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An overview of the current progress, challenges, and prospects of human biomonitoring and exposome studies

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ABSTRACT

Human Biomonitoring (HB), the process for determining whether and to what extent chemical substances penetrated our bodies, serves as a useful tool to quantify human exposure to pollutants. In cases of nutrition and physiologic status, HB plays a critical role in the identification of excess or deficiency of essential nutrients. In pollutant HB studies, levels of substances measured in body fluids (blood, urine, and breast milk) or tissues (hair, nails or teeth) aid in the identification of potential health risks or associated adverse effects. However, even as a widespread practice in several countries, most HB studies reflect exposure to a single compound or mixtures which are measured at a single time point in lifecycle. On the other hand, throughout an individual's lifespan, the contact with different physical, chemical, and social stressors occurs at varying intensities, differing times and durations. Further, the interaction between stressors and body receptors leads to dynamic responses of the entire biological system including proteome, metabolome, transcriptome, and adductome. Bearing this in mind, a relatively new vision in exposure science, defined as the exposome, is postulated to expand the traditional practice of measuring a single exposure to one or few chemicals at one-time point to an approach that addresses measures of exposure to multiple stressors throughout the lifespan. With the exposome concept, the science of exposure advances to an Environment-Wide Association Perspective, which might exhibit a stronger relationship with good health or disease conditions for an individual (phenotype). Thus, this critical review focused on the current progress of HB and exposome investigations, anticipating some challenges, strategies, and future needs to be taken into account for designing future surveys.

KEYWORDS

Human biomoniotoring; exposome; metals; emerging contaminants; challenges; lifestyle; stressors; future trends

Human biomonitoring (HB)

Since the last century, with the expansion of industry and agriculture, humans have been exposed to an increasing number of chemicals, both in the workplace and macroenvironment. Bearing this in mind, it was important to conduct studies on exposure to environmental chemical contaminants, taking into account the presence and severity of adverse effects and potential risks that these substances exert on human health. The periodic measurement of a given chemical or metabolite in a particular population, known as human biomonitoring (HB), developed into an essential tool for assessing human exposure to chemicals present in an external or working environment, as well as indicating the quantity of compounds either ingested or absorbed via the lungs or skin from exogenous sources by individuals. Thus, HB is the most direct way to (1) identify and quantify exposure and risk, (2) understand the mechanisms underlying observed toxic effects, and (3) consequently deciding actions to be taken to reduce that exposure (Angerer, Ewers, and Wilhelm 2007; Gouveia et al. 2014; Levy et al. 2007; Martins et al. 2018; Needham, Calafat, and Barr 2007; Tohon et al. 2018).

Human biomonitoring was initially designed to assess exposures to "target" chemicals taking into account that the dose–effect relationship is known. However, in many circumstances, the choice of analytes resides more in the ease of detection as well as availability of instrumentation and

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methodology (Dennis et al. 2017). HB is useful for establishing baseline values for specific groups and identifying populations at threat (nutritional and toxicological risk), which support the prioritization of government actions (public policies). In general, concentrations of chemicals or metabolites are monitored in blood, saliva or urine matrices (defined as the internal dose biomarkers) (Alves et al. 2017; Angerer, Ewers, and Wilhelm 2007; Barbosa et al. 2009, 2005; Batista et al. 2009; Da Silva et al. 2017; Freire et al. 2014, 2015; Harmon et al. 2018; Jansen et al. 2017; Needham, Calafat, and Barr 2007; Nunes et al. 2010; Rimbaud et al. 2017; Rocha et al. 2017, 2016; Rodrigues et al. 2009; Shim et al. 2017; Slezakova et al. 2017; Takeda et al. 2017).

In addition to providing information on exposure conditions of a given population, several HB investigations attempted to correlate the concentration of some chemicals or metabolites in the body with various disease outcomes, including diabetes (Jaacks et al. 2016; Shapiro et al. 2016, 2015), obesity (Carwile and Michels 2011; Do et al. 2017; Ko et al. 2014; Merlo et al. 2018), hypertension (Cai et al. 2016; Martins et al. 2018; Shiue and Hristova 2014), neurological disorders (Berghuis et al. 2015; Chen et al. 2017; LaKind, Anthony, and Goodman 2017; Marie et al. 2017; Wu et al. 2017), hormonal alterations (Hyun Kim et al. 2018) and cancer (Arrebola et al. 2016; Barry, Winquist, and Steenland 2013; Bonefeld-Jørgensen et al. 2014; Chang et al. 2015).

Global human biomonitoring studies

At present, predominantly in underdeveloped countries the practice of HB is still in its infancy and requires experimental sophistication to generate acceptable, relevant meaningful data. Most HB studies were undertaken in the United States and Europe. In the United States, the National Biomonitoring Program, conducted by the CDC, was devoted to the monitoring of toxic substances and essential nutrients in the US population. These data are published in two documents for: i) toxic substances, the National Report on Human Exposure to Environmental Chemicals, and ii) essential nutrients, the National Report on Biochemicals of Diet and Nutrition in US Population. More than 300 substances (toxic and essential nutrients) (CDC 2017) are regularly monitored. The two American National Programs constitute the National Health and Nutrition Examination Survey (NHANES), which provides data for numerous scientific investigations. A quick search in PUBMED identified that 2178 articles published in 2017, mentioned the use of NHANES dataset (Pubmed 2019).

The nutritional assessment component of the current NHANES also includes a first 24 hr dietary recall interview for participants of all ages and a second dietary interview for all participants who complete the in-person recall. The second nutritional recall is collected by telephone and scheduled 3 to 10 days later (CDC 2017).

In Europe, the leading HB program is Consortium for the Human Biomonitoring on European Scale (COPHES), which brings together 35 research groups from 24 European member countries, plus Croatia, Norway and Switzerland (Joas et al. 2012). In addition, several European countries conduct their own National Nutritional and Health Survey which may include data on toxic and essential substances, such as the German Environmental Survey (GerES) and the French National Survey on Nutritional and Health (Černá et al. 2017; Pino et al. 2017). Similar National Health surveys also exist in Israel (Berman et al. 2017), Korea (Choi et al. 2017) and Japan (Karube et al. 2014).

In the last two decades, the number of publications related to HB has increased significantly. A single search for the term "Human biomonitoring" on the Web of Science platform demonstrates this trend. There was a growing rise in research in this area between 2004 and 2017, jumping from just over 70 articles to more than 300, respectively.

Some of the primary compounds and metabolites examined by HB programs, selected clinical matrix, and predominant analytical instrumentation for the analysis are presented in Table 1. It is interesting to note that the change in the tendency to select priority toxic substances to be monitored over the years in well-established HB programs. As an example, data extracted from the 2005–2006 NHANES demonstrated the levels of 249 environmental chemicals in the North American population (Figure 1). From these, 26% (65 chemicals) were volatile compounds, 23% (58 chemicals) were

Table 1. Some of the most predominant substances determined in human biomonitoring programs, matrix and the principal instrumentation selected for the analysis.

Chemical compound	Matrix	Method
Essential and Toxic Elements	WB and urine	ICP-MS
Bisphenols (BP) and other phenols	WB and urine	LC-MS/MS
Cotinine	Urine	LC-MS/MS
Metabolites of Polycyclic aromatic hydrocarbon (PAHs)	Urine	GC-MS LC-MS/MS
Polychlorinated biphenyls and dibenzodioxins (PCB and PCDD)	WB and urine	GC-MS
Metabolites of Phthalates	Urine	LC-MS/MS
Metabolites of perfluorinated substances (PFOS)	WB and urine	LC-MS/MS
Metabolites of organophosphate pesticides	Urine	LC-MS/MS
Metabolites of aromatic amines	Urine	LC-MS/MS
Parabens	WB and urine	LC-MS/MS
Triclosan (TCS) and triclocarban (TCC) and their metabolites	Urine	LC-MS/MS

*WB: whole blood; ICP-MS: inductively coupled plasma mass spectrometry; LC-MS/MS: liquid chromatography coupled to tandem mass spectrometry; GC-MS: gas chromatography coupled to mass spectrometry.

polychlorinated agents and 17% (42) pesticides. Subsequently, 2013–2014 NHANES lowered the number of assessed substances to 201. Surprisingly, only 10 pesticides were examined which constituted 5% of the total substances assessed. However, the contribution of metal (and metalloids) increased from 8% (21) to 14% (29), from 2005–2006 and 2013–2014 surveys, respectively. An interesting point to consider is the elevated number of emerging contaminants assessed in the 2013–2014 survey, predominantly flame retardants, phthalates, polyfluorochemicals (PFCs) and the new class termed personal care and consumer product chemicals which includes bisphenols (Figure 1).

Suspect screening and nontarget analysis for human biomonitoring studies

Despite the significant advancement in HB studies in recent years, it is well known that the number of compounds determined in clinical samples is still minimal which may be attributed to some factors such as cost, instrumentation limits, time of sampling (season) or population characteristics (rural vs urban). Current HB data represents only a small fraction of the quantity of compounds present in various media to which humans are exposed environmentally. One hundred fifty-three million unique compounds are currently listed on the Chemical Abstracts Service Registry (CAS) (CAS 2019). Further, more than 30,000 of these chemicals are often used in consumer products (Howard and Muir 2011).

Since the US EPA initiated the ExpoCast program in 2009 with the aid of developing novel approaches and tools for evaluating and classifying chemicals, high-throughput far-field and near-field exposure prediction models were employed to provide rapid exposure estimates for thousands of chemicals based upon potential for biologically relevant human exposure (Cohen-Hubal 2009). In addition, two other strategies to advance knowledge of chemicals to which humans are exposed are gaining considerable popularity. Both these strategies utilize data derived from the clinical specimen analyzed by advanced

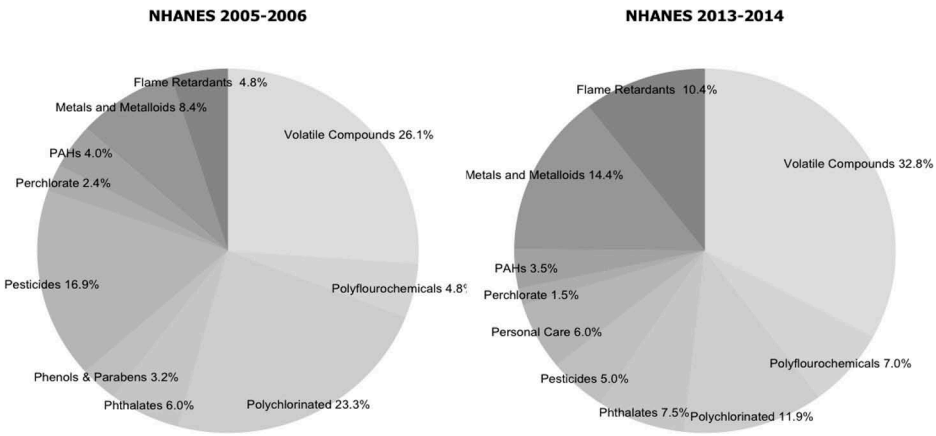

Figure 1. Classes of chemicals determined in the national health and nutrition examination survey (NHANES): a) NHANES (2005–2006) and b) NHANES 2013–2010. Represent as the fraction (%) of the total compounds evaluated.

high-resolution mass spectrometry (HRMS) or tandem HRMS instrumentation. These strategies match unknown sample characteristics to compounds within spectral databases. The first strategy termed "Suspect Screening Analysis (SSA)," refers to analytical chemistry techniques that compare molecular features observed within samples to databases of known chemical agents to identify potential matches. The second manner categorized as "Non-Target Analysis (NTA)," seeks to identify compounds in samples without the aid of chemical agent lists. In contrast to traditional HB methods, NTA and SSA strategies enable investigation of thousands of chemicals within a sample (Newton et al. 2018; Phillips et al. 2018).

However, since both strategies are qualitative or semi-quantitative analyses, these technologies require developing and validating "targeted" methodologies. Consequently, future directions of HB studies may merge to target SSA/NTA approaches. However, two significant limitations of the SSA/NTA approaches are: (1) lower sensitivity of the HRMS instruments compared to instrumentation available for "target" quantification and, (2) limited number of compounds with known spectral features in the available databases.

From the HB to the exposome

Despite the rise in the number of substances examined in some established HB programs, the majority of investigations still only consider exposure to one or a few chemical substances at a given time point (Barbosa 2017; Patel 2017; Shaw 2017). Unfortunately, hypotheses are constructed with minimal information regarding a complete scenario of exposure including physical, chemical, or lifestyle factors.

On the other hand, in daily life, humans are exposed to many essential nutrients and stressors from (i) chemical (essential and toxic substances), (ii) physical and (iii) lifestyle origins. While the essential nutrients originate from the same dietary source, most of the stressors are associated with different origins including the macroenvironment such as ultraviolet (UV) radiation, climate or microenvironment such as food contaminants or air pollutants. Humans daily experience interactions between receptors and stressors, promoting simultaneous, dynamic and complex reactions of attack and defense mechanisms. In addition, throughout the lifecycle, exposure processes may be modified several times due to changes in individual attitudes and lifestyle including stress, specific diet, smoking habits, altered sleep, physical activity, depression, or drug use leading to conditions of higher predisposition to particular pathologies. Further, human genetic variations may also alter health risk by modulating responsiveness to compounds (Barcelos et al. 2015a, 2015b, 2013; Crovella et al. 2018; De Marco et al. 2012; Fernandes et al. 2015). Consequently, few studies that address the exposure–effect relationships and associated mechanisms for a single or mixtures are available. Unfortunately, these observations do not reflect realistic human life conditions (Patel 2017).

Similar to genome-wide association studies which generated extensive data on genetic variants in different individuals to determine if any variant was associated with a trait or risk, exposure-wide association studies (EWAS) may provide information on the effects of multiple environmental exposures related to potential adverse health risks. In 2005, Dr. Christopher Wild, a cancer epidemiologist, in his article "Complementing the genome with an exposome: the outstanding challenge of environmental exposure measurement in molecular epidemiology", proposed for the first time the term "exposome", as the complementary environmental component to the genome, in determining the risk of a particular disease (Wild 2005). Exposome was initially defined as the set of environmental exposures of an individual throughout his lifespan (Wild 2005). By combining the concept of exposure in traditional investigations of HB to EWAS, a significant advancement and refinement in conventional exposure assessments was developed (Dennis et al. 2017). Thus, over the last few years the term "exposome" has moved from concept to reality with an improvement in definition to "cumulative measures of environmental influences and associated biological responses throughout the life of an individual, including exposures of the environment, diet, lifestyle and endogenous processes" (Johnson et al. 2017; Miller and Jones 2013; Siroux, Agier, and Slama 2016; Stiegel et al. 2017; Valdiglesias et al. 2017). As initially proposed, the exposome was intended to complement (not compete) genomic research, taking into account our current recognition

of the importance of gene–environment interactions for specific diseases and the emphasis of the environment on epigenetic expression (Buck Louis and Sundaram 2012). Thus, a significant advancement in the coming decades may better define the manner in which the combination of genome and exposome contribute to assessing disease risk, based upon GWAS and EWAS approaches (Patel, Bhattacharya, and Butte 2010).

Exposomics and generation of the exposome

It is worthwhile noting that the exposome is: (1) the cumulative sum of (external) environmental exposure and associated biological responses (internal exposure), (2) an aggregate of an extensive set of biological markers (internal dose and effect) and (3) an encompassment of entire life of an individual; thus, exposomics is the application of analytical technologies for the generation of the exposome (Wild 2005, 2008, 2011, 2012).

In the human organism, different classes of substances in an exposome vary considerably in concentration ranges (5–6 orders of magnitude). In general, environmental pollutants are present in the order of fmolar to μmolar, while endogenous metabolites between nmolar to mmolar (Rappaport et al. 2014). These vast concentration differences in substance classes require the use of the most modern and diverse analytical instrumentation in addition to a multidisciplinary approach which results in an expensive investment to set up a lab to undertake exposome analysis. Only the aggregation of highly experienced researchers within various fields of investigation can leverage the quality of examining an exposome.

The levels of chemicals of external origin such as contaminants in air or water, or dietary nutrients, can be monitored in the organism (internal exposome) by selecting the appropriate biomarker of internal dose measured in one or two biological matrices (Barbosa et al. 2005; Branco et al. 2017; Cervinkova et al. 2017; Hinchliffe, Rudge, and Reed 2016; Karppi et al. 2008; Pleil and Sobus 2016; Pleil et al. 2018; Serrazina et al. 2018). In addition, some compounds monitored in biological fluids may be associated with specific dietary habits. For example, levels of urinary excretion of chlorogenic acid, gallic acid, epicatechin, naringenin or hesperetin may be employed as particular biomarkers to assess consumption of coffee, wine, tea or cocoa, and citrus juices, respectively (Ito et al. 2005).

Target and nontarget exposomics

Exposome studies may be advanced with either pre-established "targets," defined as target exposome which are known analytes that may be monitored or without adoption of pre-set "targets" or nontarget exposomics. Nontarget exposomics requires more complex instrumentation, generating hundreds or thousands of biological data (Dennis et al. 2017; Go et al. 2015; Jones 2016).

For the internal exposome (body constituents), target or nontarget proteins, metabolites, expressed genes, or microbes are measured in blood, plasma, urine, and feces by utilizing several "omics" high-throughput platforms, in addition to levels of target pollutants and nutrients traditionally assessed in HB studies. The strategy uses the concept of "system biology" (Badimon, Vilahur, and Padro 2016). Systems biology conglomerates a quantitative analysis of large networks of molecular and functional changes that occur in multiple levels of biological organization (Sauer et al. 2015; Sturla et al. 2014; Van Ommen et al. 2017). Systems biology also offers advanced strategies to obtain mechanistic knowledge, combining molecular data acquisition on a large scale, through multi-omic platforms (transcriptomic, proteomic, metabolomic/adductomic/lipidomic, metallomic) with data integration by employing data mining. Selected algorithms may characterize (classify) a specific health condition, with multiples and specific biological markers of disease (Azuaje, Devaux, and Wagner 2009; Caberlotto and Lauria 2014; Wang et al. 2010). Figure 2 depicts the design of an exposome study.

Omics tools encompassing the internal exposome

Epigenomics

Variations in the linear sequence of the genetic code, such as single nucleotide polymorphisms (SNPs), may play a key role in explaining inter-individual differences in structure and function, as

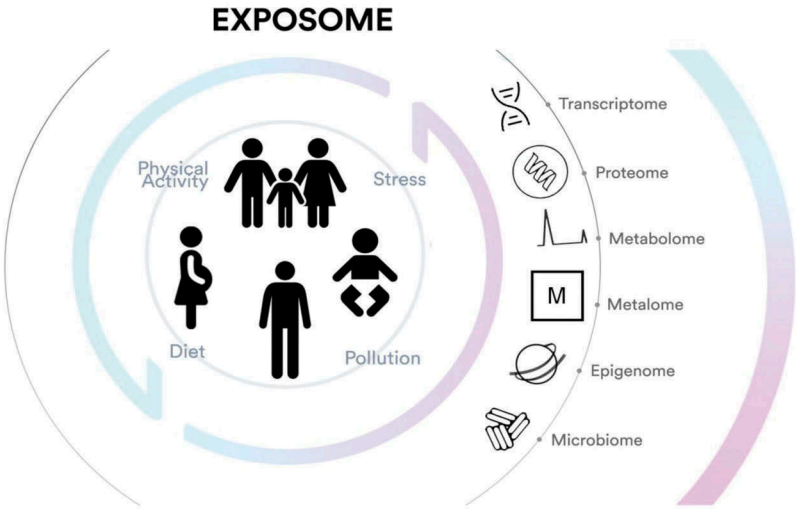

Figure 2. The diagram of the exposome.

well as insight into disease susceptibility and resistance. However, the purpose of our genome is also dependent upon epigenetic mechanisms, which are by definition "beyond the genome," and include alterations of chromatin structure, involving covalent modification of the central DNA molecule itself, as well as the complex macromolecules that form chromatin. The rapidly evolving field of epigenetics is contributing to our understanding of gene–environment interactions, as epigenetic mechanisms provide additional information on transcriptional control that regulates gene expression (Stricker, Köferle, and Beck 2017).

Transcriptomics

The transcriptome or gene expression profile is used to study alterations in the expression of all mRNAs in a population of cells, tissues, or organisms. Transcriptomic analysis is also the best-established approach to identify perturbed biological networks and thus obtain a mechanistic view of the response of the system to an exposure (Dopazo 2014; Sturla et al. 2014). The current technological basis underlying transcriptomic measurements for systems biology studies involves oligonucleotide microarrays and, more recently, new generation sequencing (SNG).

Oligonucleotide microarrays represent the most significant technological advancement in transcriptomics of the last decade and were established with the introduction of high-density array printing by Affymetrix. It is now possible to design a series of oligomer probes that encompass the entire transcriptome of any organism for which the genome sequence is known. These microarrays enable high-throughput analyses of many samples derived from a particular model system. With the concomitant progress of complete sequencing of cDNA and RNA by new generation sequencing technologies, current microarrays consider each gene or its exons such arrangements of exons are already available for humans, mice and rats (Sturla et al. 2014).

Utilizing these advancements, the transcriptome between subpopulations with different characteristics or exposures was extensively evaluated to (i) define new biomarkers of exposure and effect or (ii) identify relevant gene–environment interactions (McHale et al. 2013; Van Breda et al. 2015). Hebels et al. (2011) investigated adult women participating in the "NewGeneris" European biomarkers research project (www.newgeneris.org) and, found that urinary excretion levels of N-nitroso compounds (NOC) and micronucleus frequency in lymphocytes were associated with the peripheral blood transcriptome. When constructing a gene network, it was observed that exposure was related to biological effects as evident by MN induction at the level of gene expression. The genes present in the network were involved in processes relevant to carcinogenesis. Data clearly demonstrated that this type of approach (transcribed gene network analysis) may be employed to establish potential

biomarkers of gene expression, and these biomarkers might provide information on molecular mechanisms predisposed to initiation of carcinogenicity.

Proteomics

The complex mechanisms of biological processes involved in the effects associated with exposure to various chemicals may be assessed through primary components of cellular events such as proteins. Expression of proteins in a genome or tissue, known as proteome, is not a fixed feature of an organism as in the case of the genome. Moreover, there are many more proteins in the proteome than genes in the genome (Kennedy 2002; Liebler 2002).

In order to understand how at the molecular level a cell functions in a sick individual versus a healthy person it is necessary to know (1) the proteins and other cellular components that are present, (2) the manner in which these components interact, and (3) the resulting consequences of these interactions. Therefore, protein level analysis is required as the study of genes through gene sequencing cannot adequately predict the dynamic structure of proteins. It should be noted that many cellular processes occur at the level of proteins and these cell constituents are associated with disease development. Consequently, proteins serve as a target of many medicinal drugs. Thus, proteomics is a direct method for identifying, quantifying, and examining post-translational modifications of proteins in a cell, tissue, or organisms (Lee et al. 2003). In this case, candidate proteins may also be identified as biological markers and may be used to diagnose an early outcome.

The term proteomics was introduced in 1995 to describe all proteins that are expressed in a genome (Wasinger et al. 1995). Defining all aspects of proteomics is difficult since today it is more a concept than a well-defined science. Proteomics may be viewed as a selection methodology in molecular biology, which aims to (1) document the general distribution of cellular proteins, (2) identify and characterize individual proteins of interest, and (3) elucidate protein associations and functions. Therefore, proteomics as a whole is based upon biochemical, biophysical and bioinformatics principles to quantify and identify expressed proteins, since these change according to the development of an organism as well as in response to environmental factors (Humphery-Smith 2015).

In the last 10 years, there have been extensive investigations in proteomics using high-resolution mass spectrometers such as MALDI-MS or ESI-TOF-MS and some database software with established peptide sequence. It became possible to identify the positions of any modifications within a series of peptides and with information on the entire protein sequence defining the sites of the change in the protein itself (Becker and Bern 2011). Currently, investigators working in this area are seeking to answer two fundamental questions: what are the targets of reactive intermediates? what are the outcomes related to protein modification? The elucidation of these questions might solve many problems in contemporary research. This ability to establish relationships between the endpoints and protein markers enables the detection of unique protein profiles (Geyer et al. 2017).

From gene expression to metabolic flows: metabolomics

The metabolome forms the set of all small molecules involved in chemical reactions that maintain cell and organ functioning. Alterations made in the human genome (genetic material), epigenome (a chemical compound that directs the genome to act) and proteome (the set of proteins expressed by the genome) are readily detected in the metabolome. While the human genome applies to the whole body, every organ system is designed to have a different metabolome.

The metabolome of a system is most frequently obtained using mass spectrometry (MS) techniques, which enables identification of several compounds of endogenous or exogenous origin in a biological fluid (Hou et al. 2017; Roig et al. 2017). Although magnetic nuclear resonance (NMR) has also been utilized (Carrola et al. 2011; Ouyang et al. 2011; Rocha et al. 2011; Zhou et al. 2013), NMR is less sensitive compared to MS. It is estimated that a complete metabolome may

contain more than 200,000 different chemical compounds, depending upon the organism or class of organisms considered. (Hall 2002; Kind, Scholz, and Fiehn 2009).

In recent years, targeted metabolome analyses have become more rapid and straightforward with the ability to measure several target compounds with the use of several commercial kits (Siskos et al. 2017). For these analyses, methods were developed for the selected metabolite(s), which undergoes an analytical validation, after standardized protocols that examine selectivity, precision, linearity, limits of detection (LOD) and limits of quantification (LOQ), and robustness before application. Internal standards and compounds with labeled isotopes are used to improve accuracy and handle matrix effects. A Certified Reference Standard (SRM) for human plasma was recently produced by NIST (National Institute of Standards and Technology) which displays the capacity to identify approximately 100 metabolites and environmental contaminants with certified values (Simón-Manso et al. 2013). The use of this material enables an advancement in the validation of results in routine metabolomic analysis (Phinney et al. 2013).

For the nontarget metabolome, advances in high-resolution MS instrumentation (q-TOF and Orbitrap), enabled identification and discovery of numerous metabolites (Ciborowski et al. 2012; Jeong et al. 2018; Monnin et al. 2018; Quifer-Rada et al. 2017; Sun et al. 2018). Currently, blood and urine samples, as well as reconstituted breath aerosols, are assessed using liquid chromatography MS-MS, ToF, and Orbitrap instrumentation that capture many features in small samples. For further information on this topic, a recent review article is recommended (Andra et al. 2017).

In metabolomics, raw data are subjected to a pre-processing step according to the type of analytical platform used. For NMR, data processing includes phasing, baseline correction, alignment, and normalization. Commercial software and algorithms such as PERCH (PERCH Solution Company Ltd.), ChenomxRMNSuite (Chenomx Inc.), MestReNova (MestreLab Research), MetaboLab, AutoFit, TopSpin (Bruker Corp.) and MATLAB (The MathWorks Inc.) are routinely employed. On the other hand, using MS techniques, data processing includes spectral deconvolution, dataset creation, grouping, alignment, filling of data gaps, normalization, and transformation of data (Sussulini 2017). The obtained data are preprocessed with the utilization of free tools such as XCMS, MZmine, MAVENeMetaboAnalyst, as well as commercial software SIMCA-P, SAS (Alden et al. 2017). Numerous databases are available to aid in the identification of metabolites (Human metabolome database (HMDB)), METLIN, NIST MS Library, KEGG (Kamburov et al. 2011; Wishart et al. 2007). However, a critical limitation of nontarget analysis of metabolites of exogenous origin such as pollutants is the lack of sufficient sensitivity of instrumentation used to obtain data (MS with higher resolution power, example q-TOF or Orbitrap). These analytes are usually found in clinical specimens in concentrations lower than femtogram.

Metallomics

The physiology of living systems cannot be maintained only with genes and proteins. It is essential to contain several crucial chemical elements including Ca, Mn, K, Mg, Se, Cu, Zn, and Cr in order for organ systems to carry out their physiologic and metabolic functions. In addition, the presence in the body of elements considered toxic, such as Pb, Hg, Cd and As, is known to of disrupt the activity of several proteins involved in the reproductive and endocrine systems (Al Bakheet et al. 2013; Pizzino et al. 2014; Roh, Lee, and Choi 2006; Zawia et al. 1998). These metals may also alter the expression pattern of numerous genes involved in detoxification processes. Exposure to heavy metals is likely to produce a rise in oxidative DNA damage with increased urinary concentrations of 8-hydroxy-2′-deoxyguanosine (8-OHdG) (Sughis et al. 2012). Thus, knowledge of the profile of the chemical elements in a given condition (health/disease) and an organic system are fundamental to complete the information of an exposome. A new field of research associated with the study of metals and metalloids that complements the genome, transcriptome, and metabolome is termed metallome (Grasso 2017; Haraguchi 2017; Ogra and Hirata 2017; Shi and Chance 2008).

The term metallome was first introduced by Dr. Robert Williams, similar to the proteome, as

the distribution of ions of a chemical element in all compartments of a system (Williams 2001). The term metallomic was incorporated as the study of the metallome. In 2004, Hiroki Haraguchi (2004) provided an alternative definition to "metallome" as metalloproteins or any other biomolecule, and "metallomic" as the study of such biomolecules. Szpunar (2004) defined metallomics as "a comprehensive analysis of the species of a metal or metalloid in biological tissue or fluid". Chemical species of interest for metallomics include trace element complexes associated with endogenous biomolecules such as organic acids, proteins, fatty acids, and DNA fragments (Szpunar 2004).

Advances in analytical instrumentation for the detection of chemical elements in several clinical samples are mainly associated with coupled inductively coupled plasma mass spectrometry (ICP-MS). It is possible to detect and quantify at least approximately 70% of chemical elements present in biologically relevant concentrations in humans (Parsons and Barbosa 2007). Several studies demonstrated characteristic metallome profiles in certain abnormal health conditions such as individuals with amyotrophic lateral sclerosis (ALS) (De Benedetti et al. 2017), breast cancer (Burton et al. 2016), and diabetes mellitus (Roverso et al. 2015).

Advancement of metallomics also permits one to identify which elements and in which chemical form these constituents are associated with the biological system. Oxidation state and ability to form stable or labile bonds modulate the functions of chemical elements in the biological systems and, consequently, their bioavailability. This pratice is known as chemical speciation analysis (Carneiro, Grotto, and Barbosa 2014, 2013; De Souza et al. 2010; Parsons and Barbosa 2007).

Adductomics

Continuous exposure to toxic substances generates reactive species (electrophilic compounds) in the body that modify nucleophilic DNA sites and functional proteins (Carlsson, Rappaport, and Törnqvist 2019), initiating a wide range of adducts that are associated with toxicological consequences (Cooke et al. 2018; Farmer 2004). Over the last few years, these DNA or protein "adducts" were recognized as *in vivo* biomarkers of exposure and correlated with many human diseases including neurodegeneration, diabetes, asthma, arthritis, cardiovascular diseases and cancer (Cooke et al. 2018; Matsuda et al. 2013; Pathak et al. 2016).

In general, studies in this scientific area focused on untargeted analysis of protein adducts in human serum albumin (HSA) due to (1) reactivity at Cys-34 and other nucleophilic loci, (2) abundance of approximately 40 g/L in serum, and (3) long physiological half-life of approximately 3 weeks. For these reasons, adducts of HSA appear to be more informative than those of DNA (Preston and Phillips 2019; Preston et al. 2017; Rappaport et al. 2012). Adductomics is thus defined as a simultaneous determination of a wide variety of known and unknown DNA and protein adducts (adductome) that may be formed as a result of human exposure to toxic agents (Klaene et al. 2013). Mass spectrometry, especially LC-MS/MS, is the technique of choice for quantifying adducts in clinical specimens.

Although LC-MS/MS adductomatic approaches are currently powerful, there are still major difficulties in identifying unknown adducts due to predominantly large amounts of isotopes (Chang et al. 2018). Consequently, high-resolution instruments such as orbitraps (Carlsson and Törnqvist 2017) and database tools have been used to facilitate adducts recognition. With these new perspectives, adductomics might then become an important tool for understanding the human exposome (Dennis et al. 2017). However, current methodological protocols still need to be addressed and refined including but not limited to the development of new analytical methods and also the production of adduct libraries for annotation.

Role of microbiota and interaction with the exposome

Humans reside in association with a large population of bacteria, viruses, fungi, and archaea, collectively termed the Human Microbiome (Cho and Blaser 2012; Minot et al. 2011; Ursell et al. 2012). The intestinal lumen is one of the habitats most densely populated by microorganisms and may contain up to 1011 bacterial cells/ml. Thousands

of different bacterial species inhabit this environment with most as yet not isolated and comprehensively examined (Cho and Blaser 2012; Frank and Pace 2008).

Feeding, drug use, exposure to chemical agents are among the many factors that modulate the human intestinal microbiome (Robert et al. 2017). Among these, a relationship between general patterns of food intake and at least two microbial profiles in human populations was detected (Arumugam et al. 2011; Wu et al. 2011). These profiles, termed enterotypes, are marked by the abundance of one or more bacteria. An example is the regular intake of carbohydrates and the presence of more excessive quantities of the intestinal *Prevotella* genus, whereas individuals who generally ingest a diet richer in protein and fat exhibit a predominance of the genus *Bacteroides*. Although these studies have now been replicated by several groups, these investigations are predominantly based upon surveys conducted in the United States and Europe. However, it should be noted that intestinal microbiome profiles in several other populations around the world do not conform to either of these two standards (Clemente et al. 2015; Gomez et al. 2016; Obregon-Tito et al. 2015; Schnorr et al. 2018).

This unique ecosystem present in the human intestine exerts systemic effects on the health of its host. These effects include regulation of energy balance, intestinal angiogenesis, hormonal control, vitamin status, and immune system development (Hooper 2001). The relationship between the microbiome and its human host is considered symbiotic, and the collapse of this harmonic relationship is now known as dysbiosis. Examples of the influence of dysbiosis in the intestinal microbiome were previously demonstrated in several diseases, such as obesity, hypertension, colon cancer, as well as several inflammatory bowel diseases (Belizario and Napolitano 2016). Among the health parameters that are known to be associated with the intestinal microbiome including blood hemoglobin, serum HDL cholesterol, body mass index (BMI), plasma uric acid, and hepatic alanine transaminase were found in large European cohorts (Falony et al. 2016).

Although few data are available regarding the relationship between intestinal microbiota and exposure to environmental contaminants, especially in humans, studies in animal models demonstrated a dose-dependent effect of exposure to several metals affected bacterial gene groups present in the intestinal microbiome, suggesting a possible form of exposure to such metals (Richardson et al. 2018). In a zebrafish model, Xia et al. (2018) observed a causal relationship between exposure to mercury and changes in several intestinal bacterial groups as well as a change in hepatic metabolism. Direct effects of exposure to cadmium were associated with alterations in the intestinal microbiota and increased permeability in intestinal mucosa, and both were related to systemic inflammation (Tinkov et al. 2018), an outcome known to be increasingly involved in non-chronic, communicable diseases.

Selecting clinical specimens for HB and exposome studies

For each compound measured in the human body, a specific fluid or tissue needs to be selected as an exposure marker (internal dose or effect). The selection of the specimen takes into account several variables; however, the kinetics of the compound in the human body is a determinant factor. The same applies for the choice of biofluids for measuring general effects such as proteome, metabolome, adductome, and inflammatory markers. On the other hand, in many cases, the biological matrix selected for measuring the effect(s) varies from that for determining the internal dose marker. In this manner, it is clear that in both HB or exposome studies the use of more than one specimen should provide more information for the whole spectrum of the exposure and associated outcomes. Further, in many cases, one biomarker might complement the information achieved by the other.

Blood, plasma/serum and urine alone or combined are the most common matrices used in HB and exposome studies (Wallace, Kormos, and Pleil 2016). While blood or plasma/serum is invasive upon collection, urine involves other encumbrances such as privacy. A less invasive way to collect blood is from the finger (capillary blood) (Tang et al. 2017). However, the analyte content

should not differ in venous and capillary blood specimens. Other biological matrices, such as hair and nails offer inherent advantages for HB and exposome investigations (Barbosa et al. 2005). These matrices are simply and noninvasively collected, with minimal cost, and easily stored and transported (Barbosa et al. 2005; Rodrigues et al. 2008). However, the most attractive potential of these specimens is probably the potential to provide a more extended exposure timeframe. However, although hair or nail analysis may be able to answer some specific questions regarding environmental exposure to a few substances, the employment of these tissues often raises more questions than answers leading to skepticism by the scientific community on their reliability as biomarkers (Barbosa et al. 2005).

Teeth primarily deciduous seem to be an interesting matrix for HB and exposome studies. Teeth provide past exposure information mainly in the fetal stage based upon deposition of contaminants and nutrients. This information may be relevant to establish relationships between exposures in the uterine phase and neurological effects in youth (Almeida et al. 2007; Andra, Austin, and Arora 2015a, 2016; Andra et al. 2015b; Arora and Austin 2013; Arora et al. 2014; Bauer et al. 2017; Chiu et al. 2017; Morishita and Arora 2017; Shepherd et al. 2012; Wahlberg et al. 2017).

One of the most exciting advances is utilizing exhaled gases and aerosols as a non-invasive biological matrix for recording part of the human exposome (Kim, Jahan, and Kabir 2012). Exhaled breath (EB) is a relatively simple, rapid and non-invasive method (Wallace et al. 2019). EB is composed of multiple volatile organic compounds (VOCs) originating from both endogenous and exogenous sources that differentiate diseased from healthy individuals (Kim, Jahan, and Kabir 2012; Pereira et al. 2015). Further, it would be more difficult to detect most of the volatiles determined in EB with analysis of blood samples (Kim, Jahan, and Kabir 2012). Analysis of the EB compartment may reveal the volatile composition of the bloodstream, and for compounds originated endogenously EB levels may correlate with the bloodstream concentration (Pereira et al. 2015).

As a limitation, breath analysis only provides information for VOCs and is more attractive for monitoring biomarkers of effect. Moreover, this technique still suffers from insufficient accuracy with many VOCs found at low concentrations (ppb level or lower) and from contamination from external air during sample collection. Breath analysis is also subject to the influence of several factors including but not limited to age, gender, and diet. Certain types of food, such as yoghurt and seafood, contain a number of VOCs that rapidly and directly appear after ingestion (Jia et al. 2019). Thus, the technique seems to be a promising procedure for exposome studies to complement data obtained from the analysis of conventional matrices such as whole blood, plasma or serum and urine. However, future studies in this scientific area need to deal with improving techniques for sample collection and resolve challenges for long-term sample storage (Sakumura et al. 2017). For further information on this topic, it is recommended the reading of recent reviews (Kim, Jahan, and Kabir 2012; Lawal et al. 2017; Pereira et al. 2015; Pleil 2016; Wallace and Pleil 2018).

The use of microsampling techniques for sample collection, transportation and storage

HB and exposome studies demand well-established protocols for collection, transportation, and storage of samples. In many cases, these two important steps are complex requiring greater challenges not to compromise the integrity of the samples. Traditionally protocols for collection of clinical specimens have been invasive, stressful, labor intensive, time-consuming and costly. In addition, in some cases, it requires the removal of large blood volumes from volunteers. This may result in a physiological or emotional burden, particularly for neonates or pediatric patients. Further, the creation of large-scale biobanks might require alternative procedures for sample storage that offer the reduction of sample size and improve stability of analytes for longer periods. Therefore, microsampling procedures were proposed as an interesting alternative in order to resolve such challenges (Demirev 2013; Kim and Kannan 2018). One of the first microsampling strategies proposed a microdrop of blood (10–30 µl) collected from the finger or toe and then drawn

onto a specially manufactured absorbent filter paper. The blood is then allowed to thoroughly saturate the paper and dry for min or hr at room temperature (Li and Tse 2010). The procedure is termed Dried Blood Spot (DBS) and is currently common in neonatal screening programs around the world and becoming a key part of public health programs (Botler, Camacho, and Da Cruz 2012; Nordfalk and Ekstrøm 2019). Further, other clinical specimens, such as plasma or urine, might also be stored on the filter paper surface using this same procedure (Kolocouri, Dotsikas, and Loukas 2010). This strategy can extend the stability of samples and analytes for months or even years without freezing (Demirev 2013). Several other microsampling devices/techniques were proposed that include: (i) Capillary microsampling (CMS) and (ii) Volumetric absorptive microsampling (VAMS) (Denniff and Spooner 2014; Nys et al. 2017). In general, microsampling techniques offer a number of distinct advantages over conventional collection procedures:

(1) In the case of blood collection, this procedure makes possible a less invasive sampling in which the collection is obtained from the finger or heel rather than conventional venous puncture, which favors the collection of blood in neonates.
(2) The storage of the sample is simpler and transport less complex, as there is no requirement for freezers or dry ice. The sample in this method is easily collected by the patients or tutors with minimal training and mailed to the designated lab, avoiding unnecessary costs.
(3) This collection procedures require a small sample volume, less than 100 µl, compared to more than 4 ml, which is usually obtained by conventional sample collection in HB or exposome studies. This advantage also enables a significant simplification in the collection of clinical specimens from newborns, children or other subjects.
(4) Microsampling approaches enable implementation of at-home sampling.

Establishing exposomic signatures

The quantity and complexity of information obtained in an exposomic study make data integration into one of the most critical steps. Results inform or distinguish the primary molecular mechanisms associated with a health condition through molecular signatures (fingerprints) or may even establish specific and early biomarkers for defined, personalized, or preventive use. The application of data mining tools may help in this issue (Heinonen et al. 2012; Li, Ng, and Wang 2013; Swan et al. 2013).

Data mining is the process of automatically discovering useful information in large data repositories. Data mining exhibits techniques that use machine learning combined with linear algebra calculations and mathematical optimization to uncover results in a set of data that pass unnoticed through traditional analysis methods. Data mining is an integral part of database knowledge discovery (KDD), which is the general process of converting raw data into useful information and consists of a series of transformation steps such as those set out in Figure 3 (Maione 2016; Tan, Steinbach, and Kumar 2005).

Machine learning is a basic procedure for performing most of the data mining processes. Derived from the artificial intelligence field, it encompasses methods of computational statistics, mathematical optimization, and computational fundamentals to shape algorithms and make

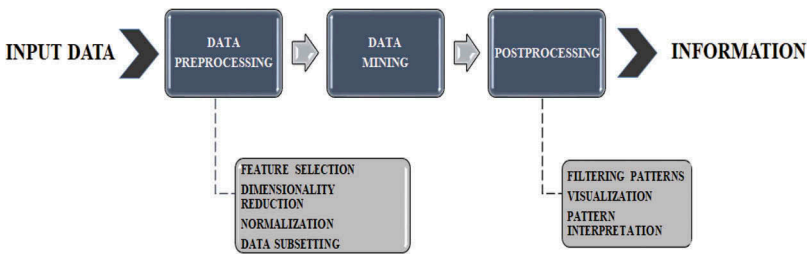

Figure 3. The process of knowledge discovery in databases (KDD) (Adapted from Tan, Steinbach, and Kumar 2005).

them capable of making automatic discoveries of patterns and information in datasets that lead to decision-making (Bishop and Nasrabadi 2010). Data mining problems, which involve the analysis of databases (such as those contemplated in this research), are not solved by standard static algorithms and require that these algorithms evolve and adapt autonomously as the scenario surrounding the solution is modified, and in these cases, machine learning is especially useful.

In the context of data mining and pattern recognition, a database (or set) is defined as a finite set of examples E = {e1, e2, …, en} representing linear combinations of a given set of variables X = {x1, x2, …, xm}. In other words, each example (or sample) is described by a finite input vector corresponding to the values of its characteristics. Thus, a set of data refers to an n × m matrix, where n is the number of examples available and m the number of variables, or characteristics, which describe the examples. Machine learning enables one to model algorithms capable of observing the behavior of the examples of a given set of data (for example, the exposome) and their characteristics and trying to predict information in new and unknown examples, or even to identify patterns and profiles between the examples of this dataset (Maione 2016).

The objectives of the KDD are summarized as follows: i) verification, which constitutes limiting itself to verify the hypothesis of the user; and ii) discovery, in which there is the discovery of new standards (Da Costa, Castro, and Barbosa 2016; Fayyad and Stolorz 1997). The detection of patterns is subdivided into prediction and description. The prediction uses the models found to predict new samples. The report explains the patterns noted such that the user might understand them. In an exposome, machine learning tools apply algorithms to detect variables (biomarkers) that are predictive of an outcome (phenotype) (Patel 2017).

The main algorithms used in machine learning include, neural networks, decision trees, random forests, association and sequence discovery, gradient boosting and bagging, support vector machines, nearest-neighbor mapping, k-means clustering, maps self-organizing, local search optimization techniques (e.g., genetic algorithms), expectation maximization, multivariate analysis, adaptive regression splines, Bayesian networks, Kernel density estimation, singular value decomposition, and sequential coverage rule construction. These tools have been successfully utilized in the integration of metabolomic, lipidomic, and clinical data (Acharjee et al. 2016; Kenny et al. 2005).

For population studies, data mining techniques generally perform better than conventional statistical methods such as logistic regression, especially in situations that include multivariate risk factors with few effects, limited number of samples and limited knowledge among the effects of several risk factors acting simultaneously (Schadt, Friend, and Shaywitz 2009; Yu et al. 2010).

The generation of the individualized exposome through new devices and sensors

In an ideal condition, quantification of "external" exposome needs to include all exposure pathways such as inhalation, ingestion and dermal contact and relevant stressors such as air pollutants, contaminants in food and water, soil and dust, radiation, temperature, light, and noise (Loh et al. 2017). However, in most cases, it is not possible and sometimes not feasible. Further, exposure factors such as inhalation rate, consumption and frequency, and location need to be characterized. Physical, social, and individual factors such as diet, physical activity, and stress are also important when one accounts for the relationship between environment and health. This range of exposures and risk factors vary across many time and space scales, creating an extensive and challenging task for monitoring (Loh et al. 2017).

As personalized smart technologies are becoming more prevalent, there is the promise of portable, lower-cost sensor systems that may enable long-term monitoring of either personal exposure or external environment around the individual. The growing popularity of small sensors, open source programs, microcontrollers, wireless technology, and cloud computing enables the collection and integration of many types of data on a personal level. There is a growing number of groups of individuals interested in using this technology to collect direct and personalized data from their smartphones, such as location, physical activities, diet, or sleep in order to better understand their own habits

and their impact on health (Aanensen et al. 2009; Boulos et al. 2011; Loh et al. 2017).

The concept of assessing the location and combining this with environmental data collected from other instruments or sources is critical to the exposome. Currently, there are several free apps, which monitor in real time and in a relatively precise way several individualized conditions. These free apps might be easily accounted for in the external factors of exposure, such as diet, physical activity, noise, air pollution, and location. New apps might be easily created through, for example, a free tool like "ResearchKit" (http://researchkit.org/) which is an open source framework introduced by Apple that allows researchers to develop apps powerful for medical research (Jardine, Fisher, and Carrick 2015).

Preliminary exposome studies

In the last 5 years, considerable investment has been made by research promotion agencies in the USA and Europe, aiming to create groups for studies in exposome. With this new perspective, several research group indicated the potential benefits of characterizing the global exposure of an individual or a population to predict or identify mechanisms associated with several pathologies with prominent publications and impact (Andra, Austin, and Arora 2016; Buck Louis et al. 2013; DeBord et al. 2016; Lewis et al. 2013; Lioy and Rappaport 2011; Miller and Jones 2013; Rappaport 2010; Robinson and Vrijheid 2015; Rogler and Vavricka 2015; Vineis 2015; Vrijheid 2014).

Today there are several projects funded for studies in exposome in the European Union the HELIX (Human Early Life Exposome) (Potera 2014; Vrijheid et al. 2014) and HEALS (Health and Environment-wide Associations based on Large (Steckling et al. 2018) and those funded by the NIH in the USA, such as the HERCULES ((Human Exposome Research Center: Understanding Lifetime Exposures) (http://emoryhercules.com)), and the Children's Health Exposure Analysis Resource (http://www.niehs.nih.gov/research/supported/exposure/chear/). The HERCULES project coordinated by Emory University received NIH funding of $ 4.5 million in 2013 and last year (2017) plus $ 7.5 million (Robertson 2017). In 2017, the Mount Sinai School of Medicine in the United States created the Institute of Studies in Exposome (http://icahn.mssm.edu/research/exposomic/about) with financing over the U$ 10 million.

The European Community opened a call for proposals in the last July 2018 to finance projects in the theme "The Human Exposome Project: a toolbox for assessing and addressing the impact of the environment on health" (European Commission 2017). Although it is still in its infancy, the concept of exposome has been growing, and several attempts were undertaken to define and characterize this concept. The number of citations of the "exposome" in PubMed has risen from 17 in 2011 to more than 80 in 2018 (Figure 4), indicating an expanding interest in the subject.

Challenges and future directions

The interest in HB and human exposome will keep growing; however several problems and limitations remain and need to be considered for further

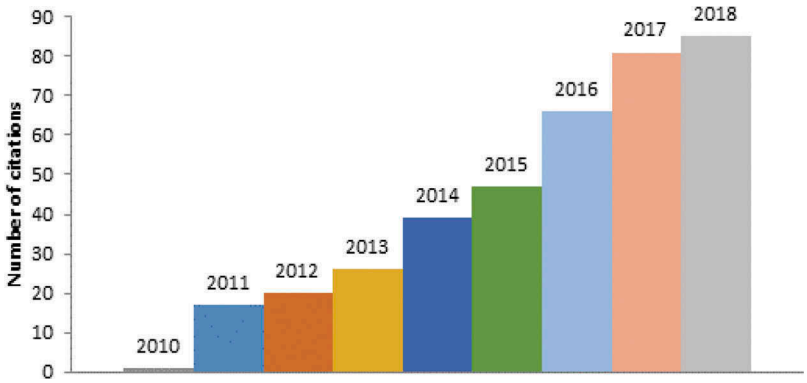

Figure 4. Citations of the term "exposome" in PUBMED in the last 10 years. Available in htpp://www.ncbi.nlm.nih.gov/pubmed/. Accessed on December 2018.

studies. Most of the HB studies are restricted to a selected group of compounds (target analytes). Further, the definition of the priority list of chemicals to be investigated is not always clear. The selection of the biological matrices in traditional HB studies or exposome approaches requires considerable attention since each biomarker provides information in different time scales of the history of exposure. Further, a simple sample of blood or urine (spot sampling) provides only a specific exposure timeframe in life. In this sense, hair and nail matrices have the potential to offer, at least in theory, a more extended picture of the exposure. On the other hand, the use of these matrices is still subject to many criticisms in the scientific literature (Barbosa et al. 2005; Rodrigues et al. 2008). In many cases, biomarkers of effect, measured as part of the internal exposome, may be an indicator of a previous external condition (past exposure or different lifestyle habits). The manner to record and quantify long-term exposure to all external stressors is still an enormous challenge. An alternative would be defining critical windows or life-stage exposome snapshots (LEnS), capturing, for example, information of repeated exposures during critical periods of the life course as proposed by Shaffer, Smith, and Faustman (2017).

The wide range of analytical instrumentation and high technical knowledge still limits the application and development of these tools for public health agencies in underdeveloped countries is hindered by follow up surveys. Moreover, even for the most developed regions, the future of exposome studies may be directly connected to the establishment of consortia with the integration of different expertise.

For exposome studies, biological effects need to be evaluated applying a system- and pathways-based perspective to (1) identify unknown biomarkers of effect, (2) separate exposures and biological responses, and (3) understand which exposures are biologically relevant, defining then future target markers of a specific lifestyle condition. However, the number of produced variables require the application of the concept of "big data" and the development of modern data mining algorithms. This makes it possible to traverse to more complex models that include biological components critical to understanding causal pathways.

Well-established harmonization protocols are required to provide comparable data between studies, and establishing quality assurance/quality control of data. In the last few years, there are several initiatives both in Europe (COPHES) and USA (CHEARS) in this direction. However, more Reference Materials and Proficiency Testing programs are required.

If HB and exposome studies are correlated, this may enhance the benefits of each one with more significant improvement to evaluate human health risks, as well as provide more detailed information directly related to diseases (Dennis et al. 2017). Further, large available databanks (example NHANES) with target analysis might also be useful for designing nontarget exposome strategies.

Implementing longitudinal studies is critical for future exposome investigations, since most of the existing exposome projects are based upon cross-sectional sampling strategies. The use of retrospective information collected from the analysis of cohort sample storage in biobanks might be an interesting alternative for the design of human exposome surveys. However, the lack of information regarding the stability of analytes frozen for years creates new challenges.

New biobanks need to be created. However, the cost of maintenance is a limitation. In addition, the long-term stability of analytes in frozen samples needs to be verified. Concomitantly, strategies to reduce the volume of samples to be collected and facilitate transport and storage was proposed. Current microsampling techniques, such as Dried Blood Spot and Volumetric Absorptive MicroSampling (VAMS) seems to be interesting methodologies to be investigated.

As new analytical instrumentation and information technologies are merged, it should become possible to acquire knowledge from simultaneous exposure with less cost. With the current improvement of instruments, greater detection capabilities will be achieved, and consequently, more compounds may be detected with better accuracy. In addition, when a new analytical methodology is proposed, it needs to consider the detection of multiple compounds in the same experiment including biomarkers of exposure and effect, if possible, or combining suspected and nontarget qualitative screening with quantitative target analysis ("All-in-one" approach), with minimal and more

rapid sample preparation steps. Further, strategies for method validation need to be improved with the production of new analytical standards and Certified Reference Materials.

Over the last few years, improvement of smartphone technology with the new era of the internet of things (IoT) enabled one to take advantage of innovative mobile apps that generate real-time information. Several validated apps are capable of controlling daily food intake, accounting for the number of calories and nutrients present in each meal by capturing the image of the food to be consumed. Other apps, quickly assess the calories consumed in physical activities, monitor the quality of sleep, and provide broadcasting air quality information in different geographic locations.

Personalized systems for the external exposome measurements (air monitoring), based upon sensor technology, are expanding rapidly, and this seems to be a tendency for future exposome studies. Usually, these systems function by passive sample collection and provide real-time monitoring with relatively low cost. However, in general, these are limited to a few groups of compounds, and accuracy is still questionable.

There are still a limited number of exposomic studies that consider the effects of social stressors. Further, populations suffering influence of endemic events, natural disasters or climate change require potential demand for future exposomic studies. Finally, researchers and environmental health agencies need to define how whole generated exposome data might be applicable to risk assessment and public health regulations.

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The authors declare that they have no potential for competing for financial or other interests.

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References

Aanensen, D. M., D. M. Huntley, E. J. Feil, F. al-Own, and B. G. Spratt. 2009. EpiCollect: Linking smartphones to web applications for epidemiology, ecology and community data collection. *PLoS ONE* 4:e6968. doi:10.1371/journal.pone.0006968.

Acharjee, A., Z. Ament, J. A. West, E. Stanley, and J. L. Griffin. 2016. Integration of etabolomics, ipidomics and linical ata sing a achine earning ethod. *BMC Bioinformatic* 17:37–49. doi:10.1186/s12859-016-1292-2.

Al Bakheet, S. A., I. M. Attafi, Z. H. Maayah, A. R. Abd-Allah, Y. A. Asiri, and H. M. Korashy. 2013. Effect of long-term human exposure to environmental heavy metals on the expression of detoxification and DNA repair genes. *Environ. Pollut.* 181:226–32. doi:10.1016/j.envpol.2013.06.014.

Alden, N., S. Krishnan, V. Porokhin, R. Raju, K. McElearney, A. Gilbert, and K. Lee. 2017. Biologically consistent annotation of metabolomics data. *Anal. Chem.* 89:13097–104. doi:10.1021/acs.analchem.7b02162.

Almeida, G. R. C., M. C. P. Saraiva, F. Barbosa, F. J. Krug, J. A. Cury, M. L. R. de Sousa, M. A. R. Buzalaf, and R. F. Gerlach. 2007. Lead contents in the surface enamel of deciduous teeth sampled in vivo from children in uncontaminated and in lead-contaminated areas. *Environ. Res.* 104:337–45. doi:10.1016/j.envres.2007.03.007.

Alves, A. C., M. S. Monteiro, A. L. Machado, M. Oliveira, A. Bóia, A. Correia, N. Oliveira, A. M. V. M. Soares, and S. Loureiro. 2017. Mercury levels in parturient and newborns from Aveiro region, Portugal. *J. Toxicol. Environ. Health A* 80:697–709. doi:10.1080/15287394.2017.1286926.

Andra, S. S., C. Austin, D. Patel, G. Dolios, M. Awawda, and M. Arora. 2017. Trends in the application of high-resolution mass spectrometry for human biomonitoring: An analytical primer to studying the environmental chemical space of the human exposome. *Environ. Int.* 100:32–61. doi:10.1016/j.envint.2016.11.026.

Andra, S. S., C. Austin, and M. Arora. 2015a. Tooth matrix analysis for biomonitoring of organic chemical exposure: Current status, challenges, and opportunities. *Environ. Res.* 142:387–406. doi:10.1016/j.envres.2015.06.032.

Andra, S. S., C. Austin, and M. Arora. 2016. The tooth exposome in children□s health research. *Curr. Opin. Pediatr.* 28:221–27. doi:10.1097/mop.0000000000000327.

Andra, S. S., C. Austin, R. O. Wright, and M. Arora. 2015b. Reconstructing pre-natal and early childhood exposure to multi-class organic chemicals using teeth: Towards a retrospective temporal exposome. *Environ. Int.* 83:137–45. doi:10.1016/j.envint.2015.05.010.

Angerer, J., U. Ewers, and M. Wilhelm. 2007. Human biomonitoring: State of the art. *Int. J. Hyg. Environ. Health* 210:201–28. doi:10.1016/j.ijheh.2007.01.024.

Arora, M., and C. Austin. 2013. Teeth as a biomarker of past chemical exposure. *Curr. Opin. Pediatr.* 25:261–67. doi:10.1097/mop.0b013e32835e9084.

Arora, M., C. Austin, B. Sarrafpour, M. Hernández-Ávila, H. Hu, R. O. Wright, and M. M. Tellez-Rojo. 2014. Determining prenatal, early childhood and cumulative long-term lead exposure using micro-spatial deciduous dentine levels. *PLoS ONE* 9:e97805. doi:10.1371/journal.pone.0097805.

Arrebola, J. P., M. Fernández-Rodríguez, F. Artacho-Cordón, C. Garde, F. Perez-Carrascosa, I. Linares, I. Tovar, B. González-Alzaga, J. Expósito, P. Torne, et al. 2016. Associations of persistent organic pollutants in serum and adipose tissue with breast cancer prognostic markers. *Sci. Total Environ.* 566–567:41–49. doi:10.1016/j.scitotenv.2016.04.188.

Arumugam, M., J. Raes, E. Pelletier, D. Le Paslier, T. Yamada, D. R. Mende, G. R. Fernandes, J. Tap, T. Bruls, J.-M. Batto, et al. 2011. Enterotypes of the human gut microbiome. *Nature* 473:174–80. doi:10.1038/nature09944.

Azuaje, F., Y. Devaux, and D. Wagner. 2009. Computational biology for cardiovascular biomarker discovery. *Brief. Bioinform.* 10:367–77. doi:10.1093/bib/bbp008.

Badimon, L., G. Vilahur, and T. Padro. 2016. Systems biology approaches to understand the effects of nutrition and promote health. *Br. J. Clin. Pharmacol.* 83:38–45. doi:10.1111/bcp.12965.

Barbosa, F. 2017. Toxicology of metals and metalloids: Promising issues for future studies in environmental health and toxicology. *J. Toxicol. Environ. Health A* 80:137–44. doi:10.1080/15287394.2016.1259475.

Barbosa, F., J. E. Tanus-Santos, R. F. Gerlach, and P. J. Parsons. 2005. A critical review of biomarkers used for monitoring human exposure to lead: Advantages, limitations, and future teeds. *Environ. Health Perspect.* 113:1669–74. doi:10.1289/ehp.7917.

Barbosa, F., M. Fillion, M. Lemire, C. J. S. Passos, J. L. Rodrigues, A. Philibert, J.-R. Guimarães, and D. Mergler. 2009. Elevated blood lead levels in a riverside population in the brazilian Amazon. *Environ. Res.* 109:594–99. doi:10.1016/j.envres.2009.03.005.

Barcelos, G. R. M., D. Grotto, K. C. de Marco, J. Valentini, A. H. Lengert, A. A. S. de Oliveira, S. C. Garcia, G. Ú. Braga, K. Schläwicke Engström, I. M. Cólus, et al. 2013. Polymorphisms in glutathione-related genes modify mercury concentrations and antioxidant status in subjects environmentally exposed to methylmercury. *Sci. Total Environ.* 463–464:319–25. doi:10.1016/j.scitotenv.2013.06.029.

Barcelos, G. R. M., K. C. de Marco, V. B. de Rezende, G. U. L. Braga, L. M. G. Antunes, J. E. Tanus-Santos, and F. Barbosa. 2015a. Genetic Effects of ENOS polymorphisms on biomarkers related to cardiovascular status in a population coexposed to methylmercury and lead. *Arch. Environ. Contam. Toxicol.* 69:173–80. doi:10.1007/s00244-015-0137-8.

Barcelos, G. R. M., M. F. de Souza, A. A. S. de Oliveira, A. H. Lengert, M. T. de Oliveira, R. B. O. G. Camargo, D. Grotto, J. Valentini, S. C. Garcia, G. Ú. Braga, et al. 2015b. Effects of genetic polymorphisms on antioxidant status and concentrations of the metals in the blood of riverside Amazonian communities co-exposed to Hg and Pb. *Environ. Res.* 138:224–32. doi:10.1016/j.envres.2015.02.017.

Barry, V., A. Winquist, and K. Steenland. 2013. Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ. Health Perspect.* 121:1313–18. doi:10.1289/ehp.1306615.

Batista, B. L., J. L. Rodrigues, L. Tormen, A. J. Curtius, and F. Barbosa Jr. 2009. Reference concentrations for trace elements in urine for the brazilian population based on Q-ICP-MS with a simple dilute-and-shoot procedure. *J. Braz. Chem. Soc.* 20:1406–13. doi:10.1590/s0103-50532009000800004.

Bauer, J. A., B. C. Henn, C. Austin, S. Zoni, C. Fedrighi, G. Cagna, D. Placidi, R. F. White, Q. Yang, B. A. Coull, et al. 2017. Manganese in teeth and neurobehavior: Sex-specific windows of susceptibility. *Environ. Int.* 108:299–308. doi:10.1016/j.envint.2017.08.013.

Becker, C. H., and M. Bern. 2011. Recent developments in quantitative proteomics. *Mutat. Res. Toxicol. Environ. Mutagen.* 722:171–82. doi:10.1016/j.mrgentox.2010.06.016.

Belizario, J. E., and M. Napolitano. 2016. Human microbiomes and their roles in dysbiosis, common diseases, and novel therapeutic approaches. *Front. Microbiol.* 6:1–16. doi:10.3389/fmicb.2015.01050.

Berghuis, S. A., A. F. Bos, P. J. J. Sauer, and E. Roze. 2015. Developmental neurotoxicity of persistent organic pollutants: An update on childhood outcome. *Arch. Toxicol.* 89:687–709. doi:10.1007/s00204-015-1463-3.

Berman, T., R. Goldsmith, H. Levine, and I. Grotto. 2017. Human biomonitoring in Israel: Recent results and lessons learned. *Int. J. Hyg. Environ. Health* 220:6–12. doi:10.1016/j.ijheh.2016.09.008.

Bishop, C. M., and N. M. Nasrabadi. 2010. Pattern recognition and machine learning. *J. Electr. Imag.* 16:140–55. doi:10.1117/1.2819119.

Bonefeld-Jørgensen, E. C., M. Long, S. O. Fredslund, R. Bossi, and J. Olsen. 2014. Breast cancer risk after exposure to perfluorinated compounds in Danish women: A case-control study nested in the Danish national birth cohort. *Cancer Causes Control* 25:1439–48. doi:10.1007/s10552-014-0446-7.

Botler, J., L. A. B. Camacho, and M. M. Da Cruz. 2012. Phenylketonuria, congenital hypothyroidism and haemoglobinopathies: Public health issues for a Brazilian newborn screening program. *Cad. Saude Publica.* 28:1623–31. doi:10.1590/s0102-311x2012000900002.

Boulos, M. N. K., A. Anastasiou, E. Bekiaris, and M. Panou. 2011. Geo-enabled technologies for independent living:

Examples from four European projects. *Technol. Disabil.* 23:7–17. doi:10.3233/TAD-2011-0300.

Branco, V., S. Caito, M. Farina, J. T. Da Rocha, M. Aschner, and C. Carvalho. 2017. Biomarkers of mercury toxicity: Past, present, and future trends. *J. Toxicol. Environ. Health B* 20:119–54. doi:10.1080/10937404.2017.1289834.

Buck Louis, G. M., E. Yeung, R. Sundaram, S. K. Laughon, and C. Zhang. 2013. The Exposome - Exciting opportunities for discoveries in reproductive and perinatal epidemiology. *Paediatr. Perinat. Epidemiol.* 27:229–36. doi:10.1111/ppe.12040.

Buck Louis, G. M., and R. Sundaram. 2012. Exposome: Time for transformative research. *Stat. Med.* 31:2569–75. doi:10.1002/sim.5496.

Burton, C., Y. Dan, A. Donovan, K. Liu, H. Shi, Y. Ma, and C. P. Bosnak. 2016. Urinary metallomics as a novel biomarker discovery platform: Breast cancer as a case study. *Clin. Chim. Acta* 452:142–48. doi:10.1016/j.cca.2015.11.014.

Caberlotto, L., and M. Lauria. 2014. Systems biology meets - Omic technologies: Novel approaches to biomarker discovery and companion diagnostic development. *Expert Rev. Mol. Diagn.* 15:255–65. doi:10.1586/14737159.2015.975214.

Cai, Y., B. Zhang, W. Ke, B. Feng, H. Lin, J. Xiao, W. Zeng, X. Li, J. Tao, Z. Yang, et al. 2016. Associations of short-term and long-term exposure to ambient air pollutants with hypertension novelty and significance. *Hypertension* 68:62–70. doi:10.1161/hypertensionaha.116.07218.

Carlsson, H., and M. Törnqvist. 2017. An adductomic approach to identify electrophiles in vivo. *Basic Clin. Pharmacol. Toxicol.* 121:44–54. doi:10.1111/bcpt.12715.

Carlsson, H., S. Rappaport, and M. Törnqvist. 2019. Protein adductomics: Methodologies for untargeted screening of adducts to serum albumin and hemoglobin in human blood samples. *High Throughput* 8:1–18. doi:10.3390/ht8010006.

Carneiro, M. F. H., D. Grotto, and F. Barbosa. 2014. Inorganic and methylmercury levels in plasma are differentially associated with age, gender, and oxidative stress markers in a population exposed to mercury through fish consumption. *J. Toxicol. Environ. Health A* 77:69–79. doi:10.1080/15287394.2014.865584.

Carrola, J., C. M. Rocha, A. S. Barros, A. M. Gil, B. J. Goodfellow, I. M. Carreira, J. Bernardo, A. Gomes, V. Sousa, L. Carvalho, et al. 2011. Metabolic signatures of lung cancer in biofluids: NMR-Based metabonomics of urine. *J. Proteome Res.* 10:221–30. doi:10.1021/pr100899x.

Carwile, J. L., and K. B. Michels. 2011. Urinary bisphenol A and obesity: NHANES 2003-2006. *Environ. Res.* 111:825–30. doi:10.1016/j.envres.2011.05.014.

CAS. 2019. *CAS Registry-The gold standard for chemical substance information*. Columbus, OH, USA: Chemical Abstracts Service. American Chemical Society. Acessed May 2019. Available: https//www.cas.org/content/chemical-substances

Center for Disease Control and Prevention (CDC). 2017. National report on human exposure to environmental chemicals - NER. Acessed May, 2019. https://www.cdc.gov/exposurereport/index.html.

Černá, M., V. Puklová, L. Hanzlíková, L. Sochorová, and R. Kubínová. 2017. 25 Years of HBM in the Czech Republic. *Int. J. Hyg. Environ. Health* 220:3–5. doi:10.1016/j.ijheh.2016.08.004.

Cervinkova, B., L. K. Krcmova, S. Klabackova, D. Solichova, and P. Solich. 2017. Rapid determination of lipophilic vitamins in human serum by ultra-high performance liquid chromatography using a fluorinated column and high-throughput miniaturized liquid-liquid extraction. *J. Separat. Sci.* 40:3375–82. doi:10.1002/jssc.201700492.

Chang, C.-H., C.-S. Liu, H.-J. Liu, C.-P. Huang, C.-Y. Huang, H.-T. Hsu, S.-H. Liou, and C.-J. Chung. 2015. Association between levels of urinary heavy metals and increased risk of urothelial carcinoma. *Int. J. Urol.* 23:233–39. doi:10.1111/iju.13024.

Chang, Y. J., M. S. Cooke, C. W. Hu, and M. R. Chao. 2018. Novel approach to integrated DNA adductomics for the assessment of in vitro and in vivo environmental exposures. *Arch. Toxicol.* 92:2665–80. doi:10.1007/s00204-018-2252-6.

Chen, C.-Y., H.-J. Hung, K.-H. Chang, C. Y. Hsu, C.-H. Muo, C.-H. Tsai, and T.-N. Wu. 2017. Long-term exposure to air pollution and the incidence of parkinson's disease: A nested case-control study. *PLoS ONE* 12:e0182834. doi:10.1371/journal.pone.0182834.

Chiu, Y.-H., B. C. Mathilda, -H.-H. L. Henn, M. P. Hsu, B. A. Pendo, C. C. Austin, G. Cagna, C. Fedrighi, D. Placidi, D. R. Smith, et al. 2017. Sex differences in sensitivity to prenatal and early childhood manganese exposure on neuromotor function in adolescents. *Environ. Res.* 159:458–65. doi:10.1016/j.envres.2017.08.035.

Cho, I., and M. J. Blaser. 2012. The human microbiome: At the interface of health and disease. *Nat. Rev. Genet.* 13:260–70. doi:10.1038/nrg3182.

Choi, W., S. Kim, Y.-W. Baek, K. Choi, K. Lee, S. Kim, S. D. Yu, and K. Choi. 2017. Exposure to environmental chemicals among Korean adults-updates from the second Korean national environmental health survey (2012–2014). *Int. J. Hyg. Environ. Health* 220:29–35. doi:10.1016/J.IJHEH.2016.10.002.

Ciborowski, M., J. Teul, J. L. Martin-Ventura, J. Egido, and C. Barbas. 2012. Metabolomics with LC-QTOF-MS permits the prediction of disease stage in aortic abdominal aneurysm based on plasma metabolic fingerprint. *PLoS ONE* 7:e31982. doi:10.1371/journal.pone.0031982.

Clemente, J. C., E. C. Pehrsson, M. J. Blaser, K. Sandhu, Z. Gao, B. Wang, M. Magris, G. Hidalgo, M. Contreras, Ó. Noya-Alarcón, et al. 2015. The microbiome of uncontacted amerindians. *Sci. Adv.* 1:e1500183–e1500183. doi:10.1126/sciadv.1500183.

Cohen-Hubal, E. A. 2009. ExpoCast: Exposure science for prioritization and toxicity testing. *Int. Soc. Expo. Sci. Annu. Meet* Minneapolis, MN.

Cooke, M. S., C. W. Hu, Y. J. Chang, and M. R. Chao. 2018. Urinary DNA adductomics – A novel approach for exposomics. *Environ. Int.* 121:1033–38. doi:10.1016/j.envint.2018.10.041.

Crovella, S., R. R. Moura, S. Cappellani, F. Celsi, E. Trevisan, M. Schneider, A. Brollo, E. M. Nicastro, F. Vita, L. Finotto, et al. 2018. A genetic variant of NLRP1 gene is associated with asbestos body burden in patients with malignant pleural mesothelioma. *J. Toxicol. Environ. Healtht A* 81:98–105. doi:10.1080/15287394.2017.1416911.

Da Costa, N. L., I. A. Castro, and R. Barbosa. 2016. Classification of Cabernet Sauvignon from two different countries in South America by chemical compounds and support vector machines. *Appl. Artif. Intell.* 30:679–89. doi:10.1080/08839514.2016.1214416.

Da Silva, A. L. C., M. R. Urbano, A. C. B. A. Lopes, M. F. H. Carvalho, M. L. Buzzo, T. S. Peixe, M. Aschner, A. E. Mesas, and M. M. B. Paoliello. 2017. Blood manganese levels and associated factors in a population-based study in southern Brazil. *J. Toxicol. Environ. Health A* 80:1064–77. doi:10.1080/15287394.2017.1357354.

De Benedetti, S., G. Lucchini, C. Del Bò, V. Deon, A. Marocchi, S. Penco, C. Lunetta, E. Gianazza, F. Bonomi, and S. Iametti. 2017. Blood trace metals in a sporadic amyotrophic lateral sclerosis geographical cluster. *Biometals* 30:355–65. doi:10.1007/s10534-017-0011-4.

De Marco, K. C., L. M. G. Antunes, J. E. Tanus-Santos, and F. Barbosa. 2012. Intron 4 polymorphism of the endothelial nitric oxide synthase (ENOS) gene is associated with decreased NO production in a mercury-exposed population. *Sci. Total Environ.* 414:708–12. doi:10.1016/j.scitotenv.2011.11.010.

De Souza, S. S., A. D. Campiglia, and F. Barbosa. 2013. A simple method for methylmercury, inorganic mercury and ethylmercury determination in plasma samples by high performance liquid chromatography–Cold-vapor-inductively coupled plasma mass spectrometry. *Anal. Chim. Acta.* 761:11–17. doi:10.1016/j.aca.2012.11.038.

De Souza, S. S., J. L. Rodrigues, V. C. O. Souza, and F. Barbosa. 2010. A fast sample preparation procedure for mercury speciation in hair samples by high-performance liquid chromatography coupled to ICP-MS. *J. Anal. Atom. Spectrom.* 25:79–83. doi:10.1039/b911696f.

DeBord, D. G., T. Carreón, T. J. Lentz, P. J. Middendorf, M. D. Hoover, and P. A. Schulte. 2016. Use of the "Exposome" in the practice of epidemiology: A primer on -omic technologies. *Am. J. Epidemiol.* 184:302–14. doi:10.1093/aje/kwv325.

Demirev, P. A. 2013. Dried blood spots: Analysis and applications. *Anal. Chem.* 85:779–89. doi:10.1021/ac303205m.

Denniff, P., and N. Spooner. 2014. Volumetric absorptive microsampling: A dried sample collection technique for quantitative bioanalysis. *Anal. Chem.* 86:8489–95. doi:10.1021/ac5022562.

Dennis, K. K., E. Marder, D. M. Balshaw, Y. Cui, M. A. Lynes, G. J. Patti, S. M. Rappaport, D. T. Shaughnessy, M. Vrijheid and D. B. Barr. 2017. Biomonitoring in the Era of the exposome. *Environ. Health Perspect.* 125:502–10. doi:10.1289/EHP474.

Do, M. T., V. C. Chang, M. A. Mendez, and M. de Groh. 2017. Urinary bisphenol A and obesity in adults: Results from the Canadian health measures survey. *Health Promot. Chronic Dis. Prev. Canada* 37:403–12. doi:10.24095/hpcdp.37.12.02.

Dopazo, J. 2014. Genomics and transcriptomics in drug discovery. *Drug Discov. Today* 19:126–32. doi:10.1016/j.drudis.2013.06.003.

European Commission. 2017. The human exposome project: A toolbox for assessing and addressing the impact of environment on health. *Eur. Comm.* Acessed on May 20 2019. http://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/sc1-bhc-28-2019.html.

Falony, G., M. Joossens, S. Vieira-Silva, J. Wang, Y. Darzi, K. Faust, A. Kurilshikov, M. J. Bonder, M. Valles-Colomer, D. Vandeputte, et al. 2016. Population-level analysis of gut microbiome variation. *Science* 352:560–64. doi:10.1126/science.aad3503.

Farmer, P. B. 2004. DNA and protein adducts as markers of genotoxicity. *Toxicol. Lett.* 149:3–9. doi:10.1016/j.toxlet.2003.12.015.

Fayyad, U., and P. Stolorz. 1997. Data mining and KDD: Promise and challenges. *Future Gener. Comput. Syst.* 13:99–115. doi:10.1016/s0167-739x(97)00015-0.

Fernandes, K. C. M., A. C. Martins, A. A. S. de Oliveira, L. M. G. Antunes, I. M. S. Cólus, F. Barbosa, and G. R. M. Barcelos. 2015. Polymorphism of metallothionein 2A modifies lead body burden in workers chronically exposed to the metal. *Public Health Genom.* 19:47–52. doi:10.1159/000441713.

Frank, D. N., and N. R. Pace. 2008. Gastrointestinal microbiology enters the metagenomics era. *Curr. Opin. Gastroenterol.* 24:4–10. doi:10.1097/mog.0b013e3282f2b0e8.

Freire, C., R. J. Koifman, D. Fujimoto, V. C. O. Souza, F. Barbosa, and S. Koifman. 2014. Reference values of lead in blood and related factors among blood donors in the Western Amazon, Brazil. *J. Toxicol. Environ. Health A* 77:426–40. doi:10.1080/15287394.2013.874303.

Freire, C., R. J. Koifman, D. Fujimoto, V. C. O. Souza, F. Barbosa, and S. Koifman. 2015. Reference values of cadmium, arsenic and manganese in blood and factors associated with exposure levels among adult population of Rio Branco, Acre, Brazil. *Chemosphere* 128:70–78. doi:10.1016/j.chemosphere.2014.12.083.

Geyer, P. E., M. H. Lesca, D. Teupser, and M. Mann. 2017. Revisiting biomarker discovery by plasma proteomics. *Mol. Syst. Biol.* 13:942. doi:10.15252/msb.20156297.

Go, Y.-M., D. I. Walker, Y. Liang, K. Uppal, Q. A. Soltow, V. Tran, F. Strobel, A. A. Quyyumi, T. R. Ziegler, K. D. Pennell, et al. 2015. Reference standardization for mass spectrometry and high-resolution metabolomics

applications to exposome research. *Toxicol. Sci.* 148:531–43. doi:10.1093/toxsci/kfv198.

Gomez, A., K. J. Petrzelkova, M. B. Burns, C. J. Yeoman, K. R. Amato, K. Vlckova, D. Modry, A. Todd, C. Jost Robinson, M. Remis, et al. 2016. Gut microbiome of coexisting baAka pygmies and bantu reflects gradients of traditional subsistence patterns. *Cell Rep.* 14:2142–53. doi:10.1016/j.celrep.2016.02.013.

Gouveia, N., R. Kuno, C. F. Asmus, P. R. G. Barrocas, V. R. R. Lemes, A. T. Tambellini, A. Meyer, V. D. M. Câmara, J. C. Moreira, A. G. D. Oliveira, et al. 2014. Projeto-piloto do primeiro inquérito nacional de populações expostas a substâncias químicas, 2008-2009. *Epidemiol. Serv. Saúde* 23:553–58. doi:10.5123/s1679-49742014000300019.

Grasso, G. 2017. Metals are main actors in the biological world. *Metals* 7:422. doi:10.3390/met7100422.

Hall, R. 2002. Plant metabolomics: The missing link in functional genomics strategies. *Plant Cell Online* 14:1437–40. doi:10.1105/tpc.140720.

Haraguchi, H. 2004. Metallomics as integrated biometal science. *J. Anal. Atom. Spectrom.* 19:5–14. doi:10.1039/b308213j.

Haraguchi, H. 2017. Metallomics: The history over the last decade and a future outlook. *Metallomics* 9:1001–13. doi:10.1039/c7mt00023e.

Harmon, M. E., J. Lewis, C. Miller, J. Hoover, A. M. S. Ali, C. Shuey, M. Cajero, S. Lucas, B. Pacheco, E. Erdei, et al. 2018. Arsenic association with circulating oxidized low-density lipoprotein in a native American community. *J. Toxicol. Environ. Health A* 81:535–48. doi:10.1080/15287394.2018.1443860.

Hebels, D. G. A. J., D. G. J. Jennen, M. H. M. Herwijnen, E. J. C. Moonen, M. Pedersen, L. E. Knudsen, J. C. S. Kleinjans, and T. M. C. M. de Kok. 2011. Whole-Genome gene expression modifications associated with nitrosamine exposure and micronucleus frequency in human blood cells. *Mutagenesis* 26:753–61. doi:10.1093/mutage/ger043.

Heinonen, M., H. Shen, N. Zamboni, and J. Rousu. 2012. Metabolite identification and molecular fingerprint prediction through machine learning. *Bioinformatics* 28:2333–41. doi:10.1093/bioinformatics/bts437.

Hinchliffe, E., J. Rudge, and P. Reed. 2016. A novel high-throughput method for supported liquid extraction of retinol and alpha-tocopherol from human serum and simultaneous quantitation by liquid chromatography tandem mass spectrometry. *Ann. Clin. Biochem.* 53:434–45. doi:10.1177/0004563215596024.

Hooper, L. V. 2001. Commensal host-bacterial relationships in the gut. *Science* 292:1115–18. doi:10.1126/science.1058709.

Hou, W., X. Meng, A. Zhao, W. Zhao, J. Pan, J. Tang, Y. Huang, H. Li, W. Jia, F. Liu, et al. 2017. Development of multimarker diagnostic models from metabolomics analysis for gestational diabetes mellitus. *Mol. Cell. Proteom.* 17:431–44. doi:10.1074/mcp.ra117.000121.

Howard, P. H., and D. C. G. Muir. 2011. Identifying new persistent and bioaccumulative organics among chemicals in commerce II: Pharmaceuticals. *Environ. Sci. Technol.* 45:6938–46. doi:10.1021/es201196x.

Humphery-Smith, I. 2015. The 20th anniversary of proteomics and some of its origins. *Proteomics* 15:1773–76. doi:10.1002/pmic.201400582.

Hyun Kim, D., S. M. Choi, D. S. Lim, T. Roh, S. J. Kwack, S. Yoon, M. K. Kim, K. S. Yoon, H. S. Kim, D. W. Kim, et al. 2018. Risk assessment of endocrine disrupting phthalates and hormonal alterations in children and adolescents. *J. Toxicol. Environ. Health A* 81:1150–64. doi:10.1080/15287394.2018.1543231.

Ito, H., M. P. Gonthier, C. Manach, C. Morand, L. Mennen, C. Rémésy, and A. Scalbert. 2005. Polyphenol levels in human urine after intake of six different polyphenol-rich beverages. *Br. J. Nutr.* 94:500–09. doi:10.1079/bjn20051458.

Jaacks, L. M., D. B. Barr, R. Sundaram, J. M. Maisog, C. Zhang, and G. M. Buck Louis. 2016. Pre-pregnancy maternal exposure to polybrominated and polychlorinated biphenyls and gestational diabetes: A prospective cohort study. *Environ. Heath* 15:1–11. doi:10.1186/s12940-016-0092-5.

Jansen, A., J. L. Lyche, A. Polder, J. Aaseth, and M. A. Skaug. 2017. Increased blood levels of persistent organic pollutants (POP) in obese individuals after weight loss—A Review. *J. Toxicol. Environ. Health B* 20:22–37. doi:10.1080/10937404.2016.1246391.

Jardine, J., J. Fisher, and B. Carrick. 2015. Apple's research kit: Smart data collection for the smartphone Era? *J. Roy. Soc. Med.* 108:294–96. doi:10.1177/0141076815600673.

Jeong, E. S., G. Kim, D. Yim, K. S. Moon, S. J. Lee, J. G. Shin, and D. H. Kim. 2018. Identification and characterization of amiodarone metabolites in rats using UPLC–ESI-QTOFMS-Based untargeted metabolomics approach. *J. Toxicol. Environ. Health A* 81:481–92. doi:10.1080/15287394.2018.1460783.

Jia, Z., A. Patra, V. K. Kutty, and T. Venkatesan. 2019. Critical review of volatile organic compound analysis in breath and in vitro cell culture for detection of lung cancer. *Metabolites* 9:52–69. doi:10.3390/metabo9030052.

Joas, R., L. Casteleyn, P. Biot, M. Kolossa-Gehring, A. Castano, J. Angerer, G. Schoeters, O. Sepai, L. E. Knudsen, A. Joas, et al. 2012. Harmonised human biomonitoring in Europe: Activities towards an EU HBM framework. *Int. J. Hyg. Environ. Health* 215:172–75. doi:10.1016/j.ijheh.2011.08.010.

Johnson, C. H., T. J. Athersuch, G. W. Collman, S. Dhungana, D. F. Grant, D. P. Jones, C. J. Patel, and V. Vasiliou. 2017. Yale school of public health symposium on lifetime exposures and human health: The exposome: Summary and future reflections. *Human. Genom.* 11:32–40. doi:10.1186/s40246-017-0128-0.

Jones, D. P. 2016. Sequencing the exposome: A call to action. *Toxicol. Rep*. 3:29–45. doi:10.1016/j.toxrep.2015.11.009.

Kamburov, A., R. Cavill, T. M. D. Ebbels, R. Herwig, and H. C. Keun. 2011. Integrated pathway-level analysis of transcriptomics and metabolomics data with IMPaLA. *Bioinformatics* 27:2917–18. doi:10.1093/bioinformatics/btr499.

Karppi, J., T. Nurmi, B. Olmedilla-Alonso, F. Granado-Lorencio, and K. Nyyssönen. 2008. Simultaneous measurement of retinol, α-tocopherol and six carotenoids in human plasma by using an isocratic reversed-phase HPLC method. *J. Chromatogr. B* 867:226–32. doi:10.1016/j.jchromb.2008.04.007.

Karube, Z.-I., A. Tanaka, A. Takeuchi, Y. Takazawa, M. Takagi, A. Kinoshita, H. Seyama, and Y. Shibata. 2014. Three decades of environmental specimen banking at the national institute for environmental studies, Japan. *Environ. Sci. Pollut. Res.* 22:1587–96. doi:10.1007/s11356-014-3039-9.

Kennedy, S. 2002. The role of proteomics in toxicology: Identification of biomarkers of toxicity by protein expression analysis. *Biomarkers* 7:269–90. doi:10.1080/13547500210127318.

Kenny, L. C., W. B. Dunn, D. I. Ellis, J. Myers, P. N. Baker, and D. B. Kell. 2005. Novel biomarkers for pre-eclampsia detected using metabolomics and machine learning. *Metabolomics* 1:227–34. doi:10.1007/s11306-005-0003-1.

Kim, K. H., S. A. Jahan, and E. Kabir. 2012. A review of breath analysis for diagnosis of human health. *Trends Anal. Chem.* 33:1–8. doi:10.1016/j.trac.2011.09.013.

Kim, U. J., and K. Kannan. 2018. Occurrence and distribution of organophosphate flame retardants/plasticizers in surface waters, tap water, and rainwater: Implications for human exposure. *Environ. Sci. Technol.* 52:5625–33. doi:10.1021/acs.est.8b00727.

Kind, T., M. Scholz, and O. Fiehn. 2009. How large is the metabolome? A critical analysis of aata exchange practices in chemistry. *PLoS ONE* 4:e5440. doi:10.1371/journal.pone.0005440.

Klaene, J. J., V. K. Sharma, J. Glick, and P. Vouros. 2013. The analysis of DNA adducts: The transition from 32P-postlabeling to mass spectrometry. *Cancer Lett.* 334:10–19. doi:10.1016/j.canlet.2012.08.007.

Ko, A., M.-S. Hwang, J.-H. Park, H.-S. Kang, H.-S. Lee, and J.-H. Hong. 2014. Association between urinary bisphenol A and waist circumference in Korean adults. *Toxicol. Res.* 30:39–44. doi:10.5487/tr.2014.30.1.039.

Kolocouri, F., Y. Dotsikas, and Y. L. Loukas. 2010. Dried plasma spots as an alternative sample collection technique for the quantitative LC-MS/MS determination of gabapentin. *Anal. Bioanal. Chem.* 398:1339–47. doi:10.1007/s00216-010-4048-2.

LaKind, J. S., L. G. Anthony, and M. Goodman. 2017. Review of reviews on exposures to synthetic organic chemicals and children's neurodevelopment: Methodological and interpretation challenges. *J. Toxicol. Environ. Health B* 20:390–422. doi:10.1080/10937404.2017.1370847.

Lawal, O., W. M. Ahmed, T. M. E. Nijsen, R. Goodacre, and S. J. Fowler. 2017. Exhaled breath analysis: A review of "breath-taking" methods for off-Line analysis. *Metabollomics* 13:110–26. doi:10.1007/s11306-017-1241-8.

Lee, C.-L., -H.-H. Hsiao, C.-W. Lin, S.-P. Wu, S.-Y. Huang, C.-Y. Wu, A. H.-J. Wang, and K.-H. Khoo. 2003. Strategic shotgun proteomics approach for efficient construction of an expression map of targeted protein families in hepatoma cell lines. *Proteomics* 3:2472–86. doi:10.1002/pmic.200300586.

Levy, L. S., K. Jones, J. Cocker, F. L. Assem, and A. C. Capleton. 2007. Background levels of key biomarkers of chemical exposure within the UK general population – Pilot study. *Int. J. Hyg. Environ. Health* 210:387–91. doi:10.1016/j.ijheh.2007.01.032.

Lewis, R. M., H. Demmelmair, R. Gaillard, K. M. Godfrey, S. Hauguel-de Mouzon, B. Huppertz, E. Larque, R. Saffery, M. E. Symonds, and G. Desoye. 2013. The placental exposome: Placental determinants of fetal adiposity and postnatal body composition. *Ann. Nutr. Metab.* 63:208–15. doi:10.1159/000355222.

Li, W., and F. L. Tse. 2010. Dried blood spot sampling in combination with LC-MS/MS for quantitative analysis of small molecules. *Biomed. Chromatogr.* 24:49–65. doi:10.1002/bmc.1367.

Li, X., S.-K. Ng, and J. T. L. Wang. 2013. *Biological data mining and its applications in healthcare. World scientific*. First Edition. T. Jason, and L. Wang. Series Editor, Vol. 8 doi:10.1142/8898.

Liebler, D. C. 2002. Proteomics and the new biology. *Introduction to proteomics. Chapter* 1:3–13. doi:10.1007/978-1-59259-130-5_1.

Lioy, P. J., and S. M. Rappaport. 2011. Exposure science and the exposome: An opportunity for coherence in the environmental health sciences. *Environ. Health Perspect.* 119:a466–a467. doi:10.1289/ehp.1104387.

Loh, M., D. Sarigiannis, A. Gotti, S. Karakitsios, A. Pronk, E. Kuijpers, I. Annesi-Maesano, N. Baiz, J. Madureira, E. Oliveira Fernandes, et al. 2017. How sensors might help define the external exposome. *Int. J. Environ. Res. Public Health* 14:434–48. doi:10.3390/ijerph14040434.

Maione, C. 2016. Mineração de dados para o reconhecimento da origem e do tipo de alimentos e outras substâncias com base em sua composição química. PhD Thesis, Universidade Federal de Goiás.

Marie, I., J.-F. Gehanno, M. Bubenheim, A.-B. Duval-Modeste, P. Joly, S. Dominique, P. Bravard, D. Noël, A.-F. Cailleux, J. Benichou, et al. 2017. Systemic sclerosis and exposure to heavy metals: A case control study of 100 patients and 300 controls. *Autoimmun. Rev.* 16:223–30. doi:10.1016/j.autrev.2017.01.004.

Martins, A. C., M. F. H. Carneiro, D. Grotto, J. A. Adeyemi, and F. Barbosa. 2018. Arsenic, cadmium, and mercury-induced hypertension: Mechanisms and epidemiological findings. *J. Toxicol. Environ. Health B* 21:61–82. doi:10.1080/10937404.2018.1432025.

Matsuda, T., H. Tao, M. Goto, H. Yamada, M. Suzuki, Y. Wu, N. Xiao, Q. He, W. Guo, Z. Cai, et al. 2013. Lipid peroxidation-induced DNA adducts in human gastric mucosa. *Carcinogenesis* 34:121–27. doi:10.1093/carcin/bgs327.

McHale, C. M., L. Zhang, R. Thomas, and M. T. Smith. 2013. Analysis of the transcriptome in molecular epidemiology studies. *Environ. Mol. Mutagen.* 54:500–17. doi:10.1002/em.21798.

Merlo, E., I. V. Silva, R. C. Cardoso, and J. B. Graceli. 2018. The obesogen tributyltin induces features of polycystic ovary syndrome (PCOS): A Review. *J. Toxicol. Environ. Health B* 21:181–206. doi:10.1080/10937404.2018.1496214.

Miller, G. W., and D. P. Jones. 2013. The nature of nurture: Refining the definition of the exposome. *Toxicol. Sci.* 137:1–2. doi:10.1093/toxsci/kft251.

Minot, S., R. Sinha, J. Chen, H. Li, S. A. Keilbaugh, G. D. Wu, J. D. Lewis, and F. D. Bushman. 2011. The human gut virome: Inter-individual variation and dynamic response to diet. *Genome Res.* 21:1616–25. doi:10.1101/gr.122705.111.

Monnin, C., P. Ramrup, C. Daigle-Young, and D. Vuckovic. 2018. Improving negative liquid chromatography/electrospray ionization mass spectrometry lipidomic analysis of human plasma using acetic acid as a mobile-phase additive. *Rapid Commun. Mass Spectrom.* 32:201–11. doi:10.1002/rcm.8024.

Morishita, H., and M. Arora. 2017. Tooth-matrix biomarkers to reconstruct critical periods of brain plasticity. *Trends Neurosci.* 40:1–3. doi:10.1016/j.tins.2016.11.003.

Needham, L. L., A. M. Calafat, and D. B. Barr. 2007. Uses and issues of biomonitoring. *Int. J. Hyg. Environ. Health* 210:229–38. doi:10.1016/j.ijheh.2006.11.002.

Newton, S. R., R. L. McMahen, J. R. Sobus, K. Mansouri, A. J. Williams, A. D. McEachran, and M. J. Strynar. 2018. Suspect screening and non-targeted analysis of drinking water using point-of-use filters. *Environ. Pollut.* 234:297–306. doi:10.1016/j.envpol.2017.11.033.

Nordfalk, F., and C. T. Ekstrøm. 2019. Newborn dried blood spot samples in denmark: The hidden figures of secondary use and research participation. *Eur. J. Human Genet.* 27:203–10. doi:10.1038/s41431-018-0276-2.

Nunes, J. A., B. L. Batista, J. L. Rodrigues, N. M. Caldas, J. A. G. Neto, and F. Barbosa. 2010. A simple method based on ICP-MS for estimation of background levels of arsenic, cadmium, copper, manganese, nickel, lead, and selenium in blood of the Brazilian population. *J. Toxicol. Environ. Health A* 73:878–87. doi:10.1080/15287391003744807.

Nys, G., M. G. M. Kok, A. C. Servais, and M. Fillet. 2017. Beyond dried blood spot: Current microsampling techniques in the context of biomedical applications. *Trends Anal. Chem.* 97:326–32. doi:10.1016/j.trac.2017.10.002.

Obregon-Tito, A. J., R. Y. Tito, J. Metcalf, K. Sankaranarayanan, J. C. Clemente, L. K. Ursell, Z. Z. Xu, W. Van Treuren, R. Knight, P. M. Gaffney, et al. 2015. Subsistence strategies in traditional societies distinguish gut microbiomes. *Nat. Commun.* 6:1–9. doi:10.1038/ncomms7505.

Ogra, Y., and T. Hirata. 2017. Metallomics: Recent analytical techniques and applications. *Met. Recent Anal. Tech. Appl.* Springer Japan. First Edition. doi:10.1007/978-4-431-56463-8.

Ouyang, X., Y. Dai, J. L. Wen, and L. X. Wang. 2011. 1H NMR-based metabolomic study of metabolic profiling for systemic lupus erythematosus. *Lupus* 20:1411–20. doi:10.1177/0961203311418707.

Parsons, P. J., and F. Barbosa. 2007. Atomic spectrometry and trends in clinical laboratory medicine. *Spectrochim. Acta B* 62:992–1003. doi:10.1016/J.SAB.2007.03.007.

Patel, C. J. 2017. Analytic complexity and challenges in identifying mixtures of exposures associated with phenotypes in the exposome Era. *Curr. Epidemiol. Rep.* 4:22–30. doi:10.1007/s40471-017-0100-5.

Patel, C. J., J. Bhattacharya, and A. J. Butte. 2010. An environment-wide association study (EWAS) on type 2 diabetes mellitus. *PLoS ONE* 5:e10746. doi:10.1371/journal.pone.0010746.

Pathak, K. V., T. L. Chiu, E. A. Amin, and R. J. Turesky. 2016. Methemoglobin formation and characterization of hemoglobin adducts of carcinogenic aromatic amines and heterocyclic aromatic amines. *Chem. Res. Toxicol.* 29:255–69. doi:10.1021/acs.chemrestox.5b00418.

Pereira, J., P. Porto-Figueira, C. Cavaco, K. Taunk, S. Rapole, R. Dhakne, H. Nagarajaram, and J. Câmara. 2015. Breath analysis as a potential and non-invasive frontier in disease diagnosis: An overview. *Metabolites* 5:3–55. doi:10.3390/metabo5010003.

Phillips, K. A., A. Yau, K. A. Favela, K. K. Isaacs, A. McEachran, C. Grulke, A. M. Richard, A. J. Williams, J. R. Sobus, R. S. Thomas, et al. 2018. Suspect screening analysis of chemicals in consumer products. *Environ. Sci. Technol.* 52:3125–35. doi:10.1021/acs.est.7b04781.

Phinney, K. W., G. Ballihaut, M. Bedner, B. S. Benford, J. E. Camara, S. J. Christopher, W. C. Davis, N. G. Dodder, G. Eppe, B. E. Lang, et al. 2013. Development of a standard reference material for metabolomics research. *Anal. Chem.* 85:11732–38. doi:10.1021/ac402689t.

Pino, A., F. Chiarotti, G. Calamandrei, A. Gotti, S. Karakitsios, E. Handakas, B. Bocca, D. Sarigiannis, and A. Alimonti. 2017. Human biomonitoring data analysis for metals in an italian adolescents cohort: An exposome approach. *Environ. Res.* 159:344–54. doi:10.1016/j.envres.2017.08.012.

Pizzino, G., A. Bitto, M. Interdonato, F. Galfo, N. Irrera, A. Mecchio, G. Pallio, V. Ramistella, F. D. Luca, L. Minutoli, et al. 2014. Oxidative stress and DNA repair and detoxification gene expression in adolescents exposed to heavy metals living in the Milazzo-Valle Del Mela area (Sicily, Italy). *Redox. Biol.* 2:686–93. doi:10.1016/j.redox.2014.05.003.

Pleil, J. D. 2016. Breath biomarkers in toxicology. *Arch. Toxicol.* 90:2669–82. doi:10.1007/s00204-016-1817-5.

Pleil, J. D., and J. R. Sobus. 2016. Estimating central tendency from a single spot measure: A closed-form solution for lognormally distributed biomarker data for risk assessment at the individual level. *J. Toxicol. Environ. Health A* 79:837–47. doi:10.1080/15287394.2016.1193108.

Pleil, J. D., M. A. G. Wallace, M. A. Stiegel, and W. E. Funk. 2018. Human biomarker interpretation: The importance of intra-class correlation coefficients (ICC) and their calculations based on mixed models, ANOVA, and variance estimates. *J. Toxicol. Environ. Health B* 21:161–80. doi:10.1080/10937404.2018.1490128.

Potera, C. 2014. The HELIX project: Tracking the exposome in real time. *Environ. Health Perspect.* 122:A169. doi:10.1289/ehp.122-a169.

Preston, G. W., and D. H. Phillips. 2019. Protein adductomics: Analytical developments and applications in human biomonitoring. *Toxics* 7:29–46. doi:10.3390/toxics7020029.

Preston, G. W., M. Plusquin, O. Sozeri, K. Van Veldhoven, L. Bastian, T. S. Nawrot, M. Chadeau-Hyam, and D. H. Phillips. 2017. Refinement of a methodology for untargeted detection of serum albumin adducts in human populations. *Chem. Res. Toxicol.* 30:2120–29. doi:10.1021/acs.chemrestox.7b00186.

Pubmed. 2019. Acessed on February, 2019. www.pubmed.com.

Quifer-Rada, P., G. Chiva-Blanch, O. Jáuregui, R. Estruch, and R. M. Lamuela-Raventós. 2017. A discovery-driven approach to elucidate urinary metabolome changes after a regular and moderate consumption of beer and nonalcoholic beer in subjects at high cardiovascular risk. *Mol. Nutr. Food Res.* 61:1–11. doi:10.1002/mnfr.201600980.

Rappaport, S. M. 2010. Implications of the exposome for exposure science. *J. Expo. Sci. Environ. Epidemiol.* 21:5–9. doi:10.1038/jes.2010.50.

Rappaport, S. M., D. K. Barupal, D. Wishart, P. Vineis, and A. Scalbert. 2014. The blood exposome and its role in discovering causes of disease. *Environ. Health Perspect.* 122:769–74. doi:10.1289/ehp.1308015.

Rappaport, S. M., H. Li, H. Grigoryan, W. E. Funk, and E. R. Williams. 2012. Adductomics: Characterizing exposures to reactive electrophiles. *Toxicol. Lett.* 213:83–90. doi:10.1016/j.toxlet.2011.04.002.

Richardson, J. B., B. C. R. Dancy, C. L. Horton, Y. S. Lee, M. S. Madejczyk, Z. Z. Xu, G. Ackermann, G. Humphrey, G. Palacios, R. Knight, et al. 2018. Exposure to toxic metals triggers unique responses from the rat gut microbiota. *Sci. Rep.* 8:6578–90. doi:10.1038/s41598-018-24931-w.

Rimbaud, D., M. Restrepo, A. Louison, R. Boukhari, V. Ardillon, G. Carles, V. Lambert, and A. Jolivet. 2017. Blood lead levels and risk factors for lead exposure among pregnant women in western French Guiana: The role of manioc consumption. *J. Toxicol. Environ. Health A* 80:382–93. doi:10.1080/15287394.2017.1331490.

Robert, H., D. Payros, P. Pinton, V. Théodorou, M. Mercier-Bonin, and I. P. Oswald. 2017. Impact of mycotoxins on the intestine: Are mucus and microbiota new targets? *J. Toxicol. Environ. Health B* 20:249–75. doi:10.1080/10937404.2017.1326071.

Robertson, M. 2017. HERCULES exposome research center receives $7.5 million grant renewal from NIH | Emory University | Atlanta, GA. Acessed on June 26, 2019. http://news.emory.edu/stories/2017/05/HERCULES_grant_renewal_NIH/.

Robinson, O., and M. Vrijheid. 2015. The pregnancy exposome. *Curr. Environ. Health Rep.* 2:204–13. doi:10.1007/s40572-015-0043-2.

Rocha, B. A., A. G. Asimakopoulos, F. Barbosa, and K. Kannan. 2017. Urinary concentrations of 25 phthalate metabolites in brazilian children and their association with oxidative DNA damage. *Sci. Total Environ.* 586:152–62. doi:10.1016/j.scitotenv.2017.01.193.

Rocha, B. A., B. R. B. Da Costa, N. C. P. de Albuquerque, A., . R. M. de Oliveira, J. M. O. Souza, M. Al-Tameemi, A. D. Campiglia, and F. Barbosa Jr. 2016. A fast method for bisphenol A and six analogues (S, F, Z, P, AF, AP) determination in urine samples based on dispersive liquid-liquid microextraction and liquid chromatography-tandem mass spectrometry. *Talanta* 154:511–19. doi:10.1016/j.talanta.2016.03.098.

Rocha, C. M., J. Carrola, A. S. Barros, A., . M. Gil, B. J. Goodfellow, I. M. Carreira, J. Bernardo, A. Gomes, V. Sousa, L. Carvalho, et al. 2011. Metabolic signatures of lung cancer in biofluids: NMR-based metabonomics of blood plasma. *J. Proteome Res.* 10:4314–24. doi:10.1021/pr200550p.

Rodrigues, J. L., B. L. Batista, J. A. Nunes, C. J. S. Passos, and F. Barbosa. 2008. Evaluation of the use of human hair for biomonitoring the deficiency of essential and exposure to toxic elements. *Sci. Total Environ.* 405:370–76. doi:10.1016/j.scitotenv.2008.06.002.

Rodrigues, J. L., B. L. Batista, M. Fillion, C. J. S. Passos, D. Mergler, and F. Barbosa. 2009. Trace element levels in whole blood of riparian villagers of the Brazilian Amazon. *Sci. Total Environ.* 407:4168–73. doi:10.1016/j.scitotenv.2009.02.041.

Rogler, G., and S. Vavricka. 2015. Exposome in IBD. *Inflamm. Bowel Dis.* 21:400–08. doi:10.1097/mib.0000000000000229.

Roh, J. Y., J. Lee, and J. Choi. 2006. Assessment of stress-related gene expression in the heavy metal-exposed nematode caenorhabditis elegans: A potential biomarker for metal-induced toxicity monitoring and environmental risk assessment. *Environ. Toxicol. Chem.* 25:2946–56. doi:10.1897/05-676R.1.

Roig, B., M. Rodríguez-Balada, S. Samino, E. W.-F. Lam, S. Guaita-Esteruelas, A. R. Gomes, X. Correig, J. Borràs, O. Yanes, and J. Gumà. 2017. Metabolomics reveals novel blood plasma biomarkers associated to the BRCA1-mutated phenotype of human breast cancer. *Sci. Rep.* 7:17831–50. doi:10.1038/s41598-017-17897-8.

Roverso, M., C. Berté, V. Di Marco, A. Lapolla, D. Badocco, P. Pastore, S. Visentin, and E. Cosmi. 2015. The metallome of the human placenta in gestational diabetes mellitus. *Metallomics* 7:1146–54. doi:10.1039/c5mt00050e.

Sakumura, Y., Y. Koyama, H. Tokutake, T. Hida, K. Sato, T. Itoh, T. Akamatsu, and W. Shim. 2017. Diagnosis by volatile organic compounds in exhaled breath from lung cancer patients using support vector machine algorithm. *Sensors* 17:287–99. doi:10.3390/s17020287.

Sauer, J. M., T. Hartung, M. Leist, T. B. Knudsen, J. Hoeng, and A. W. Hayes. 2015. Systems toxicology. *Int. J. Toxicol.* 34:346–48. doi:10.1177/1091581815576551.

Schadt, E. E., S. H. Friend, and D. A. Shaywitz. 2009. A network view of disease and compound screening. *Nat. Rev. Drug Discov.* 8:286–95. doi:10.1038/nrd2826.

Schnorr, S. L., M. Candela, S. Rampelli, S. Turroni, A. G. Henry, and A. N. Crittenden. 2018. Comment on "seasonal cycling in the gut microbiome of the Hadza Hunter-Gatherers of Tanzania". *BioRix.* 1:1–23. doi:10.1101/284513.

Serrazina, D. C., V. L. De Andrade, M. Cota, M. L. Mateus, M. Aschner, and A. P. M. Dos Santos. 2018. Biomarkers of exposure and effect in a working population exposed to lead, manganese and arsenic. *J. Toxicol. Environ. Health A* 81:983–97. doi:10.1080/15287394.2018.1509408.

Shaffer, R. M., M. N. Smith, and E. M. Faustman. 2017. Developing the regulatory utility of the exposome: Mapping exposures for risk assessment through lifestage exposome snapshots (LEnS). *Environ. Health Perspect.* 125:085003–01. doi:10.1289/EHP1250.

Shapiro, G. D., L. Dodds, T. E. Arbuckle, J. Ashley-Martin, A. S. Ettinger, M. Fisher, S. Taback, S. Taback, M. F. Bouchard, P. Monnier, et al. 2016. Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC study. *Environ. Res.* 147:71–81. doi:10.1016/j.envres.2016.01.040.

Shapiro, G. D., L. Dodds, T. E. Arbuckle, J. Ashley-Martin, W. Fraser, M. Fisher, S. Taback, E. Keely, M. F. Bouchard, P. Monnier, et al. 2015. Exposure to phthalates, bisphenol A and metals in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: The MIREC Study. *Environ. Int.* 83:63–71. doi:10.1016/j.envint.2015.05.016.

Shaw, S. D. 2017. Human responses to complex environmental exposures: Linking causes and effects. *Rev. Environ. Health* 32:301–02. doi:10.1515/reveh-2017-0043.

Shepherd, T. J., W. Dirks, C. Manmee, S. Hodgson, D. A. Banks, P. Averley, and T. Pless-Mulloli. 2012. Reconstructing the life-time lead exposure in children using dentine in deciduous teeth. *Sci. Total Environ.* 425:214–22. doi:10.1016/j.scitotenv.2012.03.022.

Shi, W., and M. R. Chance. 2008. Metallomics and metalloproteomics. *Cell. Mol. Life Sci.* 65:3040–48. doi:10.1007/s00018-008-8189-9.

Shim, Y. K., M. D. Lewin, P. Ruiz, J. E. Eichner, and M. M. Mumtaz. 2017. Prevalence and associated demographic characteristics of exposure to multiple metals and their species in human populations: The United States NHANES, 2007–2012. *J. Toxicol. Environ. Health A* 80:502–12. doi:10.1080/15287394.2017.1330581.

Shiue, I., and K. Hristova. 2014. Higher urinary heavy metal, phthalate and arsenic concentrations accounted for 3–19% of the population attributable risk for high blood pressure: US NHANES, 2009–2012. *Hypertens. Res.* 37:1075–81. doi:10.1038/hr.2014.121.

Simón-Manso, Y., M. S. Lowenthal, L. E. Kilpatrick, M. L. Sampson, K. H. Telu, P. A. Rudnick, W. G. Mallard, D. W. Bearden, T. B. Schock, and D. Tchekhovskoi, et al. 2013. Metabolite profiling of a nist standard reference material for human plasma (srm 1950): GC-MS, LC-MS, NMR and clinical laboratory analyses, libraries, and web-based resources. *Anal. Chem.* 85:11725–31. doi: 10.1021/ac402503m.

Siroux, V., L. Agier, and R. Slama. 2016. The exposome concept: A challenge and a potential driver for environmental health research. *Eur. Respir. Rev.* 25:124–29. doi:10.1183/16000617.0034-2016.

Siskos, A. P., P. Jain, W. Römisch-Margl, M. Bennett, D. Achaintre, Y. Asad, L. Marney, L. Richardson, A. Koulman, J. L. Griffin, et al. 2017. Interlaboratory reproducibility of a targeted metabolomics platform for analysis of human serum and plasma. *Anal. Chem.* 89:656–65. doi:10.1021/acs.analchem.6b02930.

Slezakova, K., M. Oliveira, J. Madureira, E. O. Fernandes, C. Delerue-Matos, S. Morais, and M. C. Pereira. 2017. Polycyclic aromatic hydrocarbons (PAH) in Portuguese educational settings: A comparison between preschools and elementary schools. *J. Toxicol. Environ. Health A* 80:630–40. doi:10.1080/15287394.2017.1286931.

Steckling, N., A. Gotti, S. Bose-O'Reilly, D. Chapizanis, D. Costopoulou, F. De Vocht, M. Garí, J. O. Grimalt, E. Heath, R. Hiscock, et al. 2018. Biomarkers of exposure in environment-wide association studies – Opportunities to decode the exposome using human biomonitoring data. *Environ. Res.* 164:597–624. doi:10.1016/j.envres.2018.02.041.

Stiegel, M. A., J. D. Pleil, J. R. Sobus, T. Stevens, and M. C. Madden. 2017. Linking physiological parameters to perturbations in the human exposome: Environmental exposures modify blood pressure and lung function via inflammatory cytokine pathway. *J. Toxicol. Environ. Health A* 80:485–501. doi:10.1080/15287394.2017.1330578.

Stricker, S. H., A. Köferle, and S. Beck. 2017. From profiles to function in epigenomics. *Nat. Rev. Genet.* 18:51–66. doi:10.1038/nrg.2016.138.

Sturla, S. J., A. R. Boobis, R. E. FitzGerald, J. Hoeng, R. J. Kavlock, K. Schirmer, M. Whelan, M. F. Wilks, and M. C. Peitsch. 2014. Systems toxicology: From basic research to risk assessment. *Chem. Res. Toxicol.* 27:314–29. doi:10.1021/tx400410s.

Sughis, M., T. S. Nawrot, V. Haufroid, and B. Nemery. 2012. Adverse health effects of child labor: High exposure to chromium and oxidative DNA damage in children manufacturing surgical instruments. *Environ. Health Perspect.* 120:1469–74. doi:10.1289/ehp.1104678.

Sun, L.-M., B.-J. Zhu, H.-T. Cao, X.-Y. Zhang, Q.-C. Zhang, G.-Z. Xin, L.-M. Pan, L.-F. Liu, and H.-X. Zhu. 2018. Explore the effects of Huang-Lian-Jie-Du-Tang on Alzheimer's disease by UPLC-QTOF/MS-based plasma metabolomics study. *J. Pharm. Biomed. Anal.* 151:75–83. doi:10.1016/j.jpba.2017.12.053.

Sussulini, A. 2017. Metabolomics: From fundamentals to clinical applications. *Adv. Exp. Med. Biol.* 965. Springer International Publishing. First Edition. doi:10.1007/978-3-319-47656-8.

Swan, A. L., A. Mobasheri, D. Allaway, S. Liddell, and J. Bacardit. 2013. Application of machine learning to proteomics data: Classification and biomarker identification in postgenomics biology. *J. Integr. Biol.* 17:595–610. doi:10.1089/omi.2013.0017.

Szpunar, J. 2004. Metallomics: A new frontier in analytical chemistry. *Anal. Bioanal. Chem.* 378:54–56. doi:10.1007/s00216-003-2333-z.

Takeda, S. H. K., R. Kuno, F. Barbosa, and N. Gouveia. 2017. Trace element levels in blood and associated factors in adults living in the metropolitan area of São Paulo, Brazil. *J. Trace Elem. Med. Biol.* 44:307–14. doi:10.1016/j.jtemb.2017.09.005.

Tan, P.-N., M. Steinbach, and V. Kumar. 2005. *Introduction to data mining*, *First* ed. (ISBN:0321321367) Boston, MA, USA: Addison-Wesley Longman Publishing Co., Inc.

Tang, R., H. Yang, J. R. Choi, Y. Gong, M. L. You, T. Wen, A. Li, X. Li, B. Xu, S. Zhang, et al. 2017. Capillary blood for point-of-care testing. *Crit. Rev. Clin. Lab. Sci.* 54:294–308. doi:10.1080/10408363.2017.1343796.

Tinkov, A. A., V. A. Gritsenko, M. G. Skalnaya, S. V. Cherkasov, J. Aaseth, and A. V. Skalny. 2018. Gut as a target for cadmium toxicity. *Environ. Pollut.* 235:429–34. doi:10.1016/j.envpol.2017.12.114.

Tohon, H., A. Nong, M. Moreau, M. Valcke, and S. Haddad. 2018. Reverse dosimetry modeling of toluene exposure concentrations based on biomonitoring levels from the Canadian health measures survey. *J. Toxicol. Environ. Health A* 81:1066–82. doi:10.1080/15287394.2018.1534174.

Ursell, L. K., J. L. Metcalf, L. W. Parfrey, and R. Knight. 2012. Defining the human microbiome. *Nutr. Rev.* 70:S38–S44. doi:10.1111/j.1753-4887.2012.00493.x.

Valdiglesias, V., M. Sánchez-Flores, A. Maseda, L. Lorenzo-López, D. Marcos-Pérez, A. López-Cortón, B. Strasser, D. Fuchs, B. Laffon, J. C. Millán-Calenti, et al. 2017. Immune biomarkers in older adults: Role of physical activity. *J. Toxicol. Environ. Health A* 80:605–20. doi:10.1080/15287394.2017.1286898.

Van Breda, S. G. J., L. C. Wilms, S. Gaj, D. G. J. Jennen, J. J. Briedé, J. C. S. Kleinjans, and T. M. C. M. de Kok. 2015. The exposome concept in a human nutrigenomics study: Evaluating the impact of exposure to a complex mixture of phytochemicals using transcriptomics signatures. *Mutagenesis* 30:723–31. doi:10.1093/mutage/gev008.

Van Ommen, B., T. V. D. Broek, I. Hoogh, M. Van Erk, E. Van Someren, T. Rouhani-Rankouhi, J. C. Anthony, K. Hogenelst, W. Pasman, A. Boorsma, et al. 2017. Systems biology of personalized nutrition. *Nutr. Rev.* 75:579–99. doi:10.1093/nutrit/nux029.

Vineis, P. 2015. Exposomics: Mathematics meets biology. *Mutagenesis* 30:719–22. doi:10.1093/mutage/gev068.

Vrijheid, M. 2014. The exposome: A new paradigm to study the impact of environment on health. *Thorax* 69:876–78. doi:10.1136/thoraxjnl-2013-204949.

Vrijheid, M., R. Slama, O. Robinson, L. Chatzi, M. Coen, P. Van Den Hazel, C. Thomsen, J. Wright, T. J. Athersuch, N. Avellana, et al. 2014. The human early-life exposome (HELIX): Project rationale and design. *Environ. Health Perspect.* 122:535–44. doi:10.1289/ehp.1307204.

Wahlberg, K., M. Arora, A. Curtin, P. Curtin, R. O. Wright, D. R. Smith, R. G. Lucchini, K. Broberg, and C. Austin. 2017. Polymorphisms in manganese transporters show developmental stage and sex specific associations with manganese concentrations in primary teeth. *Neurotoxicology* 64:103–09. doi:10.1016/j.neuro.2017.09.003.

Wallace, M. A. G., and J. D. Pleil. 2018. Evolution of clinical and environmental health applications of exhaled breath research: Review of methods and instrumentation for gas-phase, condensate, and aerosols. *Anal. Chim. Acta* 1024:18–38. doi:10.1016/j.aca.2018.01.069.

Wallace, M. A. G., J. D. Pleil, K. D. Oliver, D. A. Whitaker, S. Mentese, K. W. Fent, and G. P. Horn. 2019. Non-targeted GC/MS analysis of exhaled breath samples: Exploring human biomarkers of exogenous exposure and endogenous response from professional firefighting activity. *J. Toxicol. Environ. Health Part A* 82:244–60. doi:10.1080/15287394.2019.1587901.

Wallace, M. A. G., T. M. Kormos, and J. D. Pleil. 2016. Blood-borne biomarkers and bioindicators for linking exposure to health effects in environmental health science. *J. Toxicol. Environ. Health B* 19:380–409. doi:10.1080/10937404.2016.1215772.

Wang, S., S. Chanock, D. Tang, Z. Li, S. Edwards, W. Jedrychowski, and F. P. Perera. 2010. Effect of gene-environment interactions on mental development in African, American, Dominican, and Caucasian mothers and newborns. *Ann. Human Genet.* 74:46–56. doi:10.1111/j.1469-1809.2009.00550.x.

Wasinger, V. C., S. J. Cordwell, A. Cerpa-Poljak, J. X. Yan, A. A. Gooley, M. R. Wilkins, M. W. Duncan, R. Harris, K. L. Williams, and I. Humphery-Smith. 1995. Progress with gene-product mapping of the mollicutes: *Mycoplasma genitalium*. *Electrophoresis* 16:1090–94. doi:10.1002/elps.11501601185.

Wild, C. P. 2005. Complementing the genome with an "exposome": The outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol. Biomarkers Prev.* 14:1847–50. doi:10.1158/1055-9965.epi-05-0456.

Wild, C. P. 2008. Environmental exposure measurement in cancer epidemiology. *Mutagenesis* 24:117–25. doi:10.1093/mutage/gen061.

Wild, C. P. 2011. Future research perspectives on environment and health: The requirement for a more expansive

concept of translational cancer research. *Environ. Health* 10:S15–S19. doi:10.1186/1476-069x-10-s1-s15.

Wild, C. P. 2012. The exposome: From concept to utility. *Int. J. Epidemiol.* 41:24–32. doi:10.1093/ije/dyr236.

Williams, R. J. P. 2001. Chemical selection of elements by cells. *Coord. Chem. Rev.* 216–217:583–95. doi:10.1016/S0010-8545(00)00398-2.

Wishart, D. S., D. Tzur, C. Knox, R. Eisner, A. C. Guo, N. Young, D. Cheng, K. Jewell, D. Arndt, S. Sawhney, et al. 2007. HMDB: The human metabolome database. *Nucl. Acids Res.* 35:D521–D526. doi:10.1093/nar/gkl923.

Wu, G. D., J. Chen, C. Hoffmann, K. Bittinger, -Y.-Y. Chen, S. A. Keilbaugh, M. Bewtra, D. Knights, W. A. Walters, R. Knight, et al. 2011. Linking long-term dietary patterns with gut microbial enterotypes. *Science* 334:105–08. doi:10.1126/science.1208344.

Wu, -L.-L., W. Gong, S.-P. Shen, Z.-H. Wang, J.-X. Yao, J. Wang, J. Yu, R. Gao, and G. Wu. 2017. Multiple metal exposures and their correlation with monoamine neurotransmitter metabolism in Chinese electroplating workers. *Chemosphere* 182:745–52. doi:10.1016/j.chemosphere.2017.04.112.

Xia, J., L. Lu, C. Jin, S. Wang, J. Zhou, Y. Ni, Z. Fu, and Y. Jin. 2018. Effects of short term lead exposure on gut microbiota and hepatic metabolism in adult zebrafish. *Comp. Biochem. Physiol. C* 209:1–8. doi:10.1016/j.cbpc.2018.03.007.

Yu, W., T. Liu, R. Valdez, M. Gwinn, and M. J. Khoury. 2010. Application of support vector machine modeling for prediction of common diseases: The case of diabetes and pre-diabetes. *BMC Med. Inform. Decis. Makers* 10:16–23. doi:10.1186/1472-6947-10-16.

Zawia, N. H., R. Sharan, M. Brydie, T. Oyama, and T. Crumpton. 1998. Sp1 as a target site for metal-induced perturbations of transcriptional regulation of developmental brain gene expression. *Dev. Brain Res.* 107:291–98. doi:10.1016/s0165-3806(98)00023-6.

Zhou, A., J. Ni, Z. Xu, Y. Wang, S. Lu, W. Sha, P. C. Karakousis, and Y.-F. Yao. 2013. Application of 1H NMR spectroscopy-based metabolomics to sera of tuberculosis patients. *J. Proteome Res.* 12:4642–49. doi:10.1021/pr4007359.