative metabolites (OH-, oxo-, and carboxy-MiNP - monoisononyl phthalate)	24-h urine	15 μg/l	children (6-11 years)	EFSA, TDI (150 μg/kg/day)	(Hays et al., 2011)
			10.7 μg/l	adolescents (11-16 years)	EFSA, TDI (150 μg/kg/day)	(Hays et al., 2011)
			12.7 μg/l	men (> 16 years)	EFSA, TDI (150 μg/kg/day)	(Hays et al., 2011)
			10.6 μg/l	women (> 16 years)	EFSA, TDI (150 μg/kg/day)	(Hays et al., 2011)
	MiNP	24-h urine	0.7 μg/l	children (6-11 years)	EFSA, TDI (150 μg/kg/day)	(Hays et al., 2011)
			0.5 μg/l	adolescents (11-16 years)	EFSA, TDI (150 μg/kg/day)	(Hays et al., 2011)
			0.6 μg/l	men (> 16 years)	EFSA, TDI (150 μg/kg/day)	(Hays et al., 2011)
			0.5 μg/l	women (> 16 years)	EFSA, TDI (150 μg/kg/day)	(Hays et al., 2011)
PYR	cyfluthrin					
	4F3PBA	24-h urine	400 μg/l	/	FAO/WHO, ADI (10 μg/kg/day)	(Hays et al., 2009)
			240 μg/l	/	US EPA, chronic RfD(0.024 mg/kg/day)	(Aylward et al., 2013; Hays et al., 2009)
	DCCA	plasma	20 μg/l	adults	US EPA, RfD (0.01 mg/kg/day)	(Aylward et al., 2011)
			2 μg/l	infants and children	US EPA, RfD (0.001 mg/kg/day)	(Aylward et al., 2011)
		24-h urine	50 μg/l	adults	US EPA, RfD (0.01 mg/kg/day)	(Aylward et al., 2011)
			7 μg/l	Children (≥6 years)	US EPA, RfD, (0.001 mg/kg/day)	(Aylward et al., 2011)
Toxic and potential toxic elements						
inorganic As	inorganic As, monomethylated As, and dimethylated As	24-h urine	6.4 μg/l	/	ATSDR, chronic MRL (0.3 μg/kg/day)	(Hays et al., 2010)
Cd	Cd	24-h urine	1.2 μg/l	/	FAO/WHO, PTWI (10 μg/kg/day)	(Hays et al., 2008)
VOCs						

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Table 4 (*continued*)

Stressor group	Biomarker	Matrix	BE value	Subgroup	**Intake-based reference value** publishing institute, type of value, (value and unit)	Reference
benzene	benzene	blood	0.15 µg/l	/	US EPA, Chronic RfC (30 µg/m^3)	(Hays et al., 2012)
		urine*	0.16 µg/l	/		(Hays et al., 2012)
		blood	1.29 µg/l	/	TCEQ, chronic ReV (280 µg/m^3)	(Hays et al., 2012)
		urine*	1.42 µg/l	/		(Hays et al., 2012)
		blood	0.29 µg/l	/	California, CAL REL (60 µg/m^3)	(Hays et al., 2012)
		urine*	0.33 µg/l	/		(Hays et al., 2012)
		blood	0.04 µg/l	/	ATSDR, chronic inhalation MRL (10 µg/m^3)	(Hays et al., 2012)
		urine*	0.05 µg/l	/		(Hays et al., 2012)
ethylbenzene	ethylbenzene	blood	1 µg/l	/	ATSDR, MRL (0.25 mg/m^3)	(Aylward et al., 2010; Aylward et al., 2013)
styrene	styrene	blood	3 µg/l	/	US EPA, RfC (1 mg/m^3)	(Aylward et al., 2010; Aylward et al., 2013)
toluene	toluene	blood	50 µg/l	/	US EPA, chronic RfC (128 mg/m^3)	(Aylward et al., 2008)
			40 µg/l	/	Health Canada, chronic inhalation TDI (150 mg/m^3)	(Aylward et al., 2008)
			3 µg/l	/	WHO, lowest level of chronic occupational toluene exposure unequivocally associated with neurobehavioral functional decrement (332 mg/m^3)	(Aylward et al., 2008)
			3 µg/l	/	ATSDR, chronic inhalation MRL (132 mg/m^3)	(Aylward et al., 2008)
			30 µg/l	/	ATSDR, acute MRL (150 mg/m^3)	(Aylward et al., 2008)
triclosan	Σtriclosan (free plus conjugates)	24-h urine	2,600 µg/l	/	EC, SED (0.12 mg/kg/day)	(Krishnan et al., 2010b)
xylene	*o*-xylene	whole blood	0.3 µg/l	/	US EPA, RfC (0.1 mg/m^3)	(Aylward et al., 2010; Aylward et al., 2013)
water contamination						
THMs						
	bromoform	blood	130 pg/ml	/	US EPA, RfD(0.03 mg/kg/day)	(Aylward et al., 2013)
	BDCM	blood	80 pg/ml	/	US EPA, RfD(0.02 mg/kg/day)	(Aylward et al., 2013)
	chloroform	blood	230 pg/ml	/	US EPA, RfD (0.01 mg/kg/day)	(Aylward et al., 2013)
	DBCM	blood	20 pg/ml	/	US EPA, RfD (0.003 mg/kg/day)	(Aylward et al., 2013)

Abbreviations: µg/kg/day, microgram per kilogram per day; µg/l, microgram per liter; BE, biomonitoring equivalents; BMD-L, benchmark dose lower confidence limit; CAL REL, California Acute reference exposure levels; mg/kg/day, milligram per kilogram per day; mg/m^3, milligram per cubic meter; pg/ml, pictogram per milliliter; MRL, minimal risk level; pictogram per milliliter; PTWI, provisional tolerable weekly intake; RfC, reference concentrations; RfD, reference doses; SED, systemic exposure dose; TCEQ ReV, reference value of the Texas Commission on Environmental Quality.

* derived by using the urine to blood benzene relationship (Hays et al., 2012).

Abbreviations of stressor groups and biomarkers are explained in the list of abbreviations at the end of the manuscript.

Table 5
Opportunities to collect information about the internal exposure of stressors if no specific biomarker of exposure (BoE) is available.

Stressor group	Stressor	Opportunities
smoking		
	smoking	Besides measuring cotinine in human specimens (see Table 2) questionnaires are useful to determine internal exposure to smoking. Also, a measurement of expired carbon-monoxide (ECO) is an useful information to determine the internal exposure of smoking (Krautter et al., 2015).
air pollution		
	$PM_{2.5}$, PM_{10}	Exposure is measurable in terms of mass or number and composition of PM (like specific chemicals, e.g. metals, PAHs) (Karanasiou et al., 2014; Kolosnjaj-Tabi et al., 2015), however, no specific biomarker is currently available.
	NO_x	Products of NO_x can be measured in body fluids (Halatek et al., 2005).
	NPs	Markers of NPs exposure can range from measurements of specific NPs components, their metabolites, their reaction with cellular macromolecules such as DNA or protein or other effects on cellular processes taken in various bio specimens.
	ozone	Besides 2,3-DHBA (see Table 1), biomarkers of oxidative stress (e.g., 8-iso-PGF, 8-OHdG) in blood, urine or other fluids can be useful to identify human ozone exposure; however, the marker are not specific to ozone exposure (Chen et al., 2007; Kadiiska et al., 2013; Ren et al., 2011).
	UFPs	
noise		
	noise	There are no specific markers for noise exposure in the case of non-auditory effects. However, reactions at the organism level can be assessed in terms of effect (immune system, cardiac response). Questionnaires and measurements of the noise level are useful to determine noise exposure.
DNA-damaging agents		
EMF		Some non-specific biomarkers are discussed (e.g., hormones), however, they cannot be used as effective markers of exposure. Further research is urgently needed.
radon		Radon progeny is measurable in blood, hair, and urine, however, not specific. Radon progeny is also a BoE for radium and uranium. Because radon progeny have short half-lives, the time at which the biological sample is taken relevant to time of exposure may be important (Nazaroff and Nero, 1988).
Occupational Hazards		
	biological	Besides analyzing the biological agent in body fluids, an occupational exposure can be surveyed by requesting the job history (Nowak, 2010). A Job-Exposure-Matrix (JEM) can be used to draw conclusions about internal exposure (Pearce and Douwes, 2008).
	chemical	Besides using BoE for exposure assessment, a JEM is a possibility to identify internal exposure (Pearce and Douwes, 2008).
	mechanical	A JEM can be used to draw conclusions about internal exposure (Pearce and Douwes, 2008).
	physical	Physical stressors can be measured in specific units (e.g., hertz for the frequency of vibration (Levy et al., 2011); decibel (dB(A)) for the noise level (Nowak, 2010)). Personal dosimetry can measure ionizing radiation (Liljendahl et al., 2013). High or low temperatures as acute risk factors can be identified by changing body temperatures (Nowak, 2010). A JEM can be used to draw conclusions about internal exposure (Pearce and Douwes, 2008).
	psychological	Several instruments (questionnaires and observational instruments) are available to measure psychosocial factors in the work environment (Tabanelli et al., 2008). Job stress surveys or specific scales are developed (Levy et al., 2011). Medical history, interviews and employee surveys may give indications to possible psychological exposures during work (Nowak, 2010). Specific psychological exposures can be identified by using JEMs (Pearce and Douwes, 2008).
cultural factors		
	SES	

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Table 5 (*continued*)

Stressor group	Stressor	Opportunities
		Censuses, surveys and national data registers can provide data on SES of population, using a variety of measures at an individual (e.g. personal education or occupation, (Galobardes et al., 2006a; Galobardes et al., 2006b) household (e.g. Family Affluence Scale (FAS) (Boyce et al., 2006)) or neighbourhood scale (e.g. English Index of Multiple Deprivation, IMD (Smith et al., 2015)). The relative importance of measures of socioeconomic status varies with the location of the study so an understanding of local relevant socioeconomic status measures is paramount. In other international studies the availability of similar SES measures may be critical. Furthermore different manifestations of socioeconomic status may be relevant for different health outcomes but other studies have found the strongest relationships between housing tenure and heart disease (Woodward et al., 1992). For example elsewhere in HEALS we are using car access as a measure of socioeconomic status because it is central to time activity and exposure to air pollution. Such sources often include measures of medical conditions, mental health and wellbeing including self-report, health service records and a few surveys such as national health surveys may include biological samples (Brummett et al., 2013) Note that socioeconomic status itself may not be intrinsically linked to health. Instead it may be a marker for other exposures such as tobacco smoke or poor diet (Giesinger et al., 2014) or poor housing (Gibson et al., 2011) . Furthermore the length of exposure to low SES or low SES in childhood may be more important than current SES for some diseases (Giesinger et al., 2014).
	alcohol consumption	Acute alcohol consumption can be measured in blood (BAC: blood alcohol content), urine etc. (see Table 2). The AUDIT (Alcohol Use Disorders Identification Test) questionnaire can be used to collect data about alcohol consumption (Babor et al., 2001).
	drug consumption	Besides blood or urine analyses of the substance of interest, questionnaires (such as CRAFFT or DAST−10 from US National Institute on Drug Abuse) are useful to collect data about the internal exposure of drugs.
	nutritional status	Anthropometric, clinical, biochemical (according nutrient to be evaluated: water-soluble vitamin, fat-soluble vitamins and nutrients, trace elements, Isoflavones and Lignans; Hepatic proteins, Hormones, Nitrogen in urine) and dietary evaluation (Food Frequency Questionnaires (FFQ) such as EPIC-Norfolk and Food4Me) methods (Blössner and de Onis, 2005; CDC, 2012; Wasantwisut and Neufeld, 2012).
	physical activity	Biomarkers of physical activity and exercise are the following: Cortisol and testosterone for chronic stress and fatigue; lactate, c(CPK), creatinine, ammonia, lactate dehydrogenase (LDH), uric acid and urea are markers of overtraining; C-reactive protein (CRP), interleukin− 6 (IL−6) and leukocytes are markers of inflammation associated to physical activity (Palacios et al. 2015). The most used biomarkers to muscle fatigue are cortisol, lactate and IL− 6 and moreover ammonia, leukocytes and oxidative stress parameters are being increasingly used (Palacios et al., 2015). Reactions of organism are measurable like increased inflammation biomarkers (Margeli et al., 2005). Global Physical Activity and International Physical Activity Questionnaires (GPAQ and IPAQ) (Craig et al. 2003; Bull et al. 2009).
	consumer products	Analytical determination of endocrine disruptors and chemicals of concern contained in consumer products in biological samples are reported in several publications (Faniband et al., 2014). Use frequency and life style questionnaires. Due the complexity to analyze all the activities, consumer products, and chemicals containing in them, and the different routes of exposures the use of biomarkers of exposure to the chemicals contained in consumer products seems to be a more reasonable way to assess the exposure to this confounder (WHO, 2006).
	stress	

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Table 5 (*continued*)

Stressor group	Stressor	Opportunities
		Stress enhances cortisol in blood what can be measured (Kingston et al., 2012). Although a broad range of instruments is available to assess psychological stress, there is no measure that is appropriate for all the aspects of stress (e.g. occupational stress, anxiety, depression, daily hassles, life events, socio-environmental stressors) and for all populations (children, adolescents, adults, pregnant and postpartum women). The exact stress measure that one may choose depends on the question that is being posed (Nast et al., 2013). Questionnaires/scales are usually validated and their psychometric value is proven but the core challenge is the choice of a proper tool (Kingston et al., 2012). Exemplary instruments: Perceived Stress Scale (PSS) (Cohen et al., 1983), State-trait Anxiety Inventory (STA) (Spielberger et al., 1983), Social Readjustment Rating Scale (Holmes and Rahe, 1967), APGAR (Adaptation, Partnership, Growth, Affection, Resolve) Family Scale (Smilkstein, 1993; Smilkstein et al., 1982).

Abbreviations: APGAR, adaptation, partnership, growth, affection, resolve; AUDIT, alcohol use disorders identification Test; BAC, blood alcohol content; CRP, C-reactive protein; dB(A), decibel; DNA, deoxyribonucleic acid; ECO, expired carbon-monoxide; EMF, electromagnetic fields; FAS, family affluence scale; FFQ, food frequency questionnaires; GPAQ, global physical activity questionnaires; IL-6, interleukin-6; IMD, index of multiple deprivation; IPAQ, international physical activity questionnaires; JEM, job-exposure-matrix; LDH, lactate dehydrogenase; PSS, perceived stress scale; STA, state-trait anxiety inventory.
Abbreviations of stressor groups are explained in the list of abbreviations at the end of the manuscript.

biomonitoring. Although possible ways of representing the aggregate exposure of some stressors without specific BoEs were found (see Table 5), lack of specificity introduces uncertainties in using these to unravel the exposome. As the characteristics of environmental stressors may be very diverse, HBM measurements need to be complemented by tools and technologies that would allow effective HBM data assimilation (Sarigiannis et al., 2014) to accurate relate HBM values to actual human exposure to potential health stressors. This includes an array of technologies, employing environmental monitoring or food item analysis for chemical residuals, or ancillary exposure information retrieved from questionnaires or exposure related databases.

Currently exposure limit values used in chemical safety regulations are derived for the most part on toxicological (i.e. hazard-based) considerations using animal models and extrapolated to human exposure limit values with corrections using assessment factors that pertain to intra-species differences and inter-species variability. Given the cost and the burden to derive such acceptable limit values, they tend to be identified only for a limited number of chemicals and for an even more limited number of primary metabolites. In addition, the lack of harmonization among the various cohort and human biomonitoring studies results in a paucity of widely accepted exposure limit values based on HBM data. Most of these studies are designed to answer specific questions of limited scope, which are mostly related to the quantification of exposure levels among the study participants.

In order to derive exposure limit values, exposure characterization and quantification have to be associated with health observations. In addition, the methods used for interpretation of exposure-to-health associations, including both the statistical methods employed and proper consideration of potential modifiers (genetics, dietary, socio-economic conditions), are hardly consistent among the studies performed thus far. Several of these issues are addressed in HEALS, and they are to be addressed in the European Human Biomonitoring Initiative (HBM4EU project) (Ganzleben et al., 2017). Nonetheless, it should be noted that BEs do not address shortcomings in the derivation of current regulatory guidelines. They simply provide estimates of the urinary concentrations corresponding to the regulatory exposure limit as per the respective safety regulation.

Thus, beyond the difficulties in deriving BEs for given exposure reference values, a major problem is the lack of properly defined exposure-based limit and/or reference values. Widespread use of PBBK models will facilitate the derivation of BEs and will support the derivation of more robust associations between external exposures and biomonitoring data. Moreover, this will also allow the use of rapidly produced and inexpensive in vitro reference values, such as the ones derived by US EPA's Toxicity Forecaster (ToxCast) (US EPA, 2016). In this case, for calculating a BE, the starting point will be the biological pathway altering dose (BPAD) instead of an animal based POD. BPAD is analogous to current risk assessment metrics in that it combines dose-response data with analysis of uncertainty and population variability so as to derive exposure limits (Judson et al., 2010, 2011). The analogy is closest when perturbation of a pathway is a key event in the mode of action (MOA) leading to a specified adverse outcome. An application of this method (use of BPAD for deriving human BE) has been showcased by Sarigiannis et al. (2016) for bisphenol A. Methods for deriving BEs that are based on in vitro systems will allow the faster screening of newly produced chemicals, considering the rapidity, the lower costs and the lack of ethical concerns which occur when animal studies are used to derive PODs.

For EWAS, it is essential to consider a large range of diverse environmental stressors to enable the most complete decoding of the exposome. Relying on only one monitoring method (in this work we refer to biomonitoring) is insufficient. Although analysis of human biosamples for identifying the BoE levels is a good starting point, further elucidation of the individual exposome requires the use of additional molecular analysis such as transcriptomics, metabolomics or adductomics according to the HEALS paradigm; in turn, this requires additional computational tools that have to be used to interpret the biomonitoring and multi-omics results in the frame of a more integrative approach. This is actually one of the key aspects investigated in HEALS.

4.1. Limitations and strengths

Despite the amount of information collected in this narrative review, this work has limitations. Information was collected in an expert-driven, distributed, narrative review process which might involve individual researcher decisions. The internal review process reduced this potential researcher bias. The list of stressors included is not exhaustive but evaluated based on the joint opinion of the participating partners as a list of important stressors for the population in the EU. Completeness of the list of stressors is impossible because of the countless number of stressors available and the constant production and release of new

chemicals. This is the case of some substitutes, such as other bisphenols for BPA (e.g. BPF, BPS) (Chen et al., 2016) or non-phthalate plasticizers like DINCH (diisononyl cyclohexane-1,2-dicarboxylate) or DEHT (di(2-ethylhexyl) terephthalate) (Fromme et al., 2016; Larsson et al., 2017). There are also many other BoE for POPs, including brominated flame retardants such as TBBPA (tetrabromobisphenol A) (Lu et al., 2017) or PBB (polybrominated biphenyls) (Ploteau et al., 2016). Other examples are organic compounds like glyphosate-based herbicides (Conrad et al., 2017), carbamates (Haines et al., 2017)), or micro- as well as macro-nutrients that have not been included. While vitamin C and folate are included in our work as examples, these and further micronutrients (e.g. iodine or other trace elements, proteins, water or fat soluble vitamins) with health-relevance (e.g., deficiencies) have been discussed previously in another review (Combs et al., 2013).

The lists of reference values, exposure limit values and biomonitoring equivalents were not intended to be complete; rather, examples are listed to provide an inside in the interpretation of data. Presented are rather condensed information and stratifications by age, gender, or other subgroups were not reported. HBM itself contains limitations such as the use of diverse methods for analyses. Also, the derivation of reference and exposure limit values is based on expert decisions usually on the basis of a consensus process.

This paper's scope lies in the availability of BoEs and does not include further technical information. For example, it must be kept in mind that the half-life of BoEs is an essential piece of information for the practical use of BoEs. For example, as the biological half-life of nicotine is ~2 h (h), cotinine, the major metabolite of nicotine, with a half-life of 17 h, is a more suitable BoE (Benowitz, 1996). For biomarkers with a half-life of less than 2 h, biomonitoring is not feasible. When the half-life between 2 and 10 h, a sample collected at the end of the day reflects the exposure over the day, while with half-lives of 10–100 h, the optimal sampling time is at the end of the week, and the results reflect exposure during the preceding few days (HSE, 1992). The half-life of the marker of choice is a key parameter to be taken into account to achieve representative spot sampling results.

In addition the intraclass correlation coefficient (ICC) is important if spot-measurements are intended to estimate long-term exposures. The ICC is a value between 0 and 1 and if the value is close to 0 then repeated measurements of the BoE from the same individual would result in any test result , whereas if the ICC is close to 1 repeated measurements would be very similar (Pleil and Sobus, 2013).

Also, information about the representativeness of the samples is not included in this paper. For example, the reference values for 3PBA, diethyl phosphate, DMP, DMTP, PCP, PFOA, and PFOS are based on not representative samples of the population in Germany, as underlined by the authors (HBM-UBA, 2003; Heudorf et al., 2006; Schulz et al., 2011). In contrast, the data from the French National Survey on Nutrition and Health (InVS, 2010) and the German Environmental Survey on Children (Schulz et al., 2012) as well as the reference values for PBDEs (Gari and Grimalt, 2013) and β-HCH (Gari et al., 2014) were derived based on representative samples.

If no other reference value (e.g., RV_{95}) was available, information was included on measures of central tendency (MCT). In several cases, the presented MCTs represent arithmetic mean, geometric mean, median, or a mixture of them. It needs to be mentioned, that the mean (arithmetic mean, average) should be avoided in HBM studies, since the distribution of the values do not follow a normal distribution. Thus, mean values do not represent the central tendency.

Strengths of this work are the broad inclusion of diverse environmental stressors, the extensive list of BoEs and corresponding reference values, exposure limit values and biomonitoring equivalents as well as the inclusion of possibilities to measure the internal exposure of stressors without specific BoE.

5. Conclusions

Given the diversity of environmental stressors that need to be examined to unravel the exposome, current-day human biomonitoring is suitable for determining the internal exposome of several stressors (e.g., metals, PCBs, VOCs) but not for many others (e.g., NO_x, PM, physical activity). Most chemical and biological stressors are measureable in human specimens whereas exposure to the majority of physical, social and psychological stressors needs to be assessed using methods complementary to HBM. The joint and harmonized application of methods and tools to unravel the exposome represents the main task of the HEALS project.

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Appendices

The complete HEALS report can be downloaded from the HEALS website, http://www.heals-eu.eu/wp-content/uploads/2013/08/HEALS_D4.2.pdf.

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