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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-$Cl_2$CA | | √ | X | X |
| | | | | 63 | | cis-DCCA | | X | X | √ |
| | | | | 64 | | DCCA | | X | X | √ |
| | | | | 65 | | trans-$Cl_2$CA | | √ | X | X |
| | | | | 66 | | trans-DCCA | | X | X | √ |
| | | | | 63* | cypermethrin | cis-DCCA | | X | X | √ |
| | | | | 66* | | trans-DCCA | | X | X | √ |
| | | | | 67 | deltamethrin | $Br_2$CA | | √ | X | X |
| | | | | 62* | | cis-$Cl_2$CA | | √ | X | X |
| | | | | 68 | | DBCA | | X | X | √ |
| | | | | 65* | | trans-$Cl_2$CA | | √ | 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 | $m^7$Gua | | √ | 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<br>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<br>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<br>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) |

(*continued on next page*)

**Table 2** (*continued*)

| Stressor group<br>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<br>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<br>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-$Cl_2$CA [*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-$Cl_2$CA [*also a biomarker for* deltamethrin] | spot urine | $P_{95}$: 10.4 nmol/l | General adults (> 18 years; n: 92), UK | 2006 | (IEH, 2008) |
| | trans-$Cl_2$CA [*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 | | | | | | |
| | $Br_2$CA | 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-$Cl_2$CA [*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-$Cl_2$CA [*also a biomarker for* cyfluthrin] | spot urine | $P_{95}$: 10.4 nmol/l | General adults (> 18 years; n: 92), UK | 2006 | (IEH, 2008) |
| | trans-$Cl_2$CA [*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<br>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<br>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<br>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<br>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) |

(*continued on next page*)

**Table 2** (*continued*)

| Stressor group<br>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<br>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<br>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 | $m^7$Gua | 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<br>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<br>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) |

(*continued on next page*)

**Table 3** (*continued*)

| Stressor group<br>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 ($5 \times 10^{-4}$ 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 | |

(*continued on next page*)

**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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## Declaration of interest

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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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