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Review article

Literature review and evaluation of biomarkers, matrices and analytical methods for chemicals selected in the research program Human Biomonitoring for the European Union (HBM4EU)

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ABSTRACT

Humans are potentially exposed to a large amount of chemicals present in the environment and in the workplace. In the European Human Biomonitoring initiative (Human Biomonitoring for the European Union = HBM4EU), acrylamide, mycotoxins (aflatoxin B1, deoxynivalenol, fumonisin B1), diisocyanates (4,4′-methylenediphenyl diisocyanate, 2,4- and 2,6-toluene diisocyanate), and pyrethroids were included among the prioritized chemicals of concern for human health. For the present literature review, the analytical methods used in worldwide biomonitoring studies for these compounds were collected and presented in comprehensive tables, including the following parameter: determined biomarker, matrix, sample amount, work-up procedure, available laboratory quality assurance and quality assessment information, analytical techniques, and limit of detection. Based on the data presented in these tables, the most suitable methods were recommended. According to the paradigm of biomonitoring, the information about two different biomarkers of exposure was evaluated: a) internal dose = parent compounds and metabolites in urine and blood; and b) the biologically effective = dose measured as blood protein adducts. Urine was the preferred matrix used for deoxynivalenol, fumonisin B1, and pyrethroids (biomarkers of internal dose). Markers of the biological effective dose were determined as hemoglobin adducts for diisocyanates and acrylamide, and as serum-albumin-adducts of aflatoxin B1 and diisocyanates. The analyses and quantitation of the protein adducts in blood or the metabolites in urine were mostly performed with LC-MS/MS or GC-MS in the presence of isotope-labeled internal standards. This review also addresses the critical aspects of the application, use and selection of biomarkers. For future biomonitoring studies, a more comprehensive approach is discussed to broaden the selection of compounds.

1. Introduction

Humans are exposed to potentially harmful chemicals from various sources, including food, consumer products and the environment. Human biomonitoring (HBM) was developed (Fig. 1) to determine the exposure and effects of xenobiotics and susceptibility of individuals (Albertini et al. 2006; Farmer et al. 1987; Needham et al. 2007; Wogan and Gorelick 1985). The biomonitoring paradigm was published more than 30 years ago (CEC-IPCS-WHO-FIOH 1988; Wogan 1992). The chemical and biological steps include: (a) external exposure: air, food, water, soil, dust; (b) internal exposure via inhalation, ingestion, dermal absorption: for example, parent compound or metabolite thereof in urine or blood; (c) biologically effective dose: for example, protein and/or DNA adducts; (d) early biological effects: for example, micronuclei;

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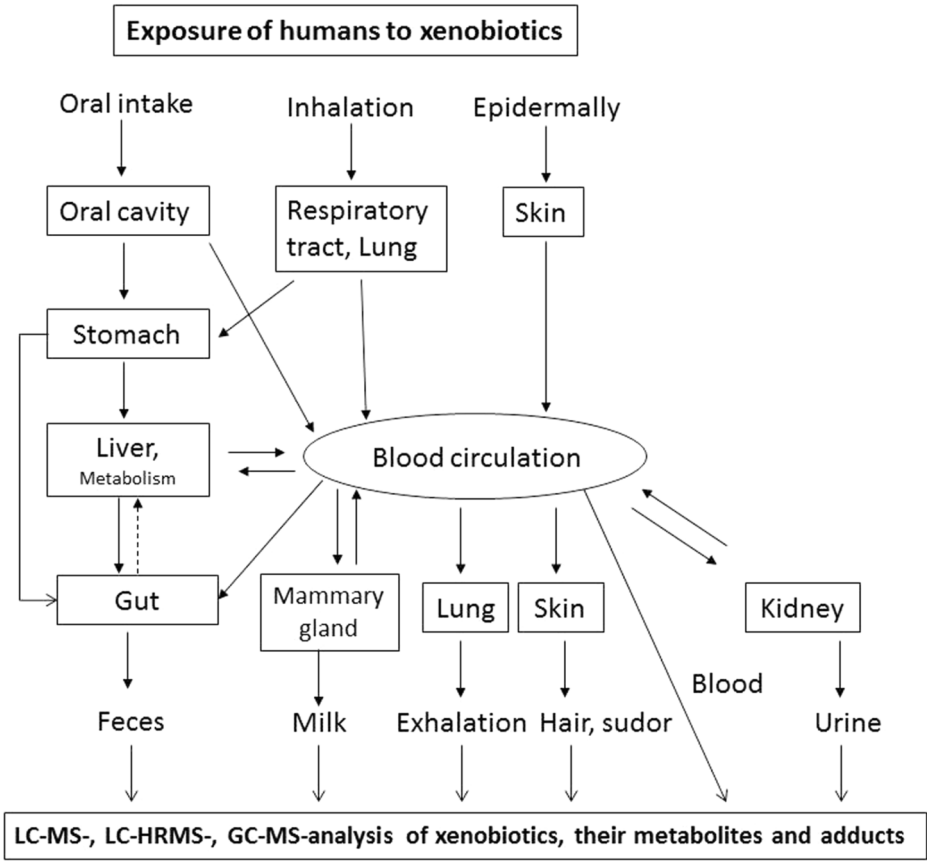

Fig. 1. Exposure to xenobiotics and biomonitoring. The prevalence of the matrix used for biomonitoring of environmental and occupational health studies increases from left to right: feces, milk, exhalation, hair, blood, urine.

(e) late biological effects: for example, altered cell structure and/or function; and (f) tumors or other diseases. The biomonitoring paradigm scheme (b to e) has been translated into a simplified adverse outcome pathway (AOP) framework (Zare Jeddi et al. 2021): b) adsorption, distribution, metabolism, excretion; c) molecular initiating events; d) early key events; e) late key events.

The following text presents the methods for the determination of the internal dose and the biologically effective dose of a specific set of chemicals or related biomarkers present in human matrices, such as urine, blood and hair (Fig. 1).

Differences in physical–chemical characteristics, toxicokinetics and metabolism require a substance-based approach to the selection of most suitable exposure biomarkers. Depending on the question to be answered, considerations of a focus on exposure or toxicity assessments can be a factor influencing the choice of biomarkers. Chemicals can be activated through metabolism and lead to genotoxic and cytotoxic effects (Farmer et al. 1987; Parke 1987; Rendic and Guengerich 2012; Rendic and Guengerich 2021). This includes the formation of adducts of xenobiotics with biomolecules, such as the hemoglobin (Hb)-, albumin-, and DNA-adducts (Henderson et al. 1989). A quantitative relationship between DNA-adducts and hemoglobin adducts in mice was reported for ethylene oxide (Ehrenberg et al. 1974) or vinyl chloride (Osterman-Golkar et al. 1976). 2-Acetylaminofluorene (Pereira et al. 1981) reacted with Hb and DNA of the target organ in a dose-dependent manner. Thus adducts with blood proteins are long-term markers of exposure and markers of the biologically effective dose. Blood protein adducts reflect the exposure history over a larger period of time than urinary metabolites, or than metabolites present in blood. Stable hemoglobin adducts have a lifetime up to 120 days (Törnqvist et al., 2002); and stable albumin adducts a half-life of 20–25 days (reviewed in Sabbioni and Jones (2002), Skipper and Tannenbaum (1990)). Reaction products with hemoglobin accumulate up to 60 times a single dose (Törnqvist et al., 2002) and albumin adducts up to 29 times (Sabbioni et al., 1987) a single dose. Urinary metabolites of xenobiotics are usually detectable up to 48 h after exposure (Henderson et al. 1989).

Internal exposures were mostly established with the determination of urinary or blood levels of xenobiotics or their metabolites. These are snapshot measurements that may lead to a misclassification of the individual exposures. Albumin and hemoglobin adducts of xenobiotics reflect the exposure of a larger time frame. It is likely that only a small fraction of xenobiotics form such adducts. In addition, adduct analyses are more work intensive than the measurement of xenobiotics and metabolites in urine and/or blood. Urinary and blood levels of chemicals can vary substantially (LaKind et al. 2019).

Which matrix to choose for HBM is determined by the toxic properties and the toxicokinetics of a given compound as well as questions of practicality. Urinary samples are collected easily and non-invasively, while blood samples are more difficult to obtain, but essential if persistent compounds or adducts are to be analyzed (Barr et al. 2005; Bravo et al. 2005). Human milk has been used for the analyses of many compounds in order to estimate the exposure of babies (Barr et al. 2005; Esteban and Castaño 2009). Hair monitoring is established for e.g. mercury (Esteban and Castaño 2009), drug monitoring, and doping control (Kintz 2021; Mannocchi et al. 2020; Salomone et al. 2016; Vincenti and Kintz 2015). Urinary or blood levels of xenobiotics have been used for the estimation of the external exposure dose using physiologically based pharmacokinetic (PBPK) models (Koch and Calafat 2009; Sarigiannis et al. 2019; Sweeney et al. 2010). For hair measurements such PBPK models have been generated for mercury (Allen et al. 2007; Pope and Rand 2021). In animal experiments, good dose–response relationships were found also for pesticides (Appenzeller et al. 2016); but for many compounds it holds the challenge of distinguishing

between exogenous and endogenous exposure, which, for example, has been discussed for flame retardants (Kucharska et al., 2015). Other matrices, such as feces, saliva, nails and exhaled breath are mainly selected to address specific compounds and research or monitoring questions, including workplace monitoring (National Research Council 2006).

A major source of results for biomonitoring studies of xenobiotics in urine and blood originates from the United States with the National Report on Human Exposure to Environmental Chemicals (NRHEEC) (CDC-NHANES 2021a). Xenobiotics in urine and blood have been measured every-two years since 1999. Currently, in about 5000 samples, exogenous and endogenous biomarkers are analyzed, and each person is analyzed only once (reviewed in (Sobus et al. 2015)). The results are published regularly on the homepage of NRHEEC (https://www.cdc.gov/exposurereport/). More than 200 environmental chemicals have been analyzed in biological samples. Hb-adducts are measured only for acrylamide and glycidamide and aflatoxin B1-serum albumin adducts in pooled samples.

In Canada (Faure et al. 2020; Haines et al. 2017), Europe (Apel et al. 2017; Černá et al. 2017; Dalsager et al. 2018; Dereumeaux et al. 2017; Lermen et al. 2019; Louro et al. 2019; Pérez-Gómez et al. 2013; Schulz et al. 2011), Korea (Choi et al. 2017), and Japan (the Environment and Children's Study, https://www.env.go.jp/en/chemi/hs/jecs/), biomonitoring programs were implemented to study exposure of the general population to several chemicals.

In Europe, national initiatives such as the German Environmental Survey (GerES) (Becker et al. 2007) and the Flemish Environmental and Human Health Studies (FLEHS) (Schoeters et al. 2017) have been supplemented by European initiatives in recent years, such as the Consortium to Perform Human Biomonitoring on a European Scale (COPHES) and its demonstration project DEMOCOPHES (Joas et al. 2015). In 2017, the research program HBM4EU was established (Ganzleben et al. 2017), bringing together scientists from 30 countries and the European Environment Agency to coordinate the ongoing studies in the single European states and advance human biomonitoring (HBM) in Europe (Ganzleben et al. 2017).

For the selection of most suitable biomarkers, matrices and analytical methods, a set of criteria was developed in HBM4EU, for example taking into account the specificity of a biomarker/matrix combination, its biological sensitivity and stability (Vorkamp et al. 2021). Analytical methods for HBM have to be sufficiently sensitive to allow reliable detections of low-level exposures of the general population and provide precise and accurate quantification to allow comparisons with reference values or establishments of time trends. The selection process for the substances designated for the present manuscript was described by Ougier et al. (Ougier et al. 2021). For the first step, relevant ministries and agencies at EU and national levels, as well as members of the Stakeholder Forum each nominated up to 5 substances/substance groups of concern for policy-makers. These nominations were collated into a preliminary list of 48 substances/substance groups, which was subsequently shortened to a list of 23 after considering the total number of nominations each substance/substance group received and the nature of the nominating entities. For the second step, a panel of 11 experts in epidemiology, toxicology, exposure sciences, and occupational and environmental health scored each of the substances/substance groups using prioritisation criteria including *hazardous properties* (carcinogenicity, mutagenicity, reproductive toxicity, developmental toxicity, endocrine activity, systemic toxicity after repeated exposure, neurotoxicity, immunotoxicity, respiratory sensitizer, skin sensitizer), *exposure characteristics* [persistency and/or bioaccumulation potential, tonnages, extent of exposure, route of exposure, passage of placental barrier, exposed populations (workers, general population, vulnerable groups exposed), levels of concern of the exposure, external exposure data], and *societal concern*. The scores were used to rank the 23 substances/substance groups. The ranking score composed equally by the hazard score and the exposure score yielded the following top rankings for the following compounds selected for the present biomonitoring study: acrylamide, mycotoxins (aflatoxin B1, deoxynivalenol, fumonisin B1), diisocyanates (4,4′-methylenediphenyl diisocyanate, 2,4- and 2,6-toluene diisocyanate), and pesticides (pyrethroids).

The objective of this study was to review the biomarkers, matrices, and the analytical methods available from the literature for the selected substances in HBM4EU and to recommend the most suitable approaches.

2. Biomarkers, matrices and analytical methods

From the large diversity of the available methods, we selected methods according to the general criteria described in Vorkamp et al. (2021) with a specific focus on the following aspects: a) Low limit of detection (LOD); b) methods that were vetted in inter-laboratory comparisons; c) methods that have been described in detail with the inclusion of the basic requirement formulated by the US food and drug administration (https://www.fda.gov/media/70858/download) or the European Medical Agency (https://www.ema.europa.eu/documents/scientific-guideline/guideline-bioanalytical-method-validation_en.pdf) for the analysis of xenobiotics in biological fluids with the main emphasis on LOD, limit of quantitation (LOQ), presence of internal standards, accuracy (within and between runs), precision (within and between runs), matrix effects, recovery experiments, range of calibration curve; d) methods that can be applied to more than one group of chemicals.

Targeted biomonitoring methods are validated in the German Working Group "Analyses in Biological Materials of the permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work" and the standard operation procedures are available online (https://doi.org/10.1002/3527600418). Further very detailed standard operation procedures specified as laboratory methods are available from biomonitoring NHANES studies (CDC-NHANES, 2015-16, 2021b).

2.1. Acrylamide

Acrylamide is synthesized for different industrial processes, but is also formed from natural sources during food production and combustion processes. Acrylamide is generated from the amino acid asparagine in the presence of reducing sugars under heat by the Maillard reaction. Thus, food products of baked, fried and roasted pastry, potatoes and coffee can contain significant amounts of acrylamide (Raffan and Halford 2019). Beside food consumption, smoking is a main predictor of acrylamide exposure (Smith et al. 2000; Vesper et al. 2007). Additionally, exposure to acrylamide can occur at specific workplaces, particularly where acrylamide is produced or used in polymer production (Huang et al. 2011; Jones et al. 2006).

After oral, dermal or inhalation exposure, acrylamide is absorbed rapidly and efficiently, distributed extensively in the body and metabolized immediately (McCollister et al. 1964). The main metabolism route is the conjugation via glutathione-S-transferase (Fennell et al. 2005). The glutathione conjugation can take place for the native compound and after oxidation via cytochrome P450 to glycidamide.

A main metabolite is *N*-acetyl-S-(2-carbamoylethyl)cysteine (AAMA) (Fig. 2, Table S1), formed from glutathione conjugation to acrylamide, subsequent cleavage of glutamic acid and glycine and acetylation (Boettcher et al. 2006; Fennell et al. 2006). AAMA can be further oxidized to *N*-acetyl-S-(2-carbamoylethyl)cysteine sulfoxide (AAMA-sulfoxide). Both AAMA and AAMA-sulfoxide can be excreted via urine (Hartmann et al. 2009). The glutathione conjugation of glycidamide results in two isomeric metabolites, *N*-acetyl-S-(2-carbamoyl-2-hydroxyethyl)cysteine (GAMA) and *N*-acetyl-S-(1-carbamoyl-2-hydroxyethyl) cysteine (isoGAMA) (Fennell et al. 2006). The highly reactive glycidamide can also be detoxificated by hydroxylation to 2,3-dihydroxypropionamide (DHPA) (Fennell et al. 2006). Moreover, two products of spontaneous reaction of acrylamide and glycidamide, respectively, with the *N*-terminal valine of the globin groups in Hb, are determined after

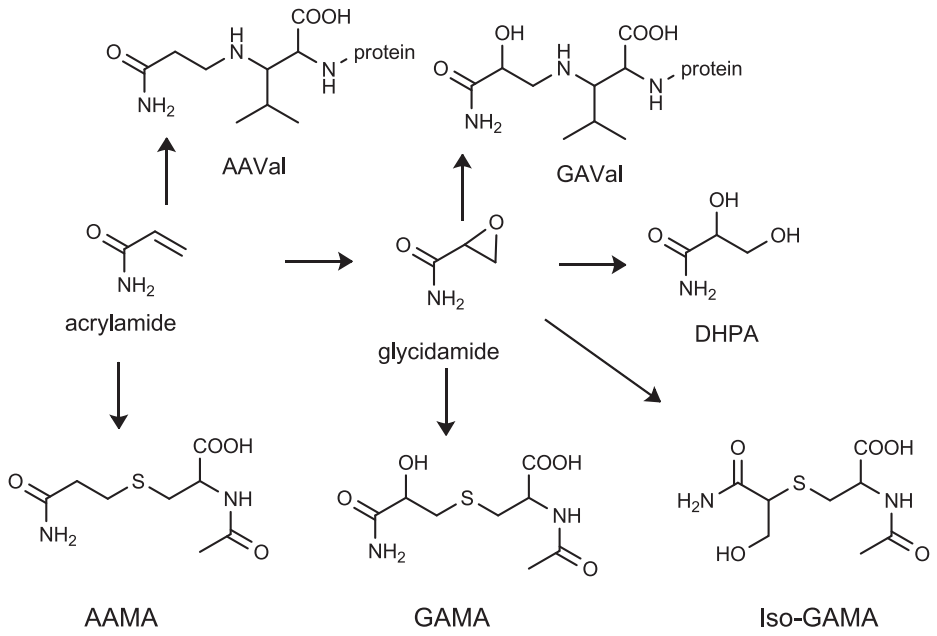

Fig. 2. Scheme of human acrylamide metabolism.

Edman degradation: N-(2-carbamoyl-ethyl)valine (AAVal) and N-(2-carbamoyl-2-hydroxyethyl)valine (GAVal) (Fennell et al. 2005).

2.1.1. Acrylamide-biomarkers in urine

N-Acetyl-S-(2-carbamoylethyl)cysteine (AAMA) represents the main metabolite in urine and is the best established urinary HBM parameter. The ratios between the cumulative renally excreted metabolites in urine after exposure to acrylamide amount approximately to 1: 0.1: 0.02: 0.7 (AAMA: GAMA: isoGAMA: AAMA-sulfoxide). In urine samples of the general population, the ratio between AAMA and GAMA is found to be approximately 1: 0.3, which may be related to the different elimination half-lives of 11 and 19 h for AAMA and GAMA/isoGAMA, respectively (Boettcher et al. 2006; Fennell et al. 2006).

Analytical methods exist for all of the five identified renally excreted acrylamide metabolites, i.e. AAMA, GAMA, isoGAMA, AAMA-sulfoxide and DHPA (Table 1). In general, LC- MS/MS procedures were applied for the quantification of the mercapturic acids in urine. All procedures detected AAMA, and most of the procedures included GAMA as well. isoGAMA and AAMA-sulfoxide were included less frequently (Bjellaas et al. 2005; Boettcher and Angerer 2005; Brisson et al. 2014; Choi et al. 2019; Kellert et al. 2006; Kopp et al. 2008; Lee et al. 2014; Pluym et al. 2015; Sams et al. 2015; Urban et al. 2006; Zhang et al. 2020). Procedures which include all of these four parameters were published by Brisson et al. (Brisson et al. 2014) and Zhang et al. (Zhang et al. 2020). The sample volume ranged from 0.1 to 4 mL. Sample preparation techniques usually included solid phase extraction (SPE), online and offline, and dilute-and-shoot procedures. Lowest limits of detection were 0.1 ng/mL urine für AAMA, 0.3 ng/mL for GAMA and 0.2 ng/mL for isoGAMA and AAMA-sulfoxide. For the determination of DHPA in urine a GC-MS procedure was developed by Hartmann et al. (Hartmann et al. 2011) and advanced by Latzin et al. (Latzin et al. 2012). The final method started with 1 mL urine, applied SPE for sample preparation and a derivatization using *N-tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide (MTBSTFA) before GC–MS analysis. The method achieved an LOD of 1 ng/mL urine.

With regard to external QA/QC, both AAMA and GAMA in urine are included in the German External Quality Assessment Scheme (G-EQUAS; Göen et al., (Göen et al., 2012b); https://www.g-equas.de). Both parameters were also included in urine samples of the QA/QC program of HBM4EU (Esteban Lopez et al. 2021).

2.1.2. Acrylamide-biomarkers in blood

N-(2-carbamoyl-ethyl)valine (AAVal) and N-(2-carbamoyl-2-hydroxyethyl)valine (GAVal) were found in the blood of the general population at the ratio of 1: 1. The different prominence ratio of acrylamide- and glycidamide-derived reaction products in urine and blood can be explained by the higher reactivity of glycidamide which compensates its lower presence compared to acrylamide. The Hb-adducts cumulate during the life span of the erythrocytes (approx. 120 days). Due to the constant depletion process of erythrocytes the Hb-adducts show a half-life of about 60 days (Fennell et al. 2005; Kopp and Dekant 2009).

Most analytical procedures for the determination of Hb-adducts of acrylamide included both AAVal and GAVal (Bjellaas et al. 2007; Chevolleau et al. 2007; Hartmann et al. 2008; Paulsson et al. 2003; Perez et al. 1999; Schettgen 2013; Schettgen et al. 2002a; Tareke et al. 2006; Urban et al. 2006; Vesper et al. 2006; Vikström et al. 2010; von Stedingk et al. 2010) (see Table 1). The determination of the Hb-adducts requires the withdrawing of blood, the subsequent separation of the erythrocyte fraction of fresh blood samples (before haemolysis) and the precipitation of globin. The matrix amount ranged between 20 and 100 mg globin. For the determination of the adduct at the *N*-terminal position of the protein a modified Edman degradation reaction was applied in all procedures using pentafluorophenylisothiocyanate (PFPITC), phenylisothiocyanate (PITC) or fluorescein isothiocyanate (FITC).

While GC-NCI-MS techniques were used originally, LC-MS/MS procedures have also been developed in recent years. In the case of GC applications, the Edman reaction product of GAVal was acetonized before analysis. Most procedures used tripeptide or octapeptide standards for calibration. Some methods calibrated the analyte levels using the reaction products themselves, but missed to consider the recovery of the Edman degradation procedure. The LOD ranged between 0.2 and 11 pmol/g globin for AAVal and 0.3 and 10 pmol/g globin for GAVal (Table 1). G-EQUAS (Göen et al. (Göen et al., 2012b); https://www.g-equas.de) offers an inter-laboratory comparison for the parameter AAVal.

2.1.3. Recommended methods

The metabolites in urine and adducts at Hb represent short-term and long-term acrylamide biomarkers, respectively. Among the urinary biomarkers AAMA features the highest sensitivity but also high

Table 1
The major methods used to biomonitor people exposed to acrylamide.

Acrylamide					
Substance	**Biomarker**	**Matrix (amount)**	**Work-up/ callibration**	**Analytical Method**	**LOD**
Acrylamide	*N*-Acetyl-S-(2-carbamoyl-ethyl)cysteine (AAMA)[k]	Urine (mL): 0.1[1], (?)[2], 1[3], 1.5[4], 1[5] 1[6], 3.5[7], 1[8], 4[9], 0.05[10], 0.1[11]	dilute[1],online-SPE[2] SPE[3], online-SPE[4],SPE[5] SPE[6] SPE[7,8,9],dilute[10,11]	LC-MS/MS[1],[2] UPLC-MS/MS[3] LC-MS/MS[4],[5] LC-APCI-MS/MS[6] LC-MS/MS[7,8,9,10,11]	0.1[1a,2a] ng/mL 0.2[3]a 0.5[4]a,0.6[5]a 0.8[6]a 1[7a],[8s], 1.5[9]a, 2.5[10]a, 9.7[11]a
	N-Acetyl-S-(2-carbamoyl-2-hydroxyethyl)cysteine (GAMA)[k]	Urine (mL): 1[3] 0.1[11], (?)[2] 1[6], 0.1[1], 1.5[4], 1[8], 4[9], 3.5[7]	SPE[3] dilute[11],online-SPE[2] SPE[6] dilute[1],online-SPE[4],SPE[8,9,7]	UPLC-MS/MS[3] LC-MS/MS[11],[2] LC-APCI-MS/MS[6] LC-MS/MS[1,4,8,9,7]	0.3[3]a ng/mL 0.36[11]a,0.5[2a,6a], 0.56[1]a, 1[4a,8b],1.5[9]a, 3[7]b
	N-Acetyl-S-(1-carbamo-yl-2-hydroxyethyl)-cysteine (isoGAMA)	Urine (mL): 1[3] 0.1[1] 3.5[7]	SPE[3] dilute[1] SPE[7]	UPLC-MS/MS[3] LC-MS/MS[1] LC-MS/MS[7]	0.2[3]a ng/mL 2.3[1]a 4 [7]b
	N-Acetyl-S-(2-carbamoyl-ethyl) cysteine sulfoxide (AAMA-sulfoxide)	Urine (mL): 1[3] 0.1[1], (?)[4]	SPE[3] dilute[1],online-SPE[2]	UPLC-MS/MS[3] LC-MS/MS[1,2]	0.2[3]a ng/mL 0.35[1]b,1[2]a
	2,3-Dihydroxypropion-amide (DHPA)	Urine (mL): 1[12]	SPE/D[12]	GC-MS[12]	1[12]a ng/mL
	N-(2-Carbamoylethyl) valine (AAVal)	Globin (mg): 20[13] (?)[14] 50[15] 20[16] 50[17] 100[18] 50[19] 100[6] 100[20] 20[21] 100[22]	ED, PITC, PTH derivative std[13] ED, FITC, FTH derivative std[14] ED, PFPITC tripeptide std[15] ED, PITC, SPE, tripeptide std[16] ED, PFPITC, incubated globin[17] ED, PFPITC, tripeptide std[18] ED, PFPITC, octapeptide std[19] ED, PFPITC, tripeptide std[6] ED, PFPITC, tripeptide std[20] ED, PFPITC, tripeptide std[21] ED, PFPITC, tripeptide std[22]	LC-MS/MS[13] LC-MS/MS[14] GC-NCI-MS[15] LC-MS/MS[16] GC-MS/MS[17] GC-NCI-MS/MS[18] LC-APCI-MS/MS[19] GC-EI-MS[6] GC-NCI-MS/MS[20] LC-NCI-MS[21] GC-NCI-MS[22]	0.2[13]a pmol/g 0.3[14]d 1[15]c 1[16]e 1[17]f 2[18]**c 3[19]h 3.5[6] 4[20]g 10[21]i 11[22]j
	N-(2-Carbamoyl-2-hydroxyethyl)valine (GAVal)	Globin (mg): (?)[14] 20[13] 50[15] 50[17] 20[16] 100[18,20] 40[23] 50[19] 20[21]	ED, FITC, FTH derivative std[14] ED, PITC, PTH derivative std[13] ED, PFPITC tripeptide std[15] ED, PFPITC, incubated globin[17] ED, PITC, SPE, tripeptide std[16] ED, PFPITC, tripeptide std[18,20] ED, PFPITC, octapeptide std[23] ED, PFPITC, octapeptide std[19] ED, PFPITC, tripeptide std[21]	LC-MS/MS[14] LC-MS/MS[13] GC-NCI-MS[15] GC-MS/MS[17] LC-MS/MS[16] GC-NCI-MS/ MS[18,20] GC-NCI-MS/MS[23] LC-APCI-MS/MS[19] LC-NCI-MS[21]	0.3[14]d pmol/g 0.4[13]a 1[15]c 1[17]f 2[16]e 2[18]**c,4[20]g 6[23]f 7[19]h 10[21]i

The chemical structures are presented in Table S1. Abbreviations: SPE solid phase extraction; D derivatization; ED Edman degradation, std standards, FITC fluorescein isothiocyanate, PITC phenylisothiocyanate; PFPITC pentafluoro isothiocyanate, PTH phenylthiohydantoin; [1] (Brisson et al. 2014); [2] (Kopp et al. 2008); [3] (Zhang et al. 2020); [4] (Kellert et al. 2006); [5] (Choi et al. 2019); [6] (Urban et al. 2006); [7] (Bjellaas et al. 2005); [8] (Sams et al. 2015); [9] (Boettcher and Angerer 2005); [10] (Lee et al. 2014); [11] (Pluym et al. 2015); [12] (Latzin et al. 2012); [13] (Chevolleau et al. 2007); [14] (von Stedingk et al. 2010); [15] (Hartmann et al. 2008); [16] (Bjellaas et al. 2007); [17] (Vikström et al. 2010); [18] (Schettgen 2013; Schettgen et al. 2016b); [19] (Vesper et al. 2006); [20] (Perez et al. 1999); [21] (Tareke et al. 2006); [22] (Schettgen et al. 2002a); [23] (Paulsson et al. 2003); a) addition of corresponding isotope-labeled internal standard (IS); b) addition of surrogate isotope-labeled IS; c) deuterium-labeled IS were synthesized by adding d_3-acrylamide or d_3-acrylonitrile to solutions of hemolyzed nonsmoker erythrocytes; d) IS = FITC derivatives of the corresponding deuterated valine adducts = AA-d_7-Val-FTH and GA-d_7-Val-FTH; e) IS = PITC derivatives = d_3-AA-Val-PTH and d_3-GA-Val-PTH; f) IS = PFPITC derivatives = GA-d_7-Val-PFPTH and GA-d_7-Val-PFPTH; g) IS = PFPITC derivatives = d_3-AAVal-PFPTH; h) IS = AA-Val($^{13}C_5^{15}N$)-HLTPEEK and GAVal($^{13}C_5^{15}N$)-HLTPEEK, i) IS = PFPITC derivatives = $^{13}C_5$-AA-Val-PFPTH and $^{13}C_5$-GA-Val-PFPTH, j) addition of non-labeled surrogate standard; k) these compounds are part of the regular round robins in the German external quality assessment scheme (G-EQUAS) for analyses in biological materials (https://www.g-equas.de/); l) this is a method validated at least by one other laboratory and is part of the MAK-commission biomonitoring method collection.

specificity. However, for risk assessment with respect to carcinogenic effects the determination of GAMA in urine will also be relevant. The LC-MS/MS technique has clearly demonstrated its applicability for the determination of the different mercapturic acids. The procedure can be combined with offline or online SPE for sample clean-up and pre-concentration. However, dilute-and-shoot procedures have also shown competitive analytical performance, if applied to benchmark LC-MS/MS equipment. Due to the ubiquitous presence of acrylamide in the general population, the sensitivity is less critical for achieving study targets; the common procedures enabled the determination of AAMA and GAMA in almost all individuals of the general population (Brantsaeter et al. 2008; Ji et al. 2013; Schwedler et al. 2021). Reference substances for the calibration are commercially available for both the native mercapturic acids and their isotope-labelled internals standards. External quality assessment can be implemented for both AAMA and GAMA through regularly organized proficiency testing.

For long-term exposure assessment, AAVal and GAVal, the Hb-adducts of acrylamide and glycidamide, respectively, showed comparable analytical sensitivity. GC- and LC-based MS methods seem equally suitable for the parameters in terms of required sample volume, LOD and method runtime. Among GC-MS methods, procedures using negative chemical ionization (NCI) and tandem-mass spectrometry are advantageous for higher sensitivity. The Edman degradation reaction is a complex reaction which can only reproduce accurately by cleavage of the *N*-terminal valine from a comparable peptide structure (Törnqvist et al. 1992). Thus, a crucial requirement for an accurate Hb adduct analysis is the application of an adduct-carrying *N*-terminal oligopeptide for calibration. Standard compounds based on tripeptide or octapeptide structures have been applied successfully and are commercially available for both parameters. External quality assessment schemes are available for AAVal only.

2.2. Mycotoxins

Mycotoxins are natural substances produced as secondary metabolites of fungi that can adversely affect human health. They commonly occur in food crops (Eskola et al. 2020) and constitute a chemically and toxicologically heterogenous group of substances (Bennett and Klich 2003). The most common ones of concern for human health include aflatoxins, deoxynivalenol (DON), fumonisins, ochratoxin A, patulin and zearalenone (Eskola et al. 2018). Aflatoxin B1 (AFB), DON and fumosinin B1 (FB1) were prioritized for HBM4EU.

2.2.1. Aflatoxin B1 (AFB)

The research about aflatoxin started with the outbreak of the turkey-X-disease in 1960 (Asao et al. 1965; Lancaster et al. 1961; Wogan 1966). Aflatoxins are carcinogenic to humans (IARC, 1993a, 2002a, 2012). The carcinogenic properties of the aflatoxins have been studied extensively in several animal species (Busby and Wogan 1984). Activity is primarily associated with Aflatoxin B1 (AFB), one of the most potent liver carcinogens known. Aflatoxins are a global health problem, particularly in developing countries where storage of food grains in conditions of high heat and humidity favors the growth of mold (Busby and Wogan 1984).

Human exposure to high levels of AFB from the diet is an important risk factor for the development of liver cancer. Strong positive correlations were found in Africa, China, and Thailand. In the USA, the incidence of liver cancer was 10 % higher in the Southeast region, the region with the highest average daily intake of aflatoxin (Wu et al. 2014). The synergistic effect of AFB exposure and hepatitis B virus infection increases up to 60-fold the risk of liver cancer (Wogan et al. 2012).

The work performed with AFB is a milestone of toxicological research and HBM (Kensler et al. 2011). Biomarkers could be related to disease, and intervention studies demonstrated the decrease of the biomarkers (Groopman et al. 2008). The critical step of AFB-metabolism (reviewed in (Sabbioni and Sepai 1998) is the formation of the *exo*-8,9-aflatoxin-epoxide (Guengerich et al. 1998) that reacts with DNA (Brown et al. 2009), proteins (Sabbioni 1990) and glutathione (Raney et al. 1992). The reaction with glutathione is a key step for detoxification of the reactive epoxide (Fig. 3).

Different markers of exposures (Table 2, S2) have been developed for people exposed to AFB (Fig. 3): a) AFB present in blood or urine; b) the metabolite aflatoxin M1 (AFM1) in urine; c) other urinary metabolites such as the aflatoxin B1 mercapturate (AFB-Cys-NAc), aflatoxin P, aflatoxin Q1; however, these have not been measured often and are not included in the present work; d) biological effective dose markers - derived from the carcinogenic intermediate AFB-epoxide - such as the AFB adducts with DNA (AFB-N7-Gua) excreted in urine or the AFB-adduct (AFB-Lys) with albumin in blood are part of this review (Fig. 3).

Biomonitoring methods of newer studies have been reviewed recently (Arce-Lopez et al. 2020b). Older studies have been reviewed in a book chapter (Sabbioni and Sepai 1998) and (Sabbioni and Turesky 2017). A number of HBM studies have been performed in Europe in recent years (Arce-Lopez et al. 2020b; De Ruyck et al. 2020; Debegnach et al. 2020; Ferri et al. 2017; Heyndrickx et al. 2015). In 2020 (De Ruyck et al. 2020), a similar number of urinary samples was positive for AFM1 and DON in subjects from Belgium, France, Czech Republic, The Netherlands, and Norway (De Ruyck et al. 2020). A striking effect - possibly deriving from climate warming - was seen in the increase of AFB-albumin-adducts in people from Texas, USA (Xue et al. 2021).

2.2.1.1. AFB-biomarkers in urine and blood. The sample amount used for urine analyses in newer methods varied from 0.1 −2 mL (Table 2). In older methods and especially for the analysis of the excreted DNA-adduct AFB-N7-guanine larger amounts of urine were necessary (20 mL) (Table 2). The metabolites (Table S2) were isolated on a solid phase extraction column and/or immunoaffinity columns in order to increase the sensitivity of the assay (e.g. LC-UV or LC-FLD).

For the determination of AFB in urine, the best LOD (5 pg AFB/mL) was obtained by using 2 mL of urine and LC-MS/MS (Huybrechts et al.

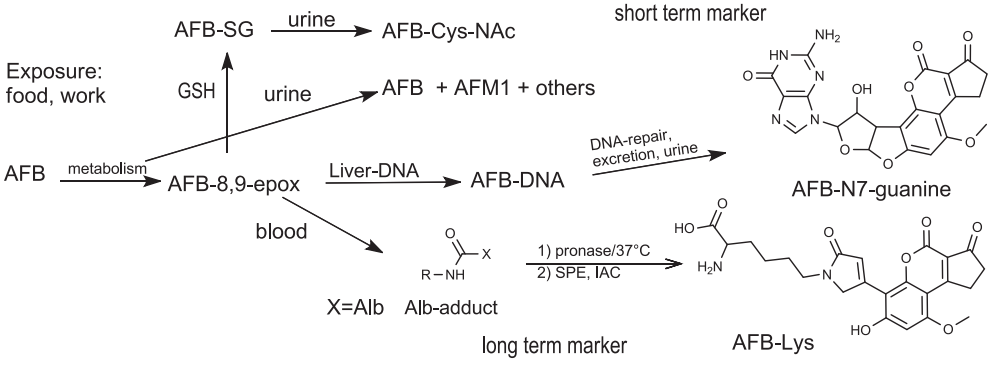

Fig. 3. Biomarkers after exposure to aflatoxins.

Table 2
The major methods used to biomonitor people exposed to aflatoxins.

Aflatoxins Substance	Biomarker	Matrix (mL)	Work up	Analytical Method	LOD
Aflatoxin B1 (AFB)	AFB-Lys	Serum: <0.1[6], greater than 0.1[5], 0.15[4,20], 0.25[3]	SPE[3,4]a, P + IAC[6,20]c, P[5]	LC-MS/MS[3,4], ELISA[5], LC-FLD[6,20]	0.25[3]d,e, 3[5], 5[20], 6[4], 9[6] pg/mg
	AFB-Lys	Dried blood spot: 0.05[7]	SPE[7]c	LC-FLD[7]	10[7] pg/mL
	AFB	Dried blood spot: 0.1[2] Dried serum spot: 0.1[2]	LLE[2]c	LC-MS/MS[2]	12[2]d pg/mL
	AFB	Plasma: 0.1[1], 0.2[18]	LLE[1]c,SPE[18]b	LC-MS/MS[1,18]	40 pg/mL[1]d,[18]d
	AFB	Urine: 0.1[11], 1[12], 2[13,19]	LLE[12]c, direct[11,13]c, IAC[19]a	LC-MS/MS[11,12,13] LC-HRMS[19]	0.8[19], 5[13]d, 50[11]d, 100[12]d pg/mL
	AFB-N7-guanine	Urine: 10[9], 20[8]	IAC/SPE[8]a, SPE[9]c	LC-MS/MS[8,9]	0.04[8], 3[9] pg/mL
Aflatoxin M1 (AFM1)	AFM1	Urine: 0.05[14], 0.1[11], 0.5[15,16], 2[13,19], 15[17]	direct[11,14]c, IAC[13]c, SPE[15]a, IAC/SPE[16,17]c, IAC[19]a	LC-MS/MS[11,13,15,16], ELISA[14], LC-FLD[17], LC-HRMS [19]	0.3[15]d, 1.3[19], 2[13]d, 3[17], 15[14], 25[11]d, 60[16]d pg/mL
	AFM1	Plasma: 0.2[18]	SPE[18]b	LC-MS/MS[18]	180[18]d pg/mL

The chemical structures are presented in Table S2. Abbreviations: IAC = immuno affinity chromatography: SPE = solid phase extraction; LLE = liquid–liquid extraction; P = pronase digestion of the protein; direct = without work-up. [1] (Slobodchikova and Vuckovic 2018); [2] (Osteresch et al. 2017); [3] (McCoy et al. 2005); [4] (Jager et al. 2016); [5] (Gong et al. 2003) (Chapot and Wild 1991); [6] (Sabbioni 1990; Sabbioni et al. 1990); [7] (Xue et al., 2016); [8] (Egner et al. 2006); [9] (Jager et al. 2016); [11] (Gerding et al. 2014); [12] (Escriva et al. 2017); [13] (Huybrechts et al. 2015); [14] (Chen et al. 2018b); [15] (Sarkanj et al. 2018); [16] (Solfrizzo et al. 2011); [17] (Schwartzbord et al. 2017); [18] (Arce-Lopez et al., 2020a); [19] (Debegnach et al. 2020); [20] (Wang et al. 1996); a) addition of corresponding isotope-labeled internal standard; b) addition of surrogate isotope-labeled internal standard; c) without internal standard; d) multi-method that determines other mycotoxins; e) method used in the NHANES biomonitoring study (CDC-NHANES 2012; Schleicher et al. 2013).

2015). For the determination of AFM1, the best LOD (5 pg/mL) was reached by using 0.5 mL of urine and LC-MS/MS (Sarkanj et al. 2018). For the determination of DNA adducts (AFB-N7-gua) in urine, the best LOD (0.04 pg/mL) was yielded using 10 mL of urine and LC-MS/MS (Egner et al. 2006). For urinary AFM1, method performance characteristics have been adequately reported. Inter-laboratory comparisons are usually not part of the methods applied for the determination of AFB and/or AFM1. The method descriptions do not mention the use of certified reference material.

In general, newer methods do not only measure aflatoxins, but many mycotoxins in the same analysis. They do not usually include internal isotope labeled standards, but rely on external calibration curves without the control of an internal standard.

2.2.1.2. AFB-biomarker of the biologically effective dose: albumin-adduct. It has been shown in rats, that AFB – a liver carcinogen- forms DNA-adducts in the target organ and with serum albumin in a dose dependent way (Wild et al. 1986a) (Fig. 3). Given the carcinogenicity of AFB, the albumin adduct AFB-Lys is an excellent marker for the biological effect of AFB. While cheaper and less sensitive methods were frequently used in studies with high exposure populations, current methods are usually based on LC-MS/MS. The LOD-levels increase in the following order: LC-MS/MS, ELISA, LC-FLD (McCoy et al. 2008). The methods yield different absolute values but the same rank of the values. Intercomparisons of the methods were performed also in other studies (Wild et al. 1992; Wild et al. 1990).

In population studies (e.g. Africa) with high exposures and low budgets, cheaper methods such as radioimmunoassays, enzyme-linked immunosorbent assays (ELISA) (Wild et al., 1986b), HPLC with fluorescence (Sabbioni 1990; Sabbioni et al. 1987) and UV detection were used (reviewed in (Sabbioni and Sepai 1998)).

Usually not more than 0.25 mL of serum are used for the analysis of albumin-adducts. The best LOD (0.25 pg AFB-Lys/mg albumin) was obtained using 0.25 mL of serum and LC-MS/MS (McCoy et al. 2005). This method was applied to the analysis of 2051 people in the NHANES 2009–2010 study (Schleicher et al. 2013). However, only 1.2 % of the samples contained AFB-Lys.

Albumin adducts of AFB were measured with LC-MS/MS, LC-FLD and ELISA (McCoy et al. 2008; Scholl et al. 2006). AFB-Lys is not commercially available, but has to be synthesized. For the synthesis of AFB-Lys, the alpha amino group of lysine has to be protected in order to yield the corresponding in vivo product that is generated by the reaction of the epsilon amino group of lysine with the aflatoxin-epoxide. The structure of the obtained product should be confirmed by 1H NMR, and 13C NMR spectra (Sabbioni 1990). The DNA adduct of AFB (AFB-N7-gua) with guanine is commercially available.

2.2.1.3. Recommended methods. For the analysis of AFB and AFM1, urine is the preferred matrix. The lowest LOD measuring both AFM1 and AFB was obtained by Huybrechts et al (Huybrechts et al. 2015). However, most procedures measure only AFM1, with the lowest LOD achieved by Sarkanj (Sarkanj et al. 2018). For AFB-N7-guanine (Egner et al. 2006) and AFB-Lys (McCoy et al. 2005), the best LODs were obtained by a laboratory (Prof. J.D. Groopman) with over 40 years experience in the field of aflatoxin research. The method of McCoy was used to determine AFB-Lys in the NHANES-study (CDC-NHANES 2012; Schleicher et al. 2013). For laboratories with a lower budget the method using LC-FLD or ELISA test could be used, although the analytical quality and the sensitivity are lower than for the LC-MS/MS methods (McCoy et al. 2008).

2.2.2. Deoxynivalenol (DON)

DON, also referred to as vomitoxin, is a secondary fungal metabolite produced by *Fusarium* species growing on crops, especially in temperate climates. It is one of the most frequently occurring mycotoxins in food and feed (Mishra et al. 2020), mainly affecting cereals and cereal-based products like pasta, bread and beer. Chemically, DON is classified as type B trichothecene. In addition to DON, the structurally related acetylated DON and modified forms of DON (e.g. plant-conjugates) have been found in the same type of matrices, of which 3-acetyl-DON, 15-acetyl-DON, and DON-3-glucoside are the most relevant ones (Fig. 4, Table 3). In a scientific opinion by the European Food Safety Authority (EFSA) (EFSA, 2017), the relative concentrations of 3-acetyl-DON, 15-acetyl-DON and DON-3-glucoside to DON were estimated as 10 %, 15 % and 20 %, respectively (higher DON-3-glucoside in beer) and a tolerable daily intake of 1 μg/kg bw per day was set for the sum of the four DON, as well as an acute reference dose of 8 μg/kg body weight (bw) per eating occasion. The International Agency for Research on Cancer (IARC) classified DON as a Group 3 substance (inadequate evidence in experimental animals (IARC, 1993b).

Determination of DON biomarkers of exposure was initiated in 2003 and followed by larger scale HBM of DON biomarkers in urine from 2008

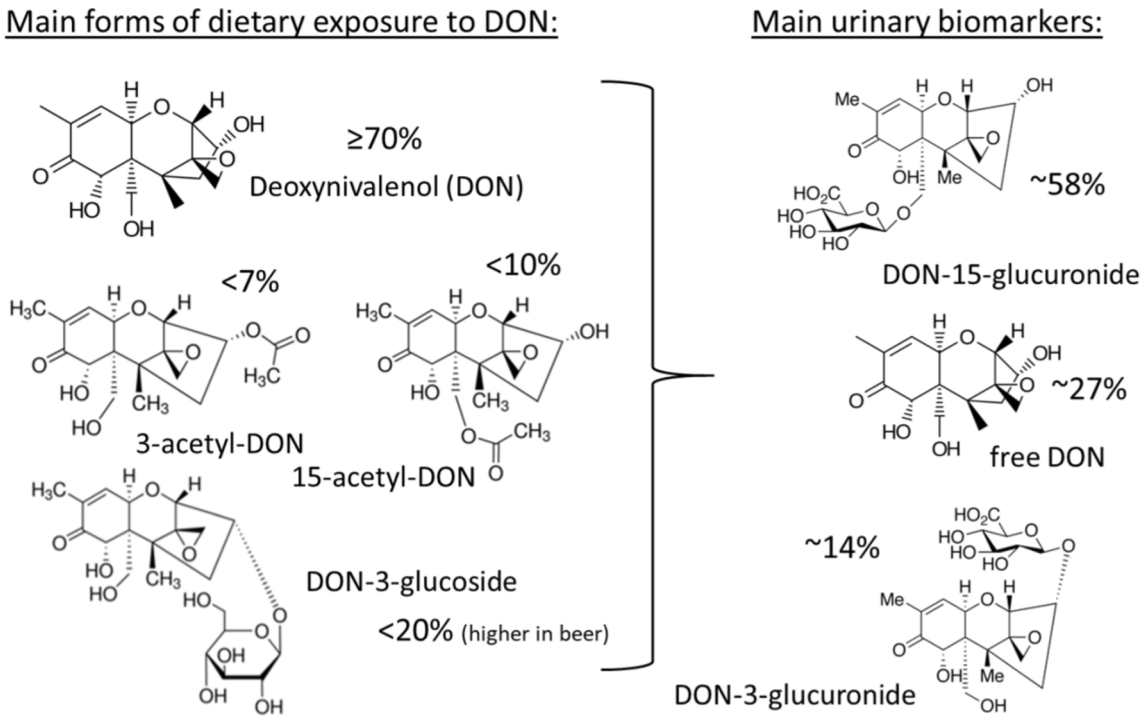

Fig. 4. Biomarkers (Vidal et al. 2018) after exposure to different forms of DON (EFSA, 2017).

Table 3
The major methods used to biomonitor people exposed to DON.

Deoxynivalenol (DON)					
Substance	**Biomarker(s)**	**Matrix: urine (mL)**	**Work up**	**Analytical Method**	**LOD (ng/mL)**
Deoxynivalenol (DON)	**Direct (without deconjugation)**				
3-acetyl-DON	DON-15-GlcA, DON-3-GlcA, free DON	0.2	Dilution/reconstitution	LC-MS/MS[a,*]	0.05–0.16 [10]
15-acetyl-DON		0.5	LLE	LC-MS/MS*	0.05–0.2 [3]
DON-3-glucoside		1.0	dispersive LLμE, derivatizationIAC	GC-MS/MS*	0.12 [12]
		10	(MM)	LC-MS/MS*	0.16 [5]
		0.3	Dilution	LC-HRMS[a,b,*]	0.17 [11]
		2.0	none	LC-MS/MS[a]	0.2–0.5 [1]
		2.0	LLE	LC-MS/MS*	0.5 [9]
		0.1	Dilution	LC-MS/MS	0.5–1.8 [2]
		0.1	none	LC-MS/MS*	1 [4]
		10	LLE, dSPE, derivatization	GC-MS/MS*	2.25–2.85 [6]
		10	LLE/SPE	LC-MS/MS*	4–6 [7]
		0.1	Dilution	LC-MS/MS[a]	10 [8]
	Indirect (with deconjugation, determination of total DON)				
	total DON (c)	0.5	SPE [d]	LC-MS/MS[a,*]	0.05[13]
		1.0	IAC [d]	LC-MS; LC-HRMS[a]	0.005–0.25[14]
		3.0	SPE [d]	LC-MS/MS[a,*]	0.05 (LOQ)[23]
		1.0	SPE [e], derivatization	GC-MS[a]	0.08[16]
		3.0	IAC [e]	LC-MS/MS[a]	0.16[15]
		4.0	IAC [d] (MM)	LC-MS/MS[a,*]	0.33[21]
		1.0	IAC [d]	LC-MS/MS[a]	0.5 (LOQ)[20]
		1.0	μSPE [d]	LC-MS/MS[a]	0.5[19]
		4.0	IAC [d]	LC-MS[a]	0.6 (LOQ)[18]
		6.0	SPE, IAC [e]	LC-MS/MS*	1.5 (LOQ)[17]
		0.55	filterpaper liquid extr. [d]	LC-MS/MS[f,*]	3.0[22]

The chemical structures are presented in Table S2. [1] (Vidal et al. 2018) (also included DON-3-glucoside); [2] (Warth et al. 2016) (also included DON-sulfates); [3] (Huybrechts et al. 2015) (also included acetyl-DONs and acetyl-DON-glucuronides); [4] (Gerding et al. 2015); [5] (Rodríguez-Carrasco et al. 2014) (only free DON); [6] (Njumbe Ediage et al. 2012) (DON-15-GlcA not included); [7] (Warth et al. 2012b; Warth et al. 2012a) (DON-15-GlcA not included); [8] (Rubert et al. 2011) (only free DON); [9] (Fan et al. 2019) (also included acetyl-DONs); [10] (De Ruyck et al. 2020) (also included acetyl-DONs and DON-3-glucoside); [11] (Collins et al. 2021); [12] (Niknejad et al. 2021) (only free DON); [13] (Sarkanj et al. 2018); [14] (Brera et al. 2015); [15] (Ali et al. 2015); [16] (Cunha and Fernandes 2012); [17] (Solfrizzo et al. 2014); [18] (Turner et al. 2008b); [19] (Deng et al. 2018); [20] (Wallin et al. 2013); [21] (Gratz et al. 2020); [22] (Schmidt et al. 2021b); [23] (Ndaw et al. 2021); a) $^{13}C_{15}$DON used as internal standard; b) $^{13}C_{15}$DON-15-GlcA used as internal standard; c) total DON after deconjugation = sum free deoxynivalenol + aglycons of DON-15-GlcA and DON-3-GlcA; d) β-glucuronidase (*E. coli*); e) β-glucuronidase/sulfatase (*Helix Pomatia*); f) 1d-DON used as internal standard. *) multi-method, also includes other mycotoxin biomarkers.

(Turner et al. 2008a). An overview of recent HBM studies was compiled in the EFSA opinion (EFSA, 2017) and further in (Deng et al. 2021).

Of the DON-related compounds, acetyl-DONs are rapidly deacetylated in the gastrointestinal tract after which further absorption and metabolism takes place of DON (Broekaert et al. 2015; Eriksen et al. 2003; Slobodchikova et al. 2019; Veršilovskis et al. 2012). This mechanism is supported by the absence of acetyl-DONs and their glucuronides in HBM studies (Cunha and Fernandes 2012; Fan et al. 2019; Huybrechts et al. 2015; Martins et al. 2019). DON-3-glucoside is cleaved to form free DON during digestion (Vidal et al. 2018). Hence, essentially, the DON derivatives first transform to DON and then follow the same metabolic pathway as DON itself.

Toxicokinetic studies in animals and humans (Mengelers et al. 2019; Vidal et al. 2018; Warth et al. 2016; Warth et al. 2013) indicate that DON is mainly excreted in urine, which is supported by HBM studies (e.g.(Deng et al. 2018; Gerding et al. 2015; Huybrechts et al. 2015; Njumbe Ediage et al. 2012; Warth et al. 2012a). The majority of the studies therefore include urinary biomarkers, although measurements in plasma have also been reported (Arce-Lopez et al. 2021; Slobodchikova and Vuckovic 2018). DON can be detectable in plasma shortly after intake, but is rapidly cleared from the blood (Broekaert et al. 2015; EFSA, 2017; Pestka and Amuzie 2008). Therefore, urine is considered as the most appropriate matrix for HBM.

2.2.2.1. DON-biomarkers in urine. From toxicokinetic studies it became apparent that the main urinary biomarker is DON-15-glucuronide, followed by free DON and DON-3-glucuronide (Fig. 4). A human volunteer study with 20 subjects revealed that DON was rapidly excreted within 24-hours (ratio, DON-15-glucuronide: free DON: DON 3-glucuronide = 58: 27: 14), and that a large amount of the total DON was excreted in the first hours (<6h) after DON administration (Mengelers et al. 2019; Vidal et al. 2018). De-epoxy-deoxynivalenol (DOM-1) and DON-3-sulfate have been identified as minor human metabolites (Warth et al. 2016). In case of exposure to DON-3-glucoside, the parent compound was found as a minor (4 %) biomarker (Vidal et al. 2018). Vidal et al. (Vidal et al. 2018) and Mengelers et al. (Mengelers et al. 2019) concluded that DON-15-glucuronide was a preferred urinary biomarker of exposure to DON (and also to DON-3-glucoside), although total DON after deconjugation could also be used. Interestingly, they further concluded that morning urine was not adequate to assess DON exposure, at least 16 h urine would be needed for a representative view.

Analytical methods for the determination of DON biomarkers can be divided in methods *without* and methods *with* a deconjugation step (direct and indirect methods, respectively). Methods without a deconjugation step typically include DON, DON-3-glucuronide, DON-15-glucuronide. In methods with a deconjugation step the (deconjugated) DON is the only target biomarker. Often, DON biomarker(s) are part of a larger set of mycotoxin biomarkers simultaneously analyzed. The various methods reported in the scientific literature are summarized in Table 3.

Direct methods can be straightforward dilute-and-shoot methods, requiring very small sample volumes, or generic liquid–liquid extraction (LLE) or solid phase extraction (SPE) procedures. In indirect methods the urine is first deconjugated, often overnight. Then an extraction/cleanup is done using SPE or immunoaffinity columns. Instrumental analysis of DON biomarkers is mostly done by LC-MS/MS, although GC–MS(/MS) after silylation has also been used. The volume of urine needed for analysis varies from 0.1 to 10 mL, with a median of 2 mL. The reported LODs vary widely, from 0.005 ng/mL to 10 ng/mL (see Table 3). The high variability in reported LODs has multiple causes: different concentration factors during sample preparation, ranging from 0.1 (10x dilution) to 50, different injection volumes in LC or GC, sub-optimal measurement conditions (in case of multi-mycotoxin biomarker methods often compromises have to be made). Furthermore, laboratories may have used different ways of calculation of LODs resulting in conservative or 'optimistic' LODs.

For DON biomarkers no certified reference materials and no interlaboratory comparison investigation programs (ICI) or external quality assurance programs (EQUAS) existed up to early 2020. Two ad-hoc interlaboratory comparisons were reported, both involving three laboratories (Brera et al., 2015; Solfrizzo et al. 2013). As part of the HBM4EU QA/QC program, a QC exercise comparable to ICIs was organized to assess the proficiency and comparability of six pre-selected laboratories, all using an indirect method (Esteban López et al., 2021). Three ICI rounds (Jan-June 2020) each with two human urine samples from the general population (0.5–33 ng total DON/mL, real-life, i.e. not spiked) were conducted. During this exercise, a negative bias was observed for participants using *Helix Pomatia*-based enzymes for deconjugation. As an HBM4EU follow up, a continuous proficiency test program amongst a larger number of laboratories would be needed to ensure generation of high quality and comparable data for DON biomarkers.

2.2.2.2. Recommended methods. Vidal et al. (Vidal et al. 2018) considered DON-15-glucuronide as the preferred biomarker for DON exposure, and hence preferred the direct method (without deconjugation). In a follow up study (Vidal et al. 2020), the same group further elaborated on this by comparing the direct method and the indirect method, reporting higher average biomarker concentrations using the direct method, suggesting incomplete deconjugation when using the indirect method. It was observed by others that the deconjugation conditions are a critical aspect for DON-glucuronides (see Fig. S1), and that the conditions used by Vidal et al. (2020) in their comparison were sub-optimal. Using the optimum conditions (*E. coli* based β-glucuronidase at pH 6.8, overnight), complete deconjugation was achieved, as reported by Warth et al. (Warth et al. 2012b; Warth et al. 2012a) and Schmidt et al. (Schmidt et al. 2021b). This makes the indirect method (determination of total DON) a suitable alternative to direct determinations, also offering the advantage that the analytical reference standard of both native DON and its isotopically labeled analogue are commercially available. The use of the isotope-labeled analogues as internal standards is considered highly beneficial for quantitative analysis of urine due to varying matrix effects in LC-MS-based methods (e.g. (Collins et al. 2021)). At the moment DON-glucuronides are only available as in-house synthesized compounds. This inhibits large scale monitoring by multiple laboratories through the direct method.

Based on the above, the currently recommended method is the determination of total DON after deconjugation using *E. coli* based β-glucuronidase at optimised pH and time. The use of the isotope labeled DON as internal standard prior to deconjugation is highly recommended to achieve reliable quantitative performance. Concentration and (some) cleanup can be achieved by SPE. The use of an immunoaffinity column instead of SPE is beneficial for selectivity, especially in the lower concentration range (<1 ng/mL), albeit at higher cost. Current monitoring data suggest that a limit of quantification in the range of 0.2–0.5 ng/mL is fit-for-purpose. LC-MS/MS is the preferred instrumental analysis technique. GC-MS/MS is possible but requires a derivatization step.

2.2.3. Fumonisin B1

Fumonisin B1 (Table S2) is the most abundant toxic form of fumonisins, produced by *Fusarium* species. FB1 primarily occurs in maize and maize-based foods (Shephard et al. 2007), but also in the other forms of cereals (rice, wheat, barley, rye, oat, and millet). Its formation is influenced by climatic factors and can occur both pre- and post-harvesting (Kamle et al. 2019).

FB1 has been classified possibly carcinogenic to humans/group 2B (IARC, 2002b). The suggested mode of action of FB1 is the toxin interferes with the sphingolipids metabolism, inducing apoptosis (Feijo Correa et al. 2018). Analyses of fumonisins in human samples date from the early 2000s and were performed in urine (Shetty and Bhat 1998), feces (Chelule et al. 2000), and hair (Sewram et al. 2003). Since then, the

Table 4
The major methods used to biomonitor people exposed to fumonisin B1.

Fumonisin					
Substance	**Biomarker**	**Matrix (mL)**	**Work-up**	**Analytical Method**	**LOD (pg/mL)**
Fumonisin B1 (FB1)	FB1	Urine: 0.1[6],[15],[3], 0.2[18],[13],[16], 0.5[1],[12], 2[10],[5],[17], 5[8], 6[11],[2], 10[9],[4],[7] Dried urine spot: 1[14]	SPE[1]a,[3]a,[5]a,[7],[8]a, IAC[2]a,[4]a, direct[6],[10]e,[15]d, PP[12]b, LLE + SPE[9]f, IAC/SPE[11]b, LLE[13]b,[14]a, [16]b,[18]a, QuEChERS[17]	LC-MS[7], LC-MS/MS[1,2],[3]g,[4–6],[8–11], [13-18], LC-MS/MS + HRMS[12]	1[1]c, 3[2]c, 4.2[3]c, 7[4]c, 10[5]c, 12.5[6]c, 20[7],[8]c, 50[9]c,[10]c,[11]c, 58[12]c, 100[13]c, 160[14]c, 200[15]c, 200[16]c, 210[17]c, 320[18]c
	FB1	Plasma: 0.05[12], 0.2[16],[18]	PP[12]b, SPE[16]a, LLE[18]a	LC-MS/MS + HRMS[12], LC-MS/MS[16],[18]	58[12]c, 200[16]c, 400[18]c
	FB1	Dried serum spot: 0.1[19] Dried blood spot: 0.1[19]	LLE[19]b	LC-MS/MS[20]	521[19]c 627[19]c
	FB1	Breast milk: 1[20], 5[22], 10[21]	LLE[20]a, QuEChERS[21], LLE[22]b	LC-MS/MS[20], LC-HRMS[22], HPLC + RSLC[22],	0.84[20]c, 5[21]c, 5.5[22]
	FB1	Hair(g): 0.5[23], 0.7–1.0[24]	SPE[23]f,[24]f	LC-MS[23],[24]	3.3 ng/g[23], 2.5 ng/g[24]c

The chemical structures are presented in Table S2. Abbreviations: IAC = imuno affinity chromatography; LLE = liquid–liquid extraction; PP = protein precipitation technique; QuEChERS procedure = Quick, Easy, Cheap, Effective, Rugged, Safe; SPE = solid phase extraction; direct = without work-up. [1] (Sarkanj et al. 2018); [2] (Franco et al. 2019); [3] (Schmidt et al. 2021a); [4] (Ahn et al. 2010); [5] (Chen et al. 2018a); [6] (Gerding et al. 2015); [7] (Gong et al. 2008); [8] (Liu et al. 2020); [9] (Njumbe Ediage et al. 2012); [10] (Huybrechts et al. 2015); [11] (Solfrizzo et al. 2011); [12] (De Ruyck et al. 2020); [13] (Huang et al. 2021); [14] (Schmidt et al. 2021b); [15] (Warth et al. 2014); [16](Fan et al. 2019); [17] (Martins et al. 2019); [18](Cao et al. 2018); [19] (Osteresch et al. 2017); [20] (Coppa et al. 2021); [21] (Rubert et al. 2014); [22] (Magoha et al. 2014); [23] (Bordin et al. 2015); [24] (Sewram et al. 2003); a) addition of corresponding isotope-labeled internal standard; b) without internal standard; c) multi-method that determines additional chemicals; d) dilute and shoot (DnS) method; e) semi-quantitative direct injection; f) sample clean-up using LLE in combination with SAX SPE; g) online SPE-UHPLC-MS/MS.

development of more efficient analytical methods for HBM has advanced (Table 4).

2.2.3.1. Fumonisin B1-biomarkers in urine. Urine was widely used as biological matrix for the exposure assessment of fumonisins in humans (Table 4). Most studies use analytical methods developed for the quantification of multi-mycotoxins in urine samples.

In Europe, FB1 was detected in 6 %, 7 %, and 56 % of urine samples from Sweden, Portugal and Italy, respectively (Martins et al. 2019; Solfrizzo et al. 2014; Wallin et al. 2015). These differences in detection rates could be affected (partly) by differences in LODs. FB1 was not quantified or detected in urine samples from Belgium (Heyndrickx et al. 2015; Huybrechts et al. 2015), Germany (Gerding et al. 2015; Gerding et al. 2014) and Spain (Rubert et al. 2011). A recent European study conducted by De Ruyck et al. (De Ruyck et al. 2020) found an incidence of FB1 mycotoxins in 26 % of the urine samples.

The prevalence of FB1 exposure is often higher in Africa than in Europe. In a study among Tanzanian infants, FB1 biomarkers were detected in up to 96 % of urine samples (Shirima et al. 2013). Several other studies from Africa have shown the presence of FB1 in urine samples from the general population (Abia et al. 2013; Ezekiel et al. 2014; Kouadio et al. 2014; Njumbe Ediage et al. 2013; Njumbe Ediage et al. 2012; Shephard et al. 2013; Shirima et al. 2013; van der Westhuizen et al. 2011; Warth et al. 2012a). To date, studies conducted in Asia have mainly been from China (Ahn et al. 2010; Cao et al. 2018; Cao et al. 2013; Liu et al. 2020; Warth et al. 2014; Xu et al. 2010). FB1 incidences of 3.1 % and 12.3 % of urine samples were detected by Fan et al. (Fan et al. 2019) and Huang et al. (Huang et al. 2021), respectively. Studies are also available from South America (Coppa et al. 2021; Franco et al. 2019; Gerding et al. 2015; Gong et al. 2008; Torres et al. 2014). In recent studies from Brazil, Franco et al. (Franco et al. 2019) found that FB1 was present in 23 % of urine samples from a farm population, while Coppa et al. (Coppa et al. 2021) did not detect FB1 in the urines from a lactating women population.

Analytical methods developed for FB1 detection in human urine samples have all been established using LC-MS/MS. The first analytical methods focused on single compounds (Gong et al. 2008; Shetty and Bhat 1998; Silva et al. 2010). Dedicated immunoaffinity columns for extraction/cleanup of FB1 (cross-reactive to FB2) exist to provide a high degree of selectivity (Silva et al. 2010). These can be beneficial for dedicated FB1 measurements, since urinary excretion is only 4 % and therefore requires very low LODs. Analytical methods developed recently have mainly been based on multi-mycotoxin detections, which present the advantage of multiple mycotoxins detection simultaneously (Gerding et al. 2014; Silva et al. 2010; Solfrizzo et al. 2011; Warth et al. 2012a). Multi-mycotoxin analysis requires adapted sample clean-up protocols, which can affect sensitivity of some compounds or become expensive if optimized for high specificity of all compounds (Sarkanj et al. 2018). In addition, fumonisins need specific conditions, like high acidic, which is not favourable for some of the other mycotoxins. Thus, multi-compound analyses are often a compromise and dedicated methods can often outperform multi-methods (multi-method = refers to the possibility to analyze different class of compounds with one method) for a specific biomarker of mycotoxins.

LODs depend on many parameters, often not discussed in the papers reviewed, and should be handled with caution. Sarkanj et al (Sarkanj et al. 2018) reported an LOQ of 10 pg/mL and a sample intake of 0.5 mL in a multi-mycotoxin analysis, using a recent UHPLC-MS/MS generation. However, the LOD of 1 pg/mL reported could be questionable, given that LOD and sample intake are interrelated. The HPLC-MS/MS used by Gerding et al. (Gerding et al. 2015) required a sample intake of 0.1 mL resulting in an LOD of 12.5 pg/mL.

2.2.3.2. Fumonisin B1-biomarkers in blood. FB1 has also been determined in blood, in animal toxicokinetics studies. However, the analytical methods developed in these studies were not suitable for the analysis of human plasma for HBM purposes, due to limitations in accurate detection. A multi-center European study found an FB1 incidence of 29.7 % in human plasma (De Ruyck et al. 2020) using a recent multiclass method for mycotoxin detection developed by Slobodchikova and Vuckovic (Slobodchikova and Vuckovic 2018) (Table 4).

Osteresch et al. (Osteresch et al. 2017) (Table 4) developed a rapid multi-mycotoxin approach for the quantification in dried whole blood and dried serum spots which are less invasive than conventional blood collection. However, to date, analytical methods for these matrices need to be further improved to be suitable for HBM of FB1.

2.2.3.3. Fumonisin B1-biomarkers in human hair and milk. Human hair samples were analyzed for FB1 only in two studies so far (Bordin et al. 2015; Sewram et al. 2003) (Table 4). Bordin et al. (Bordin et al. 2015) modified the method described by Sewram et al (Sewram et al. 2003) to assess the FB1 level in hair samples from Brazil. FB1 was detected in hair

samples of 7.2 % of participants. However, one of the main limitations of the use of hair samples remains the possible exogenous contaminations. In addition, there is no experimental data on the relationship between fumonisins intake and the level of fumonisins found in a segment of human hair (Bordin et al. 2015).

In human milk, FB1 can be excreted after the contamination of lactating mothers from diet. Breast milk would be suitable to detect FB1 contamination of lactating mothers and to assess the possible risk of FB1 exposure for newborns. However, few epidemiological studies to date investigated the levels of FB1 in human milk (Table 4). Rubert et al. (Rubert et al. 2014) did not detect fumonisins in breast milk samples from Spanish women. In contrast, Magoha et al. (Magoha et al. 2014) detected FB1 in more than 44 % of individual breast milk samples in a study in Tanzania. In addition, about 10 % of the positive samples exceeded the EU limit for total fumonisin in infants' foods (Magoha et al. 2014).

2.2.3.4. Recommended methods. Urinary FB1 appeared as the appropriate biomarker/matrix combination for the exposure assessment to FB1. Although several matrices have been evaluated in this review, some of them, such as hair, is ultimately not likely to be relevant in general biomonitoring programs. The smallest sample amounts used for urine analysis in the different studies ranged from 0.1 to 2 mL (Table 4). Several methods have been recently developed for the detection of FB1 in urines in the context of multi-mycotoxin analysis, while dedicated methods involving immunoaffinity-based cleanup were also reported. For the determination of FB1 in urine, the best LOD (1 pg/mL) was obtained using 0.5 mL of urine and LC-MS/MS (Sarkanj et al. 2018). The second best LOD (3 pg/mL) was obtained using 10 mL of urine and LC-MS/MS (Franco et al. 2019). The lowest urine sample (0.1 mL) had been used with online SPE LC-MS/MS and the LOD was 4.2 pg/mL (Schmidt et al. 2021b). FB1 and ^{13}C-labeled FB1 are commonly commercially available. Most studies on mycotoxins quantification do not mention interlaboratory comparisons, the use of certified materials, or laboratory accreditations. However, the "in-house validations" following European directives (EU Commission Decisions 2002/657/EC; 401/2006/EC) were mentioned in some of the reviewed articles. No certified reference materials and Interlaboratory comparison investigation (ICI) or external quality assurance programs (EQUAS) programs exist. An ad-hoc interlaboratory comparison was done by Solfrizzo et al. (Solfrizzo et al. 2013) between three laboratories (Solfrizzo et al. 2013). For the FB1, differences were observed that need further investigations. The implementation of ICI / EQUAS programs for FB1 analysis should further help/allow to ensure the comparability of analytical results between different laboratories.

2.3. Diisocyanates

Diisocyanates are highly reactive compounds that have a variety of commercial applications. Diisocyanates such as toluene diisocyanate (usually a mixture of 2,4-toluene diisocyanate (24TDI) and 2,6-toluene diisocyanate (26TDI)), 4,4′-methylenediphenyl diisocyanate (MDI), 1,6-hexamethylene diisocyanate (HDI) and their oligomers, are increasingly used in e.g. polyurethane foam, paints, adhesives, elastomers, coatings, insecticides and for consolidation of loose rock zones in coal mining or tunneling (Munn et al., 2005). Diisocyanates are one of the main causes of occupational asthma (Baur et al. 1994; Bernstein 1996; Grunewalder and Karol 1986). The predominant routes of occupational exposure is through inhalation and dermal absorption (Liljelind et al. 2010). There may also be a potential relationship between diisocyanates in consumer products and increasing prevalence of asthma in the general population, especially children (Krone 2004).

Due to substantial health risks, exposure monitoring is often required for chronically exposed workers (Rother and Schlüter 2021). Traditionally, personal ambient monitoring of diisocyanates has been utilized but these methods do not measure dermal exposure and cannot evaluate effectiveness of control measures such as the use of respiratory protective devices (Tinnerberg and Mattsson 2008). Air sampling may also be affected by predominant use of pre-polymeric MDI products which have low volatility and may account for non-detectable results in 75 % of personal air samples of MDI exposed workers (Booth et al. 2009). Thus, there is a need for biomarkers that reflect cumulative diisocyanate exposure from both respiratory and dermal sources.

Once absorbed into the human body disocyanates do not require any further activation to react with biomolecules (Bolognesi et al. 2001). Important vehicles for diisocyanates are their reaction products with glutathione (Pearson et al. 1991; Sabbioni et al. 2012a; Wisnewski et al. 2013). The glutathione adducts release the diisocyanate moiety to react with other nucleophiles, e.g., proteins. Therefore, glutathione adducts are thought to be responsible for the transport of isocyanate to reactive sites away from the site of diisocyanate uptake (Fig. 5). Aromatic diisocyanates metabolically release the corresponding aromatic diamines

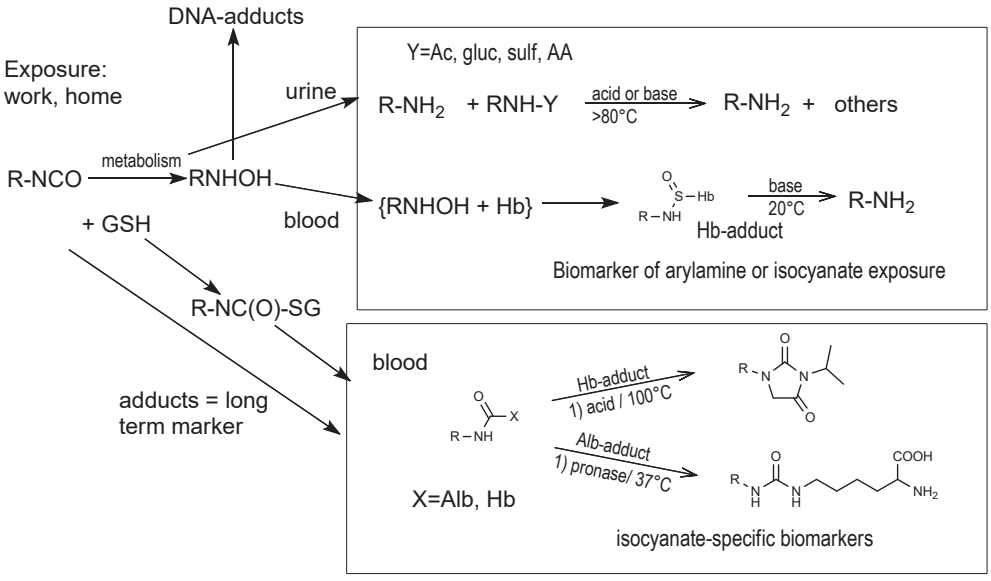

Fig. 5. Biomarkers after exposure to aromatic diisocyanates. Abbreviations: AA = amino acid conjugates, Ac = acetyl, gluc = glucuronide, sulf = sulfate, GSH = glutathione, R-NCO (aromatic diisocyanates, such as MDI, 24TDI, and 26TDI) R-NH_2 (aromatic diamines, such as MDA, 24TDA, 26TDA).

(Bolognesi et al. 2001), which are known animal carcinogens (e.g. 2,4-toluenediamine (24TDA), and 4,4′-methylenedianiline (MDA)). MDA and 24TDA are the compounds of major concern in a ranking procedure based on predicted exposure, production volume and mutagenic and carcinogenic properties (Sabbioni and Day 2020).

2.3.1. *Diisocyanate-biomarkers in urine and blood: Analysis of diamines*

In most studies biomonitoring of diisocyanate exposures were performed with urine samples as shown in Table 5 (Fig. 5, Table S3, S4) (Cocker 2011; Cocker and Jones 2017b; Sabbioni 2017; Scholten et al. 2020).

A few studies were performed with occupationally non-exposed subjects. In a study from Sweden, urine and plasma of workers (n = 121) not exposed to isocyanates were analyzed using chemical methods (acid hydrolysis) (Sennbro et al. 2005). MDA, 2,6-toluenediamine (26TDA), 24TDA, and 1,5-naphthylenediamine (NDA) in urine were found in 97 %, 15 %, 7 %, and 3 % of the participants, respectively. Similar results were found after the hydrolysis of plasma samples (Sennbro et al. 2005). In contrast to the Swedish results, recent results from NHANES showed lower detection frequencies. MDA, 24TDA, 26TDA, NDA, and 1,4-phenylenediamine (14PDA) were analyzed in the general population (n = 2608) (Bhandari et al. 2016; CDC-NHANES 2018a). 26TDA and NDA were not found. 24TDA and 14PDA were found in<10 % and 25 %, respectively, of the samples. MDA was present in about 50 % of the samples of the general population. Therefore, there is a striking difference between the prevalence of MDA and 26TDA in comparison to the results from Sweden. This might be a consequence of the different hydrolysis and analysis conditions (Table S4). Urine analyses of these metabolites do not distinguish between diisocyanate and diamine exposures.

Urine was mainly examined in workers exposed to diisocyanates (reviewed in (Cocker 2011; Cocker and Jones 2017b)). Different hydrolysis conditions (Table S4) are applied to 0.25 to 2 mL of urine (Table 5). After extractions from urine without boiling in acid or base, the corresponding amine and acetylated amine are found (Fig. 5) (reviewed in (Sabbioni 2017)). Boiling with acid or base increases the yield of amine, for example for MDI exposures, by a factor of 6 (Sepai et al. 1995). It was never investigated in *in vivo* samples which products were indeed hydrolyzed with such conditions, except for glucuronides and sulfates that can be cleaved enzymatically, and *N*-acetylated amines that can be cleaved chemically. Over the last 30 years, laboratories applied various experimental conditions for the hydrolysis of urine (Table S4). Too harsh hydrolysis conditions might lead to artifacts and too mild conditions might lead to too small yields.

After hydrolysis and extraction, the yielded diamines were derivatized with heptafluorobutyric acid anhydride (HFBA) (Cocker and Jones 2017a; Lewalter et al. 2000; Sabbioni and Beyerbach 2000) or pentafluoropropionic acidanhydride (PFPA) (Sennbro et al. 2003; Sennbro

Table 5
The major methods used to biomonitor people exposed to diisocyanates.

Diisocyanates					
Substance	**Biomarker**	**Matrix (amount)**	**Work-up**	**Analytical Method**	**LOD**
4,4'-Methylenediphenyl diisocyanate (MDI)	4,4'-methylenedianiline (MDA)[f,g]	Urine: 0.25[5], 1[1,10], 0.19[12,13], 2[8] mL	H/LLE/D[1]b, H/LLE/D[8]a, H/SPE[5]a,H/LLE/D[10]a, H/LLE[13]a, H/SPE/D[12]a	GC-MS (NCI)[1,8] LC-MS/MS[5,10,12,13]	8[10]h, 10[5]h, 50[1]h, 100[8]h, 159[13]i,397[12]h,i pg/mL
	MDI-Val-Hyd[j]	Erythrocytes, Globin: 0.1[2] g	H/LLE/D[2]a	GC-HRMS (NCI)[2]	20[2] pg/g
MDI	MDI-Lys	Serum-albumin: 9[3] mg	P/SPE[3]a	LC-MS/MS[3]	0.25[3] pg/mg
MDI	MDA[13]	Erythrocytes, Hb: 0.2[4,14]g	H/SPE/D[14]c	GC-HRMS (NCI)[14]	6.3[14]eh, 25[4]e,h (MDA)
	MDA, AcMDA[4]		H/LLE/D[4]a	GC-MS(NCI)[4]	150[4]eh (AcMDA) pg/g
2,4-Toluene diisocyanate (24TDI)	2,4-toluenediamine (24TDA)[f,g]	Urine: 0.19[12], 0.25[5], 1[1,7,10], 2[8] mL	H/LLE/D[1,7,8]a, H/SPE[5]a, H/LLE/D[10]a, H/SPE/D[12]a	GC-MS (NCI)[1,7,8] LC-MS/MS[5,10,12]	2[10]h, 30[5]h, 50[1,7], 100[8]h, 220[12]h,i pg/mL
26TDI	26TDA [f,g]	Urine: 0.19[12], 0.25[5], 1[1,7,10], 2[8] mL	H/LLE/D[1,7,8]a, H/SPE[5]a, H/LLE/D[10]a, H/SPE/D[12]a	GC-MS (NCI)[1,7,8] LC-MS/MS[5,10,12]	2[10]h, 30[5]h, 50[1,7], 100[8]h, 391[12]h,i pg/mL
24TDI	24TDA	Erythrocytes, Hb 0.2[4]g	H/LLE/D[4]a	GC-MS(NCI)[1]	25[4]eh pg/g
26TDI	26TDA	Erythrocytes, Hb 0.2[4]g	H/LLE/D[4]a	GC-MS(NCI)[1]	25[4]eh pg/g
24TDI	3A4MP-Lys[k] 2A5MP-Lys[k]	Serum-albumin: 9[6] mg	P/SPE[6]a	LC-MS/MS[6]	0.5[6] pg/mg
26TDI	3A2MP-Lys[k]	Serum-albumin: 9[6] mg	P/SPE[6]a	LC-MS/MS[6]	0.5[6] pg/mg
1,5-Naphthylene diisocyanate (NDI)	1,5-naphthylenediamine (NDA)[g]	Urine: 0.25[5], 1[1] mL	H/LLE/D[1]b, H/SPE[5]a	GC-MS(NCI)[1] LC-MS/MS[5]	30[5]h, 100[1]h pg/mL
1,6-Hexamethylene diisocyanate (HDI)	1,6-hexamethyl-enediamine (HDA)[g]	Urine: 0.19[12], 0.25[9], 1[10,11], 2[8] mL	H/LLE/D[8]a, H/LLE/D[11]d H/SPE[9]a, H/LLE/D[10]a, H/SPE/D[12]a	GC-MS (NCI)[8,11] LC-MS/MS[9,10,12]	2[10]h, 40[11], 150[9]h, 200[8]h, 581[12]h,i pg/mL

The chemical structures are presented in Table S3. Abbreviations: H = hydrolysis with acid or base (Table S3), SPE = solid phase extraction; LLE = liquid–liquid extraction; P = pronase digestion of the protein; D = derivatisation (Table S3). [1] (Sennbro et al. 2003; Sennbro et al. 2005); [2] (Gries and Leng 2013); [3] (Kumar et al. 2009; Sabbioni et al. 2010); [4] (Sabbioni and Beyerbach 2000), *N*-Acetyl-4,4′-methylenedianiline (AcMDA); [5] (Bhandari et al. 2016; CDC-NHANES 2018a); [6] (Sabbioni et al. 2012b) LOD was estimated as 1/10 of the LOQ; [7] (Skarping et al. 1994); [8] (Cocker and Jones 2017a); [9] (Bhandari et al. 2018); [10] (Marand et al. 2004); [11] (Gaines et al. 2010); [12] (Lepine et al. 2020); [13] (Lépine et al. 2019); [14] (Lewalter et al. 2000); a) addition of corresponding isotope-labeled internal standard; b) addition of surrogate isotope-labeled internal standard; c) addition of surrogate internal standard; d) without internal standard; e) method tested within the working group "Analyses of Hazardous Substances in Biological Materials", which is part of the MAK-commission (Göen et al. 2012a); f) these compounds were tested in the HBM4EU round robin; g) these compounds are part of the regular round robins in the German external quality assessment scheme (G-EQUAS) for analyses in biological materials (https://www.g-equas.de/); h) multi-method; i) authors participated successfully in G-EQUAS; j) 3-[4-[(4-Aminophenyl)methyl] phenyl]-5-(1-methylethyl)-2,4-imidazolidinedione (CAS: 264285–90-7); k) 3A4MP-Lys = N6-[[(3-Amino-4-methylphenyl)amino]carbonyl]-L-lysine (CAS: 1416719–26-0), 5A2MP-Lys = N6-[[(5-amino-2-methylphenyl)amino]carbonyl]-L-lysine (CAS:1416719–28-2), 3A2MP-Lys = N6-[[(3-Amino-2-methylphenyl)amino] carbonyl]-L-lysine (CAS:1416719–29-3).

et al. 2005) for all GC-MS methods and with HFBA for one LC-MS/MS method (Marand et al. 2004) (Table 5, S4). For the LC-MS/MS-method by Lépine et al (Lepine et al. 2020), the extracts were derivatized with acetic acid anhydride. The LC-MS/MS method of Bhandari et al (Bhandari et al. 2016) for the analysis of MDA, 24TDA, 26TDA, NDA, and 14PDA was performed without prior derivatization. This is also the case for the analysis of MDA by Lépine et al (Lépine et al. 2019).

The GC-MS method by Cocker and Jones (Cocker and Jones 2017a) was tested by other laboratories in the process of validation for the MAK-commission. Lépine et al (Lepine et al. 2020) passed successfully the German External Quality Assessment Scheme (G-EQUAS, https://www.g-equas.de/) test for MDA, 24TDA, 26TDA, and HDA. The lower test concentration (G-EQUAS, 66/2020) for MDA, 24TDA, 26TDA, NDA, and HDA are 7.23, 1.61, 1.70, 1.80, and 0.93, ng/mL respectively. To the best of our knowledge all other methods were not tested in an inter-laboratory comparison or reviewed by external laboratories.

The LODs for the single diamines vary substantially between the methods. For practical purpose the lowest LODs of methods that analyse at least 4 diamines were elucidated. The LODs decrease in the following order: (Marand et al. 2004), (Bhandari et al. 2016), (Cocker and Jones 2017b), (Lepine et al. 2020).

Aromatic diisocyanates can hydrolyze in vivo to the corresponding diamines. The aromatic diamines can be further metabolized to *N*-hydroxyarylamines, which can form DNA- and Hb-adducts (Fig. 5). Hb-adducts are generally stable over the lifetime of the erythrocytes. The analysis of Hb-adducts of arylamines is a well-established procedure (reviewed in (Sabbioni 2017; Sabbioni and Day 2022)). A tested and well-established method for MDA and other arylamines was published in the biomonitoring method collection of the MAK-commission (Lewalter et al. 2000). An alternative method for Hb-adducts of MDA, *N*-acetyl-MDA (AcMDA), 24TDA, 26TDA, and other arylamines presented by (Sabbioni and Beyerbach 2000) was successfully tested in the biomonitoring group of the MAK-commission, but it was never published. The methods for the urine analyses listed above (Bhandari et al. 2016; Cocker and Jones 2017b; Marand et al. 2004) could be modified and used for the analysis of Hb-adducts.

2.3.2. Diisocyanate- biomarkers of the biologically effective dose: isocyanate-specific albumin- and Hb-adducts

Diisocyanate-albumin conjugates are putative antigens (Bernstein et al. 2006; Budnik et al. 2013; Campo et al. 2007; Ott et al. 2007) that have been extensively investigated as potential sensitizers in workers diagnosed with diisocyanate asthma (Bernstein et al. 2002; Raulf-Heimsoth and Baur 1998; Wisnewski et al. 2000). Serologic albumin-diisocyanate adducts have been assessed as potential markers of exposure and a potential surrogate marker of diisocyanate asthma (Sabbioni et al. 2016a; Sabbioni et al. 2016b). A few studies were performed with samples from the general population (Bernstein et al. 2006; Wilder et al. 2011) by looking at the presence of isocyanate antibodies.

A method to measure isocyanate-specific biomarkers was developed in rats exposed to MDI (Fig. S2). MDI forms an adduct with the *N*-terminal valine of Hb (Sabbioni et al. 2000). This adduct can be quantified by GC-MS or LC-MS. 24TDI and 26TDI formed an adduct with the *N*-terminal valine of Hb in women with breast implants covered with polyurethane (Sabbioni et al. 2001). In workers, isocyanate-specific adducts of MDI (Sabbioni et al. 2010), 24TDI or 26TDI (Sabbioni et al. 2012b) were found with a lysine of albumin from blood. The binding level of MDI with albumin is 40-times larger than with Hb (Kumar et al. 2009).

A validated method for the determination of *N*-terminal Hb-adducts of MDI is available (Gries and Leng 2013). Work to extend this method for the analysis of naphthalene diisocyanate (NDI), 24TDI, and 26TDI is in progress (personal communication by Thomas Goen).

2.3.3. Recommended methods

For urine analyses of diisocyanate biomarkers, the validated (MAK-commission) GC-MS method is recommended (Cocker and Jones 2017a). The fastest method for urine analysis is the method published by (Bhandari et al. 2016). This is a high throughput method that enables the analysis of MDA, 24TDA, 26TDA, NDA, and 14PDA without prior derivatization with perfluorinated anhydrides such as PFPA and HFBA. The method was not validated by other laboratories, but it was used in the NHANES biomonitoring program (CDC-NHANES 2018a, 2021c).

For the analysis of Hb-adducts of the aromatic diamines, the methods specifically developed for Hb-adducts of arylamines, tested by other laboratories in the MAK-commission, are recommended (Lewalter et al. 2000; Sabbioni and Beyerbach 2000).

Urinary analyses cannot distinguish between exposure to isocyanates or exposure to their corresponding amine. Isocyanate specific Hb-adducts of MDI (Gries and Leng 2013) or TDI (Sabbioni et al. 2001) can be determined using GC-MS. The isocyanate specific albumin-adducts of MDI (Sabbioni et al. 2010) or TDI (Sabbioni et al. 2012b) are analyzed with LC-MS/MS. No other methods are available. Only the method for the analysis with the *N*-terminal valine of Hb has been validated by other laboratories for the MAK-commission (unpublished data). Albumin adducts (biologically effective dose) are a potential marker in the etiology of asthma caused by diisocyanate exposure (Raulf-Heimsoth and Baur 1998; Sabbioni et al. 2016c). Therefore, these biomarkers provide additional toxicological information, beyond their use as a biomarker of exposure. From a point of view of a toxicologist it makes more sense to measure albumin adducts than other biomarkers.

2.4. Pesticides

2.4.1. Pyrethroids

Pyrethroids (Zhu et al. 2020) are used as insecticides for textile (clothes, carpets) and wood preservation, for indoor pest control, in horticulture, forestry, and agriculture, and also in veterinary and human medicine (Zhu et al. 2020). Some pyrethroids are applied for treatment of scabies and head lice in humans. Thus, the potential human exposure is high, both from intake of residues in food and from dermal and inhalation exposures (Schettgen et al. 2016a). Among the general population, the dietary intake of pyrethroids is an important source of exposure. Residential proximity to agricultural activity, or household applications, non-dietary intake such as dust and dermal contact with contaminated surfaces such as textiles may also contribute to exposure levels.

Pyrethroids are generally neurotoxic. After high exposure to pyrethroids, humans showed mainly reversible and somehow unspecific symptoms like respiratory irritation or cough, dizziness, nausea, vomiting, paresthesia and headache (reviewed in (Saillenfait et al. 2015). The studies about the chronic effects of pyrethroids at low concentrations are controversial, especially for the effects of pyrethroids on human reproductive health and endocrine function (Saillenfait et al. 2016). Pyrethroids are lipophilic, but little accumulation occurs in tissues. It has been shown in mammals that pyrethroids are quickly eliminated from the body, due to rapid metabolism by hydrolytic and/or oxidative processes (Gammon et al. 2012; Kaneko 2011).

The major methods using urine as matrix were developed and applied in the countries with biomonitoring programs for pyrethroids: Germany (https://www.umweltbundesamt.de), Canada (https://www.canada.ca/en/health-canada) and USA https://www.cdc.gov/biomonitoring/environmental_chemicals.html). However, biomarkers are not strictly specific as the same biomarkers can originate from the exposure to different pyrethroids (Table 6, S5, Fig. 6). For example, 3-phenoxybenzoic acid (3PBA) is a urinary biomarker for many pyrethroids including acrinathrin, permethrin, deltamethrin, etofenprox, cypermethrin, phenothrin, esfenvalerate, fluvalinate, cyhalothrin, fenpropathrin, tralomethrin, cyphenothrin, flucythrinate, phenothrin. 4-Fluoro-3-phenoxybenzoic acid (4F3PBA) is a biomarker for the pyrethroids flumethrin and cyfluthrin. The reference values (95th percentile) for metabolites *cis*-DCCA, *trans*-DCCA and 3PBA in

Table 6
The major methods used to biomonitor people exposed to pyrethroids.

Pyrethroids					
Substance	**Biomarker**	**Matrix (mL)**	**Work-up**	**Analytical Method**	**LOD (pg/mL)**
Bifenthrin, λ-cyhalothrin, Tefluthrin	*cis*-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid (ClF3CA)[d]	Urine: 5[3]	H/LLE/D[3]b	GC-MS/MS[3]	10[3]
Allethrin, phenothrin, pyrethrum, resmethrin, tetramethrin	*trans*-Chrysanthemumdicarboxylic acid (*trans*-CDCA)	Urine: 2[5]	H/LLE/D[5]b	GC-HRMS (NCI)[5]	50[5]c
Acrina-, cyhalo-, fenpropa-, cypheno-, phenothrin, etofenprox, delta-, cyper-, pheno-, per-, tralomethrin, (es)fenvalerate, fluvalinate, flucythrinate	3-phenoxybenzoic acid (3PBA)[d,e]	Urine: 2[5] 5[7] 5[3] 2[1], 10[2] 1[4], 5[6], 2[8]	H/LLE/D[5]b E/LLE/D[7]a H/LLE/D[3]a H/LLE/D[1,2]b E/SPE[4,8]a, E/LLE[6]a	GC-HRMS (NCI)[5] GC-MS (NCI)[7] GC-MS/MS[3] GC-MS (EI)[1,2] LC-MS/MS[4,6,8]	10[5]c 10[7] 10[3]f 25[1]h, 50[2] 30[4]f,g,h, 15[6], 100[8]h
Flumethrin, cyfluthrin	4-fluoro-3-phenoxybenzoic acid (4F3PBA)[d,e]	Urine: 2[5] 5[7] 5[3] 2[1], 10[2] 1[4], 5[6], 2[8]	H/LLE/D[5]b E/LLE/D[7]a H/LLE/D[3]a H/LLE/D[1,2]b E/SPE[4]a[8]b, E/LLE[6]b	GC-HRMS (NCI)[5] GC-MS (NCI)[7] GC-MS/MS[3] GC-MS (EI)[1,2] LC-MS/MS[4,6,8]	5[5]c 8[7] 10[3]f 25[1]h, 50[2] 30[4]f,g, 15[6], 200[8]h
Cyfluthrin, cypermethrin, permethrin, transfluthrin	*cis*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*cis*-DCCA) [d,e]	Urine: 2[1], 10[2] 5[3], 1[4], 5[6],2[8] 2[5] 5[7]	H/LLE/D[1,2]b H/LLE/D[3]b E/SPE[4,8]b, E/LLE[6]b H/LLE/D[5]b E/LLE/D[7]b	GC-MS (EI)[1,2] GC-MS/MS[3] LC-MS/MS[4,6,8] GC-HRMS (NCI)[5] GC-MS (NCI)[7]	25[1]h, 50[2] 10[3]f 15[6], 200[8]h,400[4]f,g,h 20[5]c, 7[7]
Cyfluthrin, cypermethrin, permethrin, transfluthrin	*trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*trans*-DCCA)[d,e]	Urine: 5[3] 5[7] 1[4], 5[6], 2[8] 2[5], 2[1], 10[2]	H/LLE/D[3]a E/LLE/D[7]a E/SPE[4,8]a, E/LLE[6]aH/LLE/D[5]b H/LLE/D[1,2]b	GC-MS/MS[3] GC-MS (NCI)[7] LC-MS/MS[4,6,8] GC-HRMS (NCI)[5] GC-MS (EI)[1,2]	10[3]f 10[7] 15[6], 400[4]f,g,h, 400[8]h 20[5]f 25[1]h, 50[2]
Deltamethrin	cis-(2,2-dibromovinyl)-2,2-dimethylcyclopropanecarboxylic acid (DBCA)[d,e]	Urine: 5[7] 5[3] 1[4], 5[6], 2[8] 2[5] 2[1], 10[2]	E/LLE/D[7]b H/LLE/D[3]b E/SPE[4,8]b, E/LLE[6]b H/LLE/D[5]b H/LLE/D[1,2]b	GC-MS (NCI)[7] GC-MS/MS[3] LC-MS/MS[4,6,8] GC-HRMS (NCI)[5] GC-MS (EI)[1,2]	6[7] 10[3]f 15[6], 400[4]f,g,h, 100[8]h 20[5]c 25[1]h, 50[2]

The chemical structures are presented in Table S5. Abbreviations: H = hydrolysis with acid; SPE = solid phase extraction; LLE = liquid–liquid extraction; E = beta-glucuronidase (contains also sulfatase); D = derivatisation. [1] (Hung et al. 2019); [2] (Schettgen et al. 2002b); [3] (Schettgen et al. 2016a); [4] (CDC-NHANES 2020; Davis et al. 2013); [5] (Leng and Gries 2005; 2013); [6] (Le Grand et al. 2012); [7] (Dewailly et al. 2014); [8] (Olsson et al. 2004); a) addition of corresponding isotope-labeled internal standard; b) addition of surrogate internal standard; c) this is a method validated at least by one other laboratory and is part of the MAK-commission biomonitoring method collection; d) these compounds were tested in the HBM4EU round robin (Esteban Lopez et al. 2021); e) these compounds are part of the regular round robins in the German external quality assessment scheme (G-EQUAS) for analyses in biological materials (https://www.g-equas.de/); f) authors participated successfully in G-EQUAS; g) method used in the NHANES biomonitoring study; h) multi-method that determines additional pesticides.

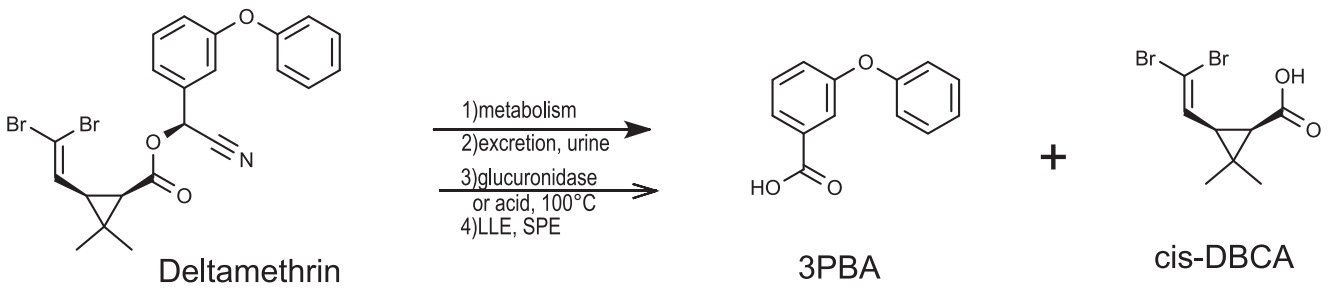

Fig. 6. Biomarkers after exposure to pyrethroids.

3–14 years children from Germany are 1, 2, and 2 ng/mL urine (Schulz et al. 2009), respectively.

2.4.1.1. Pyrethroid-biomarkers in urine. The amount of urine used for the analyses varies from 1 to 10 mL (Table 6). Therefore, the availability of urine amount might restrict the choice of the method. Work up differences exist for the urine samples. Some groups used acid hydrolysis – 2 M HCl/1h/90 °C (Schettgen et al. 2016), or 2.4 M HCl/2h/100 °C (Leng and Gries 2013) - to cleave conjugates of 3PBA, 4F3PBA, *cis*-DCCA, *trans*-DCCA, and DBCA, respectively. Other groups used enzymatic treatment of urine with beta-glucuronidase from Helix pomatia Type H1 (contains sulfatase): for example, 800units beta glucuronidase in 2 mL urine for 17 h at 37 °C (Davis et al. 2013; Olsson et al. 2004) or with Helix pomatia Type H2 (Le Grand et al. 2012).

Liquid-liquid extraction is applied to all methods except for the LC-MS/MS method by Davis (Davis et al. 2013) that uses solid phase extraction. All GC–MS methods need a derivatization step using *N-tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamid yielding *tert*-butyldimethylsilyl esters (e.g. for 3PBA = *tert*-butyldimethylsilyl 3-phenoxybenzoate) (Schettgen et al. 2016a; Schettgen et al. 2002b), or using 1,1,1,3,3,3-hexafluoroisopropanol / N,*N*-diisopropylcarbodiimide yielding hexafluoroisopropyl esters (e.g. for 3PBA = 1,1,1,3,3,3-hexafluoropropan-2-yl 3-phenoxybenzoate) (Dewailly et al. 2014; Leng and Gries 2005; 2013).

Different internal standards were applied for the methods in Table 6. 2-Phenoxybenzoic acid (2PBA) was added as internal standard in the older GC–MS methods for all analytes (Leng and Gries 2005; 2013; Schettgen et al. 2002b). In the newer GC-methods ^{13}C-labeled or deuterated compounds were used as internal standards: $^{13}C_6$-3PBA and d_6-*trans*-DCCA (Schettgen et al. 2016a); $^{13}C_6$-3PBA, $^{13}C_4$-d_3-*trans*-DCCA, and $^{13}C_6$-4F3PBA (Dewailly et al. 2014). For the LC-MS/MS methods up to four ^{13}C-labeled internal standards were used: $^{13}C_6$-3PBA and $^{13}C_3$-*trans*-DCCA (Olsson et al. 2004); $^{13}C_6$-3PBA, $^{13}C_7$-*trans*-DCCA, $^{13}C_6$-4F3PBA, and $^{13}C_7$-*trans*-DBCA (Davis et al. 2013).

The lowest LOD for most compounds were obtained with GC–MS methods, especially using negative chemical ionization (Dewailly et al. 2014; Leng and Gries 2005; 2013). The GC–MS/MS method by Schettgen (Schettgen et al. 2016a) and the LC-MS/MS by Le Grand (Le Grand et al. 2012) or by Davis (Davis et al. 2013) have similar LODs. Earlier LC-MS/MS methods (Olsson et al. 2004) are less sensitive in accordance with the technical specifications of older equipment.

3PBA, 4F3PBA, *cis*-DCCA, and *trans*-DCCA have been measured in all major HBM programs. The number of positive samples usually decreases in the following order: 3PBA > *trans*-DCCA, *cis*-DCCA, DBCA, 4F3PBA (Becker et al. 2006; Bevan et al. 2013; CDC-NHANES 2018b; Dereumeaux et al. 2018; Dewailly et al. 2014; Khoury et al. 2018). The other compounds present in the Table 6 - *cis*-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid (ClF3CA) and *trans*-chrysanthemumdicarboxylic acid (*trans*-CDCA) - were not measured in larger population studies.

3PBA, 4F3PBA, *cis*-DCCA, *trans*-DCCA, and DBCA are measured regularly in the German EQUAS test program (https://www.g-equas.de) of environmental chemicals in urine. The lowest tested values in the year 2017 were 2.6, 1.7, 0.9, 1.8 and 1.4 ng/mL for 3PBA, 4F3PBA, *cis*-DCCA, *trans*-DCCA, and DBCA respectively. *cis*-DBCA, *cis*-DCCA, *trans*-DCCA, 3PBA, 4F3PBA, and ClF3CA were also included in the laboratory quality assurance/quality control (QA/QC) program of HBM4EU (Esteban Lopez et al. 2021).

2.4.1.2. Pyrethroid-biomarkers in blood and hair. The pyrethroids were measured as parent compounds in plasma of Chinese participants (Li et al. 2018). Jeong et al (Jeong et al. 2019) developed a method to determine pyrethroids and their metabolites in human plasma using LC-MS/MS. Blood levels of metabolites were measured in toxicokinetic studies (Khemiri et al. 2017, 2018; Ratelle et al. 2015a, 2015b; 2016), but not in epidemiological studies. For the first time, nine pyrethroids (bifenthrin, cyfluthin, cypermethrin, deltamethrin, etofenprox, fenpropathrin, fenvalerate, λ-cyhalothrin, and permethrin) and their seven major metabolites (3PBA, 4F3PBA, *cis*-DBCA, *cis*-DCCA, *trans*-DCCA, *trans*-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethyl-cyclopropanecarboxylic acid, and 2-methyl-[1,10-biphenyl]-3-carboxylic acid, were simultaneously analyzed and validated in human plasma.

Pyrethroids and pyrethroid metabolites have also been analyzed in hair and detected in few study participants (Appenzeller et al. 2016; Duca et al. 2014; Hardy et al. 2015; Lehmann et al. 2018b; Lehmann et al. 2018a). Hair is a promising emerging matrix, but some issues on its suitability and the biological relevance need further research (Yusa et al. 2015).

2.4.1.3. Recommended methods. Urine is the recommended matrix to study pyrethroid exposure via their metabolites. The lowest LODs were obtained with GC–MS/MS (Lehmann et al. 2018b) or GC-HRMS (Leng and Gries 2013) after derivatization. Both methods have been validated in inter-laboratory quality assessments. Similar LODs were obtained with LC-MS/MS without derivatization (Le Grand et al. 2012). This method is less work intensive but has not been validated by other laboratories yet. The latest method used in NHANES (CDC-NHANES 2020; Davis et al. 2013) is less sensitive for some analytes but in addition to the pyrethroid metabolites 3PBA, 4F3PBA, *cis*-DCCA, *trans*-DCCA and *cis*-DBCA, it allows to determine some organophosphorous and herbicide metabolites such as 3,5,6-trichloro-2-pyridinol (TCPy), 2-isopropyl-6-methyl-4-primidiol, 2-diethylamino-6-methyl pyrimidin-4-ol, 4-nitrophenol, 2-(dimethylphosphorothioyl)sufanyl]succinic acid, and two herbicides such as 2,4-dichlorophenoxyacetic acid, and 2,4,5-trichlorophenoxyacetic acid.

3. Conclusions and outlook

Adequate biomarkers have been identified for all compounds, considering the criteria established in HBM4EU (Vorkamp et al. 2021) as well as aspects of feasibility and analytical quality. The recommended methods for the single compounds have been summarized at the end of the single chapters. The methods have been applied for the analyses of urine samples in the pan-European setting of HBM4EU (Vorkamp and Hajeb 2021): 1471 samples for pyrethroids, 2695 for acrylamide, 1604 for mycotoxins. For diisocyanates 166 urine samples were analyzed for

aromatic amines, and 103 samples for Hb-adducts of diisocyanates. The results of these analyses will be published in the near future.

The concentration of the metabolites and the parent compounds of non-persistent xenobiotics in blood and urine can fluctuate considerably in humans due to exposure pattern, uptake, metabolism, and half-life (LaKind et al. 2019). Such values obtained from biomonitoring studies are snapshots of the current exposure history. Repetitive measures of the same individuals should be evaluated as described by Shin et al (Shin et al. 2019). The variability of the individual values should be classified with an intraclass correlation coefficient (ICC). The ICC values range from 0 to 1 (LaKind et al. 2019). A value of 1 shows that all variation is due to the variability between subjects. A value of zero indicates that all variation is due to the variability within the subject. ICCs obtained from repetitive measurements of the same individuals have been applied in several studies (Pleil and Sobus 2013; Pleil et al. 2018). The ICCs varied widely from study to study and from chemical to chemical (LaKind et al. 2019). For example, the temporal variability of urinary pyrethroid metabolite levels should be considered when interpreting the results (Morgan et al. 2016; Wielgomas 2013). Morgan et al (Morgan et al. 2016) showed that a single measure of urinary 3PBA was not sufficient to characterize average exposure regardless of sample type, correction method, and time frame of collection. Poor reproducibility was found for the pyrethroid metabolites 3PBA, *trans*-DCCA, and *cis*-DCCA in both spot ($ICCs \leq 0.24$) and first-morning- void samples ($ICCs < 0.38$) collected during the 44-day study period (Li et al. 2019). A poor reproducibility ($ICC < 0.4$) of 3PBA was also reported by LaKind et al (LaKind et al. 2019). A moderate reproducibility ($ICC = 0.641$) was found for repetitive measurements of MDA in urine (Chinthakindi and Kannan 2022). For other aromatic amines, not listed in this publication, even lower ICCs were found, except for 4-chloroaniline.

The interpretation of biomarker concentrations should be done carefully, bearing in mind that they might reflect different exposure periods (LaKind et al. 2019). Furthermore, biomarkers of exposure differ in their representation of toxicity, especially in the case of reactive metabolites that have genotoxic and cytotoxic effects (Zare Jeddi et al. 2021) or causing other health effects such as immunotoxicity, developmental or reproductive toxicity.

Developments in analytical chemistry are notable towards the analysis of different class of compounds with one method (multi-method), since highly sensitive instruments can detect a variety of compounds in the same analytical run. This offers possibilities, in the long term, of combining chemical analyses of different types of biomarkers in complex HBM programs, possibly making the analysis of a long list of compounds less costly and better manageable. Furthermore, multi-methods require generic sample preparation procedures that do not compromise sensitivity, precision and accuracy.

The HBM4EU QA/QC program has taken first steps in assessing analytical quality for a wide spectrum of different chemicals. In order to ensure high analytical quality and to engage more analytical laboratories in HBM studies, proficiency testing initiatives need to be systematized, extended and integrated in all HBM studies.

Although HBM4EU covers many compounds, these are just the "tip of the iceberg" given the large number of chemicals in the global market. Non-target screening approaches (Vermeulen et al. 2020) can help with compound identification, but do not provide robust quantitative data (Sabbioni et al. 2020). In the future, a broader selection process of substances should be undertaken. Over 350,000 chemicals and mixtures of chemicals have been registered for production and use, up to three times as many as previously estimated and with substantial differences across countries/regions (Wang et al. 2020). The identities of many chemicals are publicly unknown because they are claimed as confidential (over 50000) or ambiguously described (up to 70000). Scientists from different disciplines are needed to elucidate the presence and toxicological effects of these compounds possibly present in the environment (Wang et al. 2020).

The US EPA applies software programs (ExpoCast, https://comptox.epa.gov/dashboard) to predict population exposure and intake for chemicals. At EPA, prediction of the chemicals present in the environment started from an even larger number of chemicals (479926) than the 350,000 postulated by Wang et al (Wang et al. 2020). From these chemicals, Ring et al. (Ring et al. 2019), predicted 1880 chemicals with a median population intake rates higher than 0.1 mg/kg body weight/day. Exposure predictions, toxicological databases, chemical knowledge, and media measurements can help arrive at a risk-based prioritization of chemicals to be used on biomonitoring studies (Egeghy et al. 2016; Patlewicz et al. 2018; Sobus et al. 2018; Wambaugh et al. 2013). The US-NIEHS (NTP, https://ice.ntp.niehs.nih.gov/) and the US-EPA (Breen et al. 2021; Dawson et al. 2021; Honda et al. 2019; Wambaugh et al. 2018) established models to link in vitro and with in vivo data. Using the framework of adverse outcome pathways (AOP), the data obtained in vitro could be used to predict the levels in biological samples (urine, blood) that yield adverse effects in humans (in vitro to in vivo extrapolation (IVIVE)). These predicted levels could be compared to the data obtained in biomonitoring studies (Fig. 1 in (Sabbioni and Day 2022)). Similar approaches will be included among others by the European Union in the new large program about the assessment of risks from chemicals (PARC = Partnership for the Assessment of Risks from Chemicals). In addition, disease data should be implemented in geographic information systems. This would allow to discover some potential disease clusters that can be used for targeted biomonitoring studies in order to link the disease to the exposure of the chemicals found. In general, it seems that specific socioeconomic status is associated to poorer health and higher chemical exposures. For example, in the NHANES-studies, usually higher concentrations of xenobiotics are present in Afro-Americans and Hispanics than in white people. In contrast, in a European study, higher levels per- and polyfluorinated substances were found in people with higher socioeconomic status (Buekers et al. 2018). Therefore, HBM studies should include social descriptors such as profession, lifestyle and dietary information as explanatory variables for levels of internal chemical exposure levels and health effects.

In summary, chemical models to predict the exposure, the metabolism, and the toxicity will help to reduce drastically the number of the xenobiotics that might harm health. Together with toxicological databases, exposure estimations help to prioritize chemicals for closer scrutiny and/or for biomonitoring programs (Basu et al. 2019; Bell et al. 2018; Dong et al. 2019; Gramatica et al. 2018; Wood et al. 2020). Biomonitoring analyses are time consuming and expensive (Barr et al. 2005; Vorkamp and Knudsen 2019). Therefore a thorough elucidation of the research questions and goals should be formulated prior to the analyses of thousands of samples (Sabbioni et al. 2020). However, presently we still need validated analytical methods for HBM to compare results obtained from modeling work with values obtained in humans.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary material

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