Exposome, 2021, **1(1)**, osab007
https://doi.org/10.1093/exposome/osab007
Advance Access Publication Date: 31 December 2021
Review

Historical exposomics and high resolution mass spectrometry

Dagny Aurich [1,*], Owen Miles[2], Emma L. Schymanski [1]

[1]Luxembourg Centre for Systems Biomedicine (LCSB), University of Luxembourg, 6 Avenue du Swing, Belvaux L-4367, Luxembourg
[2]Luxembourg Institute of Science and Technology (LIST), 5 Avenue des Hauts-Forneaux, Esch-sur-Alzette L-4362, Luxembourg

*To whom correspondence should be addressed: Email: dagny.aurich@uni.lu

Abstract

Awareness of the exposome and its influence on health has increased in the last decade. As past exposures can cause changes in human health many years later, delving into the past is relevant for both diagnostic and prevention purposes, but remains a challenging task. Lifestyle, diet, and socioeconomic information of the past should be well documented and compatible with modern data science methods. While chemical analysis nowadays makes use of high resolution mass spectrometry (HR-MS) for highly sensitive and comprehensive coverage of samples plus retrospective analysis, these data archives are in the very early stages. Since past measurements are often only available for a limited set of chemicals, adding to this knowledge requires careful selection of sample types and sampling sites, which may not always be available. The choice of analytes and analytical methods should be suitable for the study question which is not always clear in advance in exposomics. Data interpretation and the use of appropriate databases are indispensable for a proper exposure assessment, and as databases and knowledge grow, re-analysis of physically or digitally archived samples could enable "continuous monitoring" efforts. This review focuses on the chemical analytical approaches necessary to capture the complexity of the historical exposome. Various sample types, analytes as well as analyses and data interpretation methods are discussed in relation to chemical exposures, while the connection to health remains in focus. It ends with perspectives and challenges in assessing the historical exposome, discussing how we can "learn from the past" to build a better future.

Keywords: exposome; high resolution mass spectrometry; history; health; cheminformatics; pollutants

Background

The combination of the human genome and the exposome yields the phenotype, often represented as G × E = P.[1] However, the majority of health research so far has focused on genomics, with the Human Genome Project[2] building the foundation. In fiscal year 1991, 2.7 billion US dollars were invested in this project alone.[2] However, evidence is increasing that the environment (exposome) deserves greater attention, as several studies show that just 5%–10% of cancers and other diseases, for example, cardiovascular disease (CVD) can be attributed to genetic influences.[3-6] Many diseases are primarily influenced by the environment, also known under the terms *nurture*, the exposome or the *envirome* as J.C. Anthony called environmental factors influencing human health in 1995.[7] In 2020, the European Human Exposome Network[8]—funded with over 100 million euros—was launched to answer the need for research in this area. The exposome concept as first introduced by Wild in 2005[9,10] and later revised by Miller and Jones[6] directed the focus for the first time on *nurture* not just on *nature*. For those unfamiliar with the *nature versus nurture* concept, *nature* can often be misunderstood to mean the natural environmental factors, although in this context it actually means the genetic composition, while *nurture* covers all external factors. The exposome definition expanded by Miller and Jones considers not only environmental influences by chemical exposure, diet, or behavior, but also the associated biological responses.[6] All these factors are acting on the genome since conception onward, with environmental changes being much faster than genetic ones.[11,12] Both present and past factors have to be considered in assessing the exposome, as exposures fluctuate over various timescales: minutes to hours (eg, mealtimes and daily activities), weekly (working hours versus free time), seasonally (eg, changes in sunlight and rainfall hours or chemical application of pesticides, see eg, Wang *et al.*[13]), annually or even over decades (eg, industrialization or decommissioning of activities in an area). Pre-natal exposures during pregnancy—summarized as the maternal exposome—can play a major role and influence the health outcome of a child.[14]

The environment was divided into three subsections by Bhatnagar, visualized in the first figure of his article "Environmental Determinants of CVD."[15] The *natural environment* contains geographic and ecological conditions such as sunlight exposure, altitude, or living in green spaces.[16] The next subsection includes the *social environment*, containing culture, socioeconomic status, or social networks as well as the built environment with structures of houses or cities.[15] This could also be considered as the *urban exposome* concept.[17] Senier *et al.*[18] showed the facets of the *socio-exposome* in greater detail. Lastly, the *personal environment* deals with the important factor of lifestyle as well as income, physical activity, and habits such as smoking.[15] Nutrition plays an important role when considering the

Received: August 26, 2021. **Revised:** December 06, 2021. **Accepted:** December 14, 2021

exposome. In 2017, Cifuentes[19] elaborated on the concept of the *foodome* that is being addressed by many approaches including metabolomics as shown by Borzouie.[20] Other approaches make use of machine learning and text mining algorithms, for example, "FoodMine"[21] that aims at building databases containing the complete chemical composition of food. Most scientists agree that for assessing the whole exposome, an interdisciplinary and long-term approach is required taking together all internal and external factors including "Big Data" sources.[22,23]

Taking a look at the so-called *Anthropocene* described, for example, by Karlsson[24] in 2020, planetary health comes into focus, not only human health. Beginning with industrialization, human beings noticeably changed the environment.[25] To find and prove the origin of past pollution, historically relevant samples must be found, for example, sediment cores showing historical profiles of polychlorinated biphenyls (PCBs)[26] or chlordecone (CLD)[27] or ice cores showing lead pollution thousands of years ago.[28] This is needed for prevention of exposures and the related risks for diseases. In these cases, the assessment of the internal exposome using biomonitoring or untargeted metabolomics is likely of limited applicability.[29] The source or the route of exposure as well as spatial and temporal aspects are more likely to be found in environmental samples, as Turner *et al.*[29] demonstrate. However, information regarding the internal exposome—if present—can complement external exposomics data,[30,31] as some compounds can only be found in one matrix (eg, blood) and others in another (eg, water and ice).[32] While multi-omics techniques are needed to explore the relationship between internal and external exposome and to fully understand the exposome as a whole, these are not a specific focus of this article. For both environmental and biomonitoring, challenges such as accessibility and degradation of samples have to be considered as well as sample analysis and data interpretation. While exposomics research can be performed today using sensors or wearables,[29,33] this data are not (yet) available for the past. Questionnaires as well as literature on exposure from, for example, accidents, population data and health records can help to obtain an approximate picture of the historical exposome, but can be incomplete or inaccurate (as discussed further below).

Assessing any kind of exposure leading to disease outcomes is a quite challenging task. Most diseases, for example, neurodegenerative diseases as Parkinson disease show first effects years after possible exposures.[22] In the past such research was mainly restricted to patient questionnaires, trying to get any causalities out of patient's memories, as Coggon[34] shows. However, those questionnaires are highly subjective and some chemical exposures might not be recognized as such by patients, for example, the use of "Roundup", a glyphosate-based weed killer, in the garden is not always connected with pesticide exposure by patients. In addition, questionnaires are potentially of limited use for people already dealing with cognitive defects.[22]

To join all these factors together, this review focuses mainly on the chemical and data analytical challenges associated with the external historical exposome. The internal exposome is also briefly discussed in terms of historical relevance, with the knowledge that it can only provide partial information on external exposures of the past. Different sample types and approaches used in exposomic research are presented, as well as the challenges and potential for historical research. A focus is placed here on chemical analysis using high resolution mass spectrometry (HR-MS) and its data interpretation as it is a state-of-the-art technique for the detection of environmental pollutants.[25] The limitations currently faced in assessing present-day exposures also apply to the exploration of past exposures. This is covered later in the section "Comparability and quantification issues".

Selecting samples for historical exposomics

To obtain a complete picture of the "historical exposome", one has to consider all factors that contribute to the human exposome—a near impossible task. Besides lifestyle, diet, or socioeconomic factors, chemical pollution has a major impact on the development of certain phenotypes, especially diseases.[18,23] Chemical pollution is also, in many ways, a more tangible concept than many other exposomics factors and as such, a wide array of samples and techniques is available for use. In the following section, various sample types are examined more closely for their suitability and potential for exposomics research, especially regarding their historical information content. The influence of different pollution sources, such as agriculture, industry, or medicine in deciding which sample types may be appropriate is also discussed.

Human subjects

In the past, exposures leading to diseases in humans were mainly assessed by questionnaires, which can be problematic as mentioned above.[34] It may be possible to at least partially counteract this challenge by looking for environmental samples with "historical relevance" indicating exposure, as shown in one of the next sections or just looking at human samples. Some governmental institutions collect and store human samples in biobanks over a period of time. Countries have been collecting and storing samples over 100 years without necessarily knowing the appropriate storage conditions or sample handling, especially for example, for methods in use now that were not available in the past.[35] The establishment of standards for storing different human samples began during the last 30 years, around the time when the term "biobank" was first used.[35] Using proper documentation of the samples makes dating much easier than it is for other sample types. However, for extremely old samples, such as mummies, other dating methods must be applied. Major issues of biobanks are sample degradation and missing long-time biobanks in many countries, as many efforts have just started collecting samples in the last few years.

Human samples contain a lot of information.[5] However, it should be kept in mind that due to different metabolic processes, each sample matrix also reflects a different picture of the internal exposome, which in combination can give an overall picture (discussed further below). The most common samples, such as urine or blood, provide very transient signals for non-persistent chemicals, but can provide long-term information on environmental exposure for some persistent chemicals. Moreover, they have in the meantime well-established analytical protocols and standard materials available for analytical method development. Feces is a similarly non-invasive but relatively short-term sample type with a very complex matrix of increasing relevance given the attention to the microbiome; however, standard materials are still rare. Due to differences in diet, there is a high variability in stool samples; therefore, pooled samples have to be considered to perform individual or population studies. In the field of forensic toxicology, hair is used to provide valuable evidence on many aspects such as drug consumption that occurred, for example, up to weeks before.[36] Calafat *et al.*[37] show that baby teeth, amniotic fluid, and meconium can provide information on pre-natal exposures. Frye *et al.*[38] studied the connection of pre-natal metal exposure and autism looking at baby teeth. Spinal fluid and

vitreous fluid, which is often used for post-mortem analyses, are two valuable but invasive sample types to mention; other sample types such as various tissues may also be available but are even more invasive. The main challenges with human samples are accessibility in sufficient quantity and the complex matrix that contains compounds such as endogenous metabolites in much higher concentrations than environmental pollutants.[39] Appropriate sample preparation and highly sensitive analytical techniques such as HR-MS are needed to analyze such samples. In Figure 1, the challenge of low concentrations of pollutants in biological samples is demonstrated compared with concentrations of drugs, endogenous, or food compounds. Another major issue is the comparability of different samples and measurements, as there is no standardized method to perform corrections for, for example, urinary dilution.[40,41] Moreover, there is no standard for reporting concentrations based on the different routes of elimination. These issues still need to be addressed in the context of exposomics, even before historical studies are performed.

Rappaport suggested to use a top-down approach in exposomic studies defining exposures as "biologically active chemicals" in the internal environment of a human organism.[5] The original exposure, as well as its fingerprints in the form of metabolites and even detectable biomarkers are very valuable traces. Thus, even years after a smoker has stopped smoking, this past activity can be identified by certain changes in the human organism.[42,43] Unfortunately, this is not the case for all exposures. While metabolites can act as potential indicators for a certain disease or exposure (ie, functioning as biomarkers), they are not always new or sufficiently unique compounds. In many cases, exposure biomarkers may refer to elevated concentration of some compounds in the part of a population exposed to certain chemicals compared with lower levels in unexposed organisms as shown by Xu *et al.*[44] Not all exposures may have sufficiently specific biomarkers or associated changes in biochemical signals. However, the accessibility of "historical" human samples is a problem, as mentioned above: There are not always cohort studies or biobanks present that reach back to times of initial exposure; for instance, Luxembourg started to collect samples in 2009.[45] Moreover, not all types of exposures can be detected over a long time period in humans as for smokers, as metabolism is a very dynamic process such that most levels decrease over time, and metabolites are further transformed or eliminated.

Today, exposure assessment can be done efficiently by using wearables as shown by Hammel *et al.*[46] They can either function as sensors for environmental data or as monitoring devices for health data of the carrier.[29] The human organism is a complex sample itself, as it is influenced by many factors besides environmental pollutants; the biological response is a measure that can indicate such influences. Other factors as lifestyle, social factors, or other variables in the surrounding ecosystem play a major role, shown by example of cardiovascular risk factors as obesity or hypertension.[47,48]

Other organisms

Other organisms may carry useful information about the present health or pollution state of the (aquatic) environment they are living in, for example, as demonstrated in mussels.[49] However, not much is known about backdating contaminants found in other organisms to the time of exposure, while not all species live sufficiently long. Some cetacean species live for several hundred years and have been shown to be exposed to environmental pollution from persistent chemicals many times over via biomagnification.[50] However, such studies mainly reflect the status and pollution levels of marine organisms.

When looking for representative plant species, trees stand out as promising specimen when it comes to finding historically

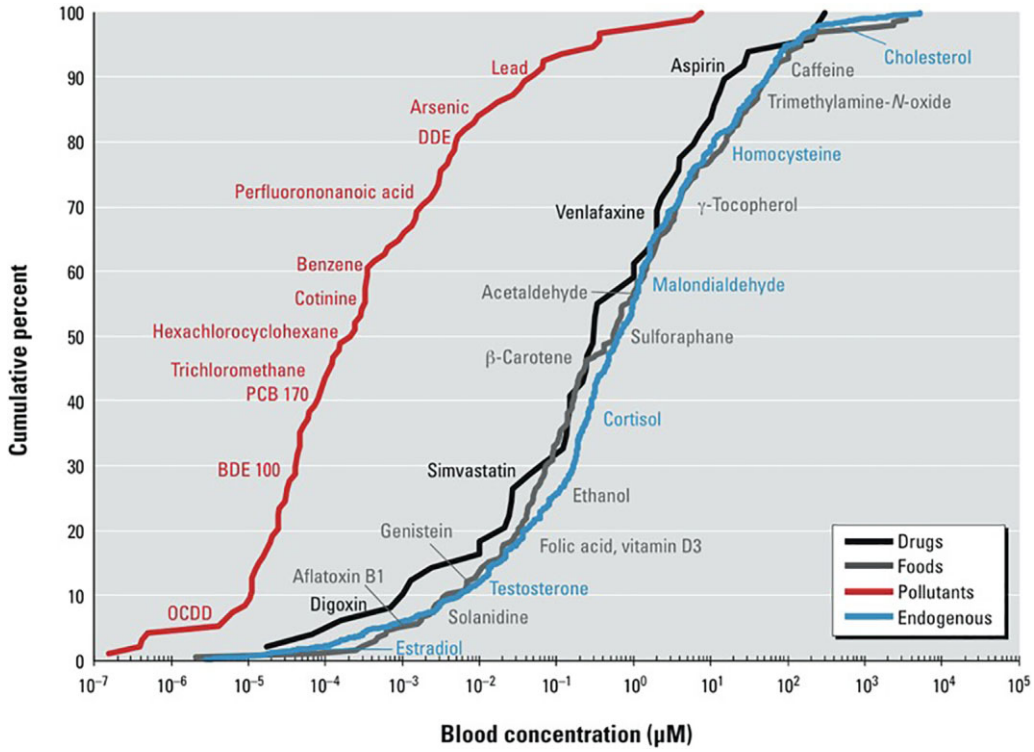

Figure 1. Concentration levels of small molecules and metals in human blood, taken from Rappaport *et al.*[39] Reproduced with permission from Environmental Health Perspectives.

relevant samples. Dendrochronologists can classify the exact age of trees via rings very accurately. It could be postulated that tree rings may yield data on air or soil pollution in chronological sections. Some studies deal exactly with this assumption, for example, Perone *et al.*[51] showed in 2018 the temporal and spatial variability of air pollution from a wide range of sources in oak tree rings looking at tree cores. However, a study by the University of Göttingen in 2006 shows how problematic this assumption is.[52] The enrichment of heavy metals in soils and the accompanying rising acidity increase the cation take-up of plants. Other factors such as growth rate and redistribution of elements determine element concentrations in each ring as well,[52] confounding the interpretation. Some studies are also investigating the use of tree needles or leaves for biomonitoring of environmental pollution.[53,54] With the help of botanical collections even spatial and temporal trends can be found.

Environmental samples

For environmental samples, so-called environmental specimen banks (ESBs) were established in many countries during the last 40 years.[55] In combination with this, there are digitally archived sample measurements available on repositories for HR-MS data such as Global Natural Products Social Molecular Networking (GNPS)[56] and NORMAN Digital Sample Freezing Platform (DSFP)[57] allowing retrospective analysis for recent years.[58] However, this will help future research, whereas historical environmental samples are most of the time not accessible any more.

The three most frequently examined sample types are soil/sediment, water, and air. Figure 2 shows the connection between these sample types and different contamination sources.

Air pollution

Outdoor

There are many different ways to detect air pollution. However, there are few studies that indicate air pollution in the past and most studies are based on theoretical models. Today there are many governmental institutions monitoring air quality of different countries in terms of ozone, particulate matter ($PM_{2.5}$; PM_{10}), nitrogen dioxide (NO_2) and other nitrogen oxides (NOx), lead (Pb) in PM_{10}, benzene (C_6H_6), sulfur dioxide (SO_2), and carbon monoxide (CO) concentrations regulated by the Ambient Air Quality Directive in Europe.[59] Many regulations still focus on atmospheric particles of a given size, although nanoparticles require attention as their toxicity is often underestimated due to the lack of data.[60] Monitoring stations usually make use of passive samplers that collect pollutants over weeks up to 1 month looking at population scale pollution.[59] Other methods also exist to detect air pollution, for example, Hissler *et al.*[61] looked at a lichen species in 2008 to examine local impact of steel production on pollutant concentration in atmospheric deposition in an industrial region of Luxembourg at community scale. Again, there is—for many countries—just data covered from the last decade due to technical facilities not being available in the past and the fact that regulations have just been introduced for many compound classes starting with air pollution acts in the 1950s.[62] In contrast, air pollution awareness and its impact on human health dates back to ancient Rome.[62]

Community scale studies on connecting industrial air pollution to diseases exist, focusing on recent years, for example, on respiratory illness in Valenti *et al.*[63] In the *Global Burden of Disease Study* by the Institute for Health Metrics and Evaluation (IHME), air pollution is shown to be a leading risk factor for diseases and death, causing an estimate of 5 million or 9% deaths in 2017 globally (see Figure 3).[64]

The *State of Global Air 2020* report by the IHME and the Health Effects Institute summarizes different burden of diseases caused by air pollution, namely fine particulate matter and ozone.[66] In 2019, 40% of chronic obstructive pulmonary disorder (COPD) deaths and 30% of lower-respiratory infection deaths were due to air pollution.[66] Air pollutants such as sulfur dioxide originating from industry were addressed in many articles, such as in the article of Calderón-Garcidueñas *et al.*[67] on air pollution causing brain damage. However, during COVID-19 shutdowns in 2020, air

Figure 2. Interconnection of pollution sources, soil, water, and air.

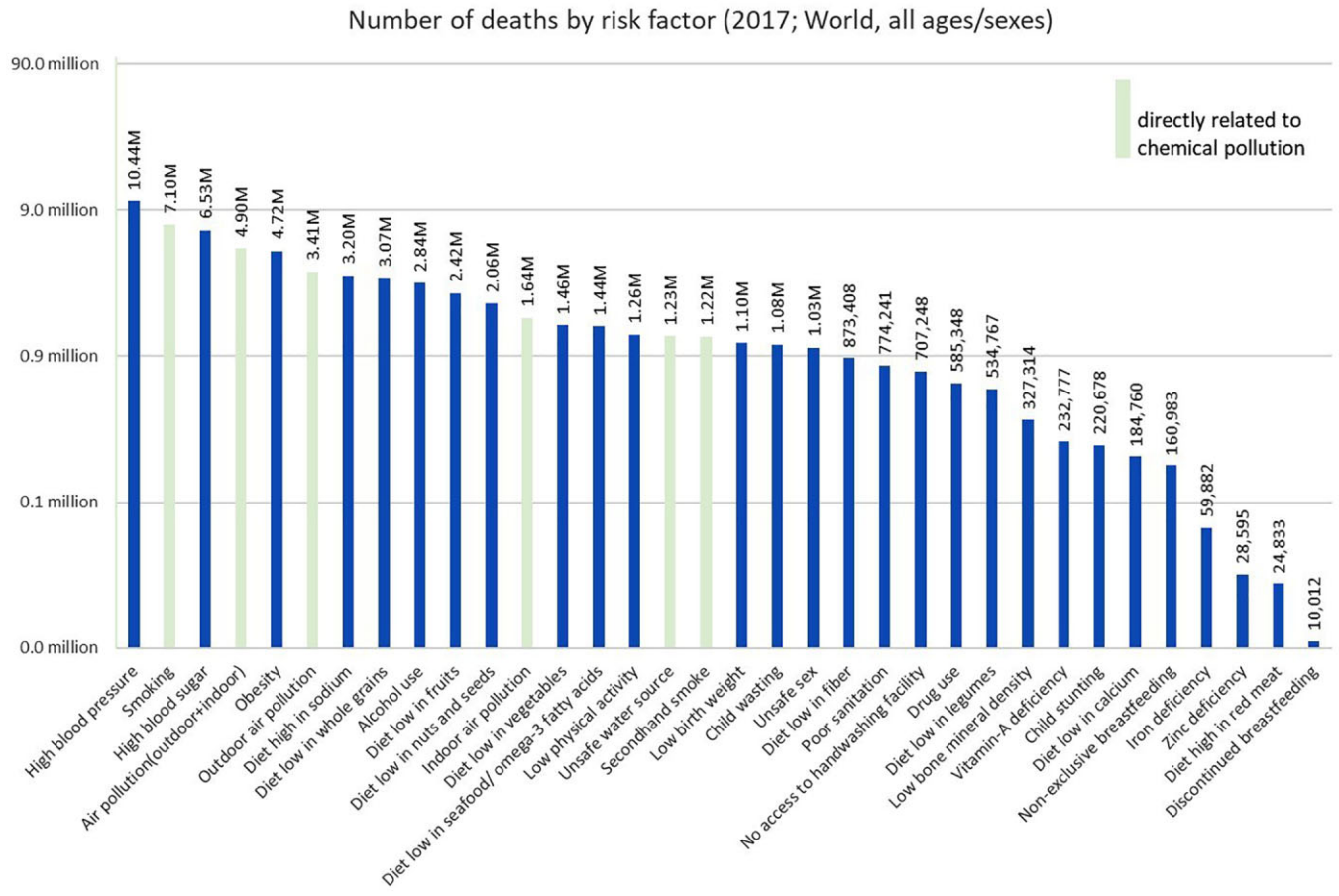

Figure 3. Number of deaths by risk factor, modified from "Our World in Data"[65].
Source: The IHME.[64] Note the logarithmic scale.

pollution levels decreased temporarily as another report of the *State of Global Air* shows. Moreover, there are indications that long-time exposure to air pollution increases the COVID-19 susceptibility as the body's immune defense is affected.[66] Most exposomics studies on air pollution are at population or community scale, presenting an overall picture of pollution issues. However, individual studies can help in case of, for example, occupational diseases to track the workers exposures directly. Personal air monitors have been gaining increased interest over the past few years, although concerns remain regarding data protection and privacy.

Indoor

Dust is a promising sample type for measuring environmental pollution, as many atmospheric pollutants accumulate in dust.[68] Through examining windowsill dust, Han *et al.*[69] showed that industrial activities lead to severe air pollution by potentially toxic metals or PTMs causing serious harm, for example, internal organ damage to a population in China. The analysis of dust on old documents would be therefore quite interesting, as old dust samples could provide information on air quality in the past. There are already quite a few studies on household dust, such as the NORMAN collaborative dust trial,[70] providing information on exposure to chemicals via different sources.[68] Those studies represent just a few possible ways to look at air pollution. Indoor dust plays a major role in chemical exposure as it is present everywhere and contact is unavoidable, especially as a lot of time is spent indoors.[71] It serves as a repository for many chemicals, such as plastic additives, pesticides, heavy metals, cigarette smoke, or personal care products coming from various sources (cooking and cleaning) and individual exposure differs.[72-74]

Water

Water can dissolve, store, and transport chemicals through the environment, making it a versatile sample type.[75] Most of the water on earth is present in the oceans as saltwater or stored in ice, and therefore unavailable for human consumption without modification.[76] The remainder is fresh liquid water and is commonly classified into groundwater and surface water. Surface water is flowing or standing at the surface, and groundwater exists in the pores between soil grains or in fractures in rock formations.

Both groundwater and surface water are consumed by humans and used in agricultural and industrial processes. In Europe, approximately 24% of water is extracted from groundwater and the remainder from surface water resources.[77] Most water is used in agriculture for irrigation and processing food (40%), while around 18% is used in industrial processes.[77]

Water in different flow systems has different residence times, such that these can be useful stores of historical environmental information.[78,79] For example, a groundwater aquifer can transport chemicals over a period of years, decades, or centuries.[78,80] Residence times for different water systems are summarized online in Table 8b-2 of Pidwirny's "Hydrologic cycle."[81]

By understanding the source of water and using different chemical signatures, the so-called "age" of water can be estimated, which is usually defined as the average time that the

water entered the flow system from the atmosphere or was released from human activities.[78,79] Care needs to be taken when using the term "age," as water is mixed in the environment, so any sample of water is really a distribution of water molecules of different ages, usually referred to as an average or mean residence time, or MRT.[82]

Groundwater MRT has been studied using environmental tracers such as isotopes or chemical signatures and combining that information with studies of the flow system with hydraulic measurements, often with the aid of numerical or analytical models.[79] This can be used to determine historical contamination at a site for tens of years. Radioisotope dating of the unstable isotopes carbon-14 and tritium are most commonly used in these studies, though other tracers can be used.[78] Uncertainty does exist in the dating, as groundwater flow is mixed with preferential pathways (areas of higher flow in the soil or rock) and radiocarbon dating can be confounded by geochemical changes in the soil and rock that can alter the carbon-14 ratios.

Deeper groundwater can also be of so-called "fossil age," where the water is on the order of thousands of years old. This water can still be mixed with more modern water, making assessment of groundwater MRT very challenging in some environments. Understanding the interactions between new and old groundwater in a deep groundwater flow system are needed to interpret the MRT of groundwater samples, and ultimately the presence and concentrations of chemicals in the systems.

Groundwater can experience chemical concentration changes as the water interacts with the chemicals in the rock and soil grains, organic material, redox conditions, and biological organisms.[75,83] Chemical signatures can be changed or transformed by these chemical or biological processes, which must also be considered when analyzing groundwater samples.

Surface water tends to have MRTs of days to years depending on the flow systems and MRTs are often more easily estimated in surface water systems than groundwater systems, owing to the ability to direct observe flow. Due to the shorter MRTs, stable isotope analysis is more easily performed on surface waters.[79] Surface waters are more rapidly mixed than groundwaters and are exposed to the sunlight and the atmosphere, which can make interpretation of chemical signatures difficult in respect to concentration and transformation effects.

With both surface water and groundwater, it is important to understand the hydraulic conditions that drive the flow and mixing as well as geochemical and biological reactions when assessing water samples.

Wastewater

Urban wastewater is usually treated in treatment plants and released to surface water or groundwater by means of direct flow, injection, or infiltration. Rural wastewater is usually treated in holding tanks or ponds and allowed to infiltrate to groundwater. Wastewater treatments usually rely on filtration followed by biological treatment to reduce organic compounds. Industrial processes often have specific wastewater treatment plants to treat the specific pollutant loads from the processes. Wastewater plants can have long records of their influent and effluent samples as part of regular plant operations.

Wastewater also has great potential for pollution assessment at the community scale.[84] In the context of historical exposomics, it is particularly interesting when it comes to inferring currently relevant diseases from medicines or industrial pollution from certain substances at a population level. Wastewater-based epidemiology (WBE) uses the potential of wastewater to monitor drug consumption and abuse of, for example, narcotics,[85] lifestyle factors such as personal care products and environmental influences such as temperature change or pollutants.[84,86-89] Wastewater also serves as a repository for viruses and bacteria that can indicate the presence of such diseases in a population (a prime example being SARS-CoV-2 WBE).[90,91] Archiving wastewater samples over time would potentially provide a comprehensive picture of the health and lifestyle of a population in a multi-omic manner, avoiding data protection issues and offering a cost-efficient model of population-based monitoring.[88] Wastewater contains a lot more information than surface or groundwater, however, its matrix is inhomogeneous and thus it is not as comparable as water (but better than feces).

Sediment and soil

Sediment sampling can yield historical information about pollutants found in different layers.[92,93] Many personal care products, biocides, or additives accumulate in sediment cores,[92] representing a complementary picture to the pollutants found in water or marine organisms and providing insight into the lifestyle aspect of the exposome (Figure 4).[94,95] Pollutants getting from surface water into sediments and even further to groundwater can endanger human health via different routes of exposure (direct or indirect ingestion and dermal contact).[96] However, there is the big limitation of having suitable water bodies with stable sedimentation patterns present in the area of interest. Turbulence and bioturbation often play a decisive role in sediments, which is why lake rather than river sediments are used.[92]

Soil samples prove to be even more problematic as backdating through the different layers is complicated. Soil evolution is a complex process and there is also bioturbation and mixing of the deposition layers taking place. Natural peat bogs could be used for backdating of samples,[97] however, geographically these are rather rare to find. Sediment as well as soil contamination in general can be monitored quite efficiently using the appropriate extraction or digestion sample preparation techniques. The best technique to use depends on the analytes of interest, for example, heavy metals, persistent organic pollutants (POPs) or emerging pollutants. Han *et al.*[69] or Yang *et al.*[98] showed the great potential of analyzing soil in the context of industrial pollution in China. Industrial pollutants migrate into soil via diffuse atmospheric depositions, sediment particle deposition during flood events in alluvial areas, waste or wastewater disposal, or direct pollution events and thus threaten the soil ecosystem health.[99]

Limitations and future strategies

For all sample types, there are limitations: For water and sediment analysis, suitable water bodies are required. To look at human samples of the past, cohort studies must exist with suitable biobanks for the respective country or region. Other samples may not be sufficiently representative to monitor industrial pollution over a time period. Industrial pollution in soil, water, and air originating from past industries could be the reason for many diseases present nowadays. However, to connect those pollution events in the past to disease outcomes years later is a difficult task. Most of the time a combination of many factors plays a role in disease development, not just a handful of chemical compounds.[23] Exposomics research focuses on making these kinds of connections, which is a very challenging task that, in the context of historical exposomics, may require making the best of available information. Today, with the data and samples available presently, historical exposomics will involve estimating a reasonable exposure assessment for the past. For the future, proactively

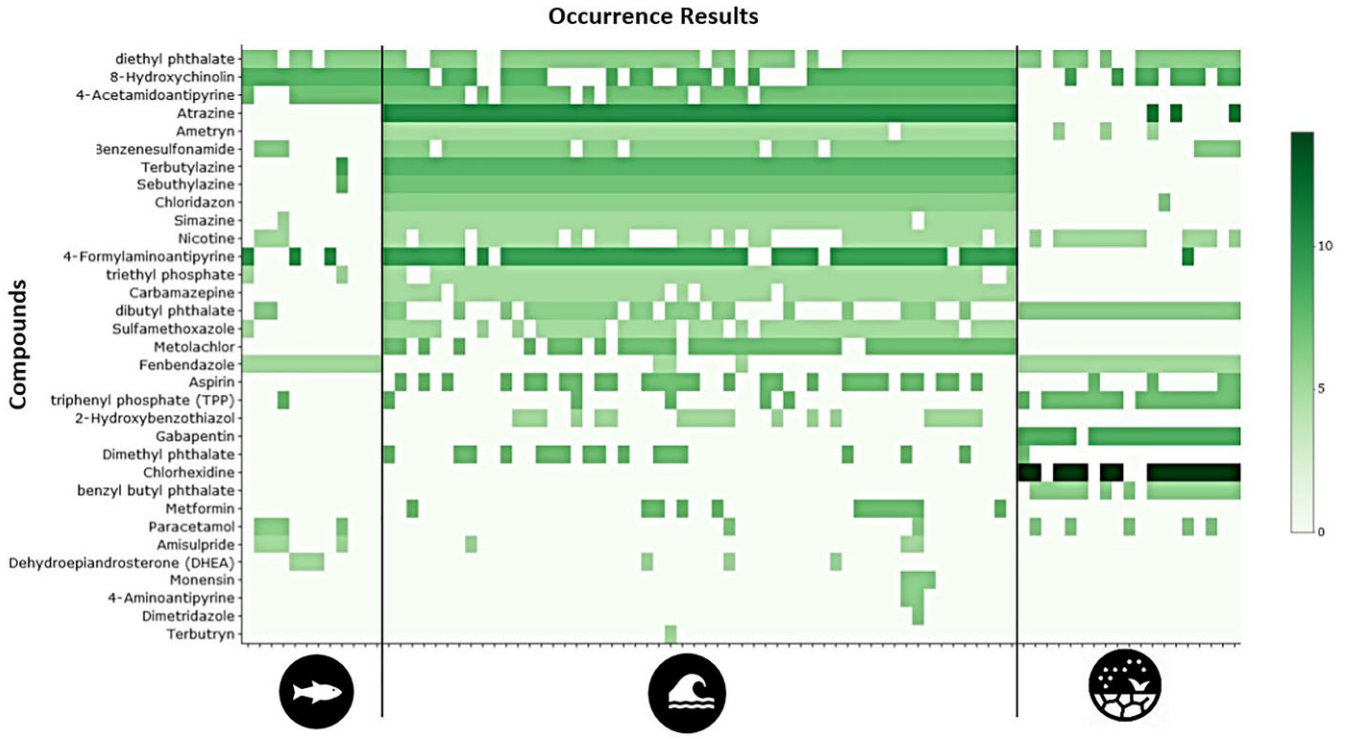

Figure 4. Heatmap showing the occurrence of different pollutants in different media (fish, water, and sediment), adapted from NORMAN-REACH DSFP[57] based on EMBLAS-II project.[95]

organized sampling campaigns could be used to gather and store all kinds of possible sample types at an early stage, to enable and simplify retrospective analyses. This type of sample retention should be in the interest of every population group, because the actual environmental cause of many diseases is often detected far too late and can then no longer be traced. If one also looks at the individual case, work-related illnesses, for example, in the military, can be traced back through previous exposure. In case one sample type is not present in a specific area, one can switch to other specimen indicating exposure, however, the comparability of different sample types is limited. Some pollutants only accumulate in certain media, like, for example, sediment, water, or fish (see Figure 4).

Analytes and analysis for historical exposomics

Environmental pollutants can be anything, from metals to macronutrients through to trace concentrations of organic compounds and organometallic compounds (often termed "micropollutants"). In the past, mostly only contaminations of a limited set of chemicals that exceeded a regulated threshold value were considered. Many other pollutants were likely present in low concentrations, but not yet regulated or monitored at that time. This was mainly due to the technical possibilities and regulatory aspects, which made analysis difficult in the past.[93] Today, techniques such as HR-MS can detect the smallest amounts of contamination in environmental samples where requirements such as ionization properties (ie, if a compound ionizes at all or how efficiently) or compensation of matrix effects and thus good sensitivity are met (see the section "Comparability and quantification issues"). Using the appropriate technique even traces at atto-gram level can be detected, such as for hydroxycholesterol, which is related to breast cancer.[100]

Metals and organometallics

Metals are typical inorganic industrial contaminants. Their toxicity depends among other things on their total concentration as well as from the speciation of elements in the system.[101] Even small amounts can bioaccumulate and have an influence on health. Many neurotoxins are metals such as aluminium (Al), arsenic (As), or mercury (Hg).[102] Lead (Pb) contamination is a major issue especially in developing countries as its use is not regulated there.[103] It is persistent, widely used (eg, paints and cars) and therefore accumulates in the environment quickly, causing serious hazards all over the world. Organometallics have a broad range of applications in plastic manufacturing or as an additive to petrol in the past.[104] Tributyltin (a biocide) and methyl mercury (MeHg, formed by microbes or as a byproduct in industry) are just two high profile organometallic environmental contaminants to be mentioned. Organometallics possess a very high toxicity (eg, Minamata disease caused by MeHg[105]), which is problematic as they are detectable in a variety of environmental samples through past or present use. An inductively coupled plasma (ICP) can be very useful as an ion source when analyzing metals via mass spectrometry (MS) and coupled to liquid chromatography (LC), even organometallics can be analyzed.[106]

Organic compounds

A larger number of organic contaminants are only relatively recently coming into focus, the so-called emerging pollutants: Pesticides like chlorpyrifos, per- and polyfluoroalkyl substances (PFAS), surfactants, pharmaceuticals or persistent, mobile, and toxic (PMT) substances in general, just to mention some groups. However, when investigating historical contamination, it is often difficult to determine the original concentration of some organic

compounds and many might not be detectable any more. Other compounds, termed POPs accumulate in the environment over decades, such as the pesticide and insecticide dichloro-diphenyl-trichloroethane (DDT), which was banned in many countries in the 1970s.[107] However, regulation and therefore replacement of those chemicals often led to new emerging pollutants accumulating in nature,[107] with different transformation products that are not yet monitored (so-called regrettable substitution). Organic micropollutants at trace levels (μg/L to ng/L) have been released via anthropogenic activities to the environment over centuries and new substances are being discovered all the time. In a comprehensive annual 2020 review PFAS, replacement flame retardants, iodinated and nitrogenous dibutyl phthalates (DBPs), and antibiotic resistance genes (ARGs) were highlighted as groups of concern.[108] Many of the above mentioned analytes are associated with neurodegenerative diseases such as Alzheimer and Parkinson disease or certain cancers.[109] These connections were only found due to new technical improvements and methods.

Analysis

The choice of the right method for each class of analytes is crucial to find contaminants even at trace levels. After sample preparation, chromatographic methods such as LC or gas chromatography (GC) are usually used to separate compounds of interest. MS is the detection tool of choice in most laboratories. Using different ion sources and mass analyzer modules such as Orbitraps can increase the sensitivity many times over. Before the actual analysis, the acquisition type must be determined. A distinction is made between targeted and non-targeted (NT) analyses.[93] Targeted analyses focus on a limited set of substances to be detected, where the reference standards are available in house in advance for method development. Some instruments are generally only used for targeted analysis (eg, triple quadrupole instruments), while others can offer both targeted and NT acquisition methods. For more details on analytical methods, several recent reviews, overviews, and comparisons exist.[110-113]

Comparability and quantification issues

Exposure can be calculated based on concentration values. However, for example, for biological samples correction methods to report concentrations are not (yet) harmonized and the values are therefore often not comparable.[40] For difficult matrices such as wastewater or feces, correction for matrix effects is essential to obtain reliable results.[114] Moreover, an inter-batch correction compensating for varying signal intensities in a study is needed to compare measurements. Using signal intensities to quantify compounds measured with HRMS is highly problematic, since each compound ionizes differently (ionization efficiency can vary by up to six orders of magnitude)[115-117] and thus intensities are not directly comparable. Semi-quantification approaches such as structural similarity, parent—transformation product proximity, close eluting, ionization efficiency, or combined approaches can be used instead.[118] Another major problem lies in the comparability of pollutant concentrations found in different media, as some pollutants only accumulate in specific matrices[95] (see Figure 4) and concentrations in organisms strongly depend on different metabolic processes. For exposomics studies, it is necessary to look at all types of pollutants and samples as, for example, viruses or bacteria in wastewater mirror the health status of a community[86] and consumer products in sediments[92] reveal information about the lifestyle, each reflecting different sides of the exposome.

Using targeted methods with reference standards to quantify compounds does not necessarily cover the full range of substances in a sample, as important transformation products or pollutants that are not yet monitored may be omitted. However, HRMS is not required to perform targeted analysis. Targeted analysis on lower resolution instruments can be both cost and time efficient for routine analyses. Routine monitoring of, for example, certain rivers in targeted mode is needed to control if regulation values are met.[119] While NT analysis covers more compounds and is more conducive to retrospective screening, is also not yet sufficiently harmonized and/or standardized for routine applications. For both historical exposomics and exposomics in general, precise definitions on how to measure each sample (number of repeats, choice of internal standards, or column, etc.) are necessary. Taking a critical look at the variety of existing methods in exposomics, there is some way to go before harmonization is sufficient for current studies, let alone for implementation into past studies. Some efforts at standardization of NTS are underway, which may pave the way for future harmonization efforts.[120]

Data analysis and interpretation

For NT MS data (hereafter NT-data), there are different data analysis options to consider: Targeted, suspect and NT screening. For targeted screening of NT-data, reference standards are required and matching MS data and retention time, preferably along with fragmentation (MS/MS) data are needed for identification of a compound.[115] Suspect screening is the next potential step: A suspect list of several compounds, for example, pharmaceuticals is used and a search is made for matching MS and—if a library is used—MS/MS. However, if this list becomes too large one easily ends up in a NT approach, where peak-picking is performed, followed by identification efforts.[115]

Databases

There are many compound databases present for use in exposomics, which can be combined with spectral libraries that include spectra and thus fragmentation information for each compound for increased identification confidence.[121] The largest compound databases now contain over 100 million entries, including CAS (184 million),[122] PubChem (111 million),[123] and ChemSpider (114 million).[124] One example of a medium sized compound database that is often used in NT-HR-MS screening approaches, particularly in metabolomics is the Human Metabolome Database (HMDB), with HMDB4.0 containing 115 398 metabolite entries linked to 5702 protein sequences.[23,125] Major sources for suspect lists include the CompTox Chemical Dashboard with >300 lists and the NORMAN Suspect List Exchange with >80 lists, with individual lists containing 10 s up to >100 000 chemicals.[126-128] Using information of existing databases to generate new exposomic resources can be a useful approach to limit the number of chemicals considered in exposomics studies. The Blood Exposome Database was constructed using text mining and information from various databases, resulting in approx. 65 000 entries.[129] The Exposome Explorer, on the other hand, is a much smaller database of approx. 1000 entries.[130] Health-related databases using, for example, cohort studies or exposome databases like the Toxin-Toxin-Target Database (T3DB)[131] can help to find a connection between exposures and health or specific phenotypes. As a database, T3DB is unique in that it shows mechanisms of toxicity as well as target proteins for each toxin, thus linking toxins (3678) and toxin targets (2073).[131] PubChem are integrating many resources and presenting the interlinking of gene, protein,

enzyme, disease, and chemical information as knowledge panels.[132] Building a suspect list on, for example, industrial pollutants can be done by patent search of the PubChem[123] database and reducing the overlaps between different fields. The choice of the database always depends on the study question and often databases are too big. For some databases such as PubChem,[123] subsets exist to limit the number of compounds, for example, PubChemLite for Exposomics[133] contains the most relevant and annotated subset of chemicals in PubChem for exposomics. Besides compound databases, there are spectral libraries containing either experimentally or *in silico* predicted spectra of different compounds. Examples of databases containing compound and spectral information are GNPS,[56] MassBank of North America (MoNA),[134] National Institute of Standards and Technology (NIST),[135] METLIN,[136] and MassBank[137,138] with NIST 20 having for example 1.3 million tandem spectra compared with MoNA with 200 000 spectral records. More detailed numbers can be found in other articles on the topic.[139]

A general issue lies within the use of databases: Using large databases yields many candidates per mass, providing many new ideas for possible chemicals, or leaving users juggling interpretations of various scoring terms. However, smaller databases containing just substances related to, for example, a disease or industrial use bear the risk of containing just "old knowledge" and not revealing any new knowledge. Thus, there is still a lot of work remaining until complete and comparable exposomics research is feasible, especially since harmonization and standardization is required in terms of terminology, methods, and reporting.

Software

In untargeted analysis or suspect screening, there is the challenge of peak picking or feature detection, followed by annotation efforts to decipher the identity of the chemicals causing the features. A typical feature count can be of the order of tens of thousands of features per sample using NT-HR-MS.[140] There are several tools enabling (partially) automated data analysis, for example patRoon,[141] XCMS,[142] or MS-DIAL[143] (see Figure 5) that can be used to look for specific masses or compounds present in a sample. In 2019, Wang *et al.*[140] presented PAVE, a peak annotation and verification engine for metabolomics, which includes the "cleaning" of the data and results in the matching metabolite formula. However, this approach requires stable isotope labeling, which is not feasible for most specimen in exposomics.

One speaks intentionally of peak annotation instead of identification as a full identification of a chemical can only be achieved using reference standards (ie, confirmation with target compounds).[93] However, as many standards are difficult to obtain, feature annotation using different computational tools is an alternative approach to tentatively identify chemicals of interest for further confirmation efforts. Feature annotation and compound identification are based on different parameters: The exact mass of the compound paired with its fragmentation pattern can be compared, for example, to experimental or *in silico* spectra using open source software such as MS-DIAL[143] or MetFrag.[144] In addition, retention time can improve identification, depending strongly on the method and instrument used.[145] Blaženović *et al.* used for their analysis of urinary metabolites a combination of several computational tools as CSI: FingerID[146] or NIST hybrid search[147] in order to annotate all metabolites found.[139] There are many other ways to annotate features; the software approaches provided by vendors of MS devices are also a good option for many, but are not covered in detail here. Figure 5 shows various ways of analyzing NT MS data resulting in the different identification levels.[121]

Usually, a statistical analysis follows after annotation (sometimes even before), including uni- and multivariate analysis as well as a validation of the study design and the interpretation of the results. The statistical evaluation methods will not be further elaborated here.[148] Statistics can be used to understand the

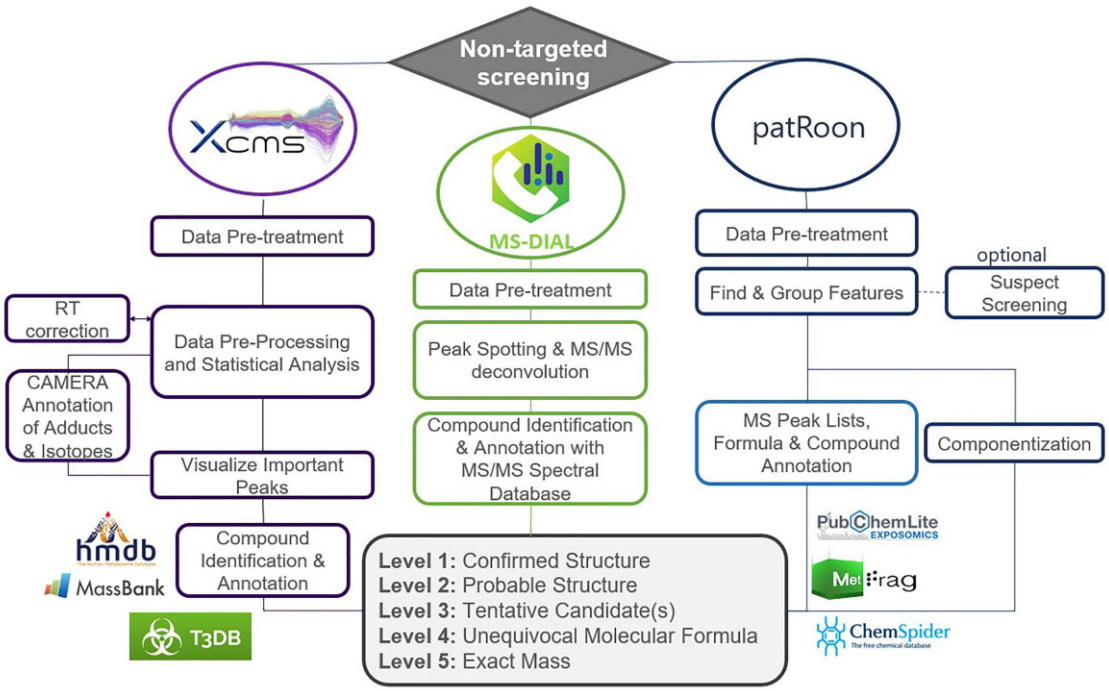

Figure 5. NT screening performed with three different (partially) automated workflows using XCMS,[142] MS-Dial,[143] and patRoon[141] with example databases resulting in reported annotations of various confidence.[121]

individual, community, and ecological exposome changes over time and the resulting health outcomes by interconnecting different data types and analyzing exposure values. This is required in order to understand environmental influences and their impact on health better (eg, for occupational diseases) and to act according to precautionary principles with regards to certain prevention measures (regulations, etc.). Typical strategies in exposomics studies include risk-based prioritization of chemicals and estimating the environmental disease burden.[149] Models for exposure risk and hazard assessment can then be applied in environmental policies and regulations.

Further exposome resources

There are computational tools in development to enter exposure data and analyze it using standard methods from, for example, Bioconductor.[150] The R-package "rexposome" can be used to connect exposures to phenotypes in exposome association studies.[151] The input data in such tools can be acquired by many disciplines, not just chemically using HR-MS. HExpMetDB was developed as a risk-prioritized human exposome database containing physiochemical properties and risk prediction with a graphical user interface (GUI) which enables searching.[152] Finding the connection to health is quite challenging. Health-related databases—as the ones mentioned above—can assist in finding this connection. Health records can be of great value when looking at past events. However, it is not just about doing an epidemiological study looking at several pollutants in connection to a health risk.

Association studies

The interconnection of exposures in chemical networks as well as other factors influencing the health of an organism have to be analyzed.[23] Therefore, environment-wide association studies and even exposome-wide association studies are appropriate ways of finding the connection between exposure and health.[23,153] Metabolome wide association studies find connections between metabolic profiles and disease risk, look for biomarkers of exposure, and even predict future disease onset. However, for all those studies, it is challenging to find relationships between thousands of molecular markers and disease phenotypes with minimal false positive associations.[154] Analytical techniques such as HR-MS or nuclear magnetic resonance enable metabolic profiling and exposure assessment. This makes association studies, metabolic pathway enrichment as well as looking at molecular networks possible.[155] Machine learning can help recognize patterns and make predictions thereafter. However, the limitations of all those approaches have to be considered: Dealing with thousands of features per sample, annotation and identification (with a certain confidence) become difficult and there is still a lack of automation. Moreover, the diversity of chemicals and chemical mixtures has to be taken into account with many unknown variables remaining.[156] Today, it is no longer a problem to measure the samples with sufficient sensitivity in a short time, but rather to draw the right conclusions from the results. Another issue is the terminology that differs between the research fields and the urgent need for harmonization. Association studies require strong international collaborations and high level networking, which is nearly impossible without establishing common terminology.[156]

Geographical information systems-based exposomics

Spatial and geographic data can be used in many ways for exposomics purposes. Geographical information systems (GIS) can connect different types of information that seem completely unrelated.[29] For exposomics it can be helpful to look at various sample types as presented above, at literature and health records to derive facts about historical exposure from those sources and link them geographically. Historical maps or aerial photographs often provide a good source of information on possible contaminated areas to establish connections to industrial sites, landfills, main traffic routes, and bigger cities as these may be more likely to have high levels of pollutants.[29] GIS helps in combining these different information sources by overlaying maps or aerial photographs, integrating data of environmental exposures and health-related data, and analyzing changes over time.[29] Distances between the source of exposure, for example, a closed landfill and affected people can be monitored,[157] as well as mobility of people and factors such as the density of grocery stores offering healthy options.[158] GIS can help in risk assessment and future planning as well as with environmental models.[159] Presenting information on environmental issues in a spatial and graphical way makes analysis easier and enables planning for future needs.

Conclusion

This review covers just a few studies from exposomic research to demonstrate how challenging a historical, retrospective study of the human exposome can be. Sample types have to be chosen carefully as their inter-comparability and suitability for the research question and their availability are limiting factors. If there is no cohort study or no representative sampling site, one has to choose a different sample type to determine exposure in the past. Moreover, analytes and finding the right method for analysis are important as well as the choice of databases for identification efforts. NT-HR-MS is often used for looking at environmental samples and their chemical composition even at trace levels. There are many possibilities to interpret experimental data and various computational tools can be applied. However, the choice of method is often a matter of availability at the institute, or personal preference. Harmonization efforts will be needed in the coming years to increase the comparability between methods.

To fully assess the human exposome, an interdisciplinary approach is required including also other efforts beyond the workflows presented here. In order to obtain an estimate of the historical exposome, a database containing environmental pollutants from different sample measurements, geographical, historical, socioeconomic, and population data as well as health records would be needed to find networks and interconnections and develop prevention strategies for the future. Changes in lifestyle, neighborhoods, and environment can decrease the risk of several diseases when the risk is recognized as such.[15] Thus, it is important not only to monitor health and pollution sources nowadays, but to pay attention to the past influencing factors on health as well. Such infrastructure is a major investment that is only possible at a high level (beyond a single institute) and the recent announcement of a dedicated European Infrastructure for the Exposome (EIRENE) is a very positive sign for this growing field.[160]

A possible topic for future research based on exposomic databases would be the implementation of an Exposome Risk Score.[23] This could be a measure indicating, for example, higher risks for CVD. All in all, as the European Human Exposome Network[8]

demonstrates, research is well on the way to shifting the focus to the exposome as well, not just the genome.

Acknowledgments

We acknowledge Aida Horaniet Ibanez and Andreas Fickers from the Luxembourg Centre for Contemporary and Digital History, Reinhard Schneider from the Bioinformatics Core group of the Luxembourg Centre for Systems Biomedicine, Christophe Hissler and Laurent Pfister from the Luxembourg Institute of Science and Technology for their comments, and all LuxTime colleagues who participated in the discussions.

Funding

D.A. acknowledges funding support from the University of Luxembourg through its Institute for Advanced Studies for the project LuxTIME (Audacity-2019); E.L.S. acknowledges funding support from the Luxembourg National Research Fund (FNR) for project A18/BM/12341006.

Conflict of interest statement

None declared.

References

1. Miller GW. The exposome: Purpose, definitions, and scope. In: Washinton K, ed. Exposome. Elsevier; 2020:1–26. https://doi.org/10.1016/B978-0-12-814079-6.00001-8
2. The Human Genome Project. Genome.gov. Accessed April 20, 2021. https://www.genome.gov/human-genome-project
3. Anand P, Kunnumakara AB, Sundaram C, *et al.* Cancer is a preventable disease that requires major lifestyle changes. Pharm Res. 2008;25(9):2097–2116. https://doi.org/10.1007/s11095-008-9661-9
4. Rappaport SM, Smith MT. Environment and disease risks. Science. 2010;330(6003):460–461. https://doi.org/10.1126/science.1192603
5. Rappaport SM. Implications of the exposome for exposure science. J Expo Sci Environ Epidemiol. 2011;21(1):5–9. https://doi.org/10.1038/jes.2010.50
6. Miller GW, Jones DP. The nature of nurture: Refining the definition of the exposome. Toxicol Sci. 2014;137(1):1–2. https://doi.org/10.1093/toxsci/kft251
7. Anthony JC, Eaton WW, Henderson AS. Looking to the future in psychiatric epidemiology. Epidemiol Rev. 1995;17(1):240–242. https://doi.org/10.1093/oxfordjournals.epirev.a036182
8. European Exposome Network—Human Exposome. Accessed April 21, 2021. https://www.humanexposome.eu/
9. Wild CP. Complementing the genome with an "exposome": The outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev. 2005;14(8):1847–1850. https://doi.org/10.1158/1055-9965.EPI-05-0456
10. Wild CP. The exposome: From concept to utility. Int J Epidemiol. 2012;41(1):24–32. https://doi.org/10.1093/ije/dyr236
11. Forschungsverbund Berlin. Climate changes faster than animals adapt. *ScienceDaily*. Published 2019. Accessed April 19, 2021. https://www.sciencedaily.com/releases/2019/07/190723121912.htm
12. López-Maury L, Marguerat S, Bähler J. Tuning gene expression to changing environments: from rapid responses to evolutionary adaptation. Nat Rev Genet. 2008;9(8):583–593. https://doi.org/10.1038/nrg2398
13. Wang X, Shen Z, Zeng Y, *et al.* Day–night differences, seasonal variations and source apportionment of PM10-bound PAHs over Xi'an, Northwest China. Atmosphere. 2018;9(2):62. https://doi.org/10.3390/atmos9020062
14. Wright ML, Starkweather AR, York TP. Mechanisms of the maternal exposome and implications for health outcomes. ANS Adv Nurs Sci. 2016;39(2):E17–E30. https://doi.org/10.1097/ANS.0000000000000110
15. Bhatnagar A. Environmental determinants of cardiovascular disease. Circ Res. 2017;121(2):162–180. https://doi.org/10.1161/CIRCRESAHA.117.306458
16. Mueller W, Steinle S, Pärkkä J, *et al.* Urban greenspace and the indoor environment: Pathways to health via indoor particulate matter, noise, and road noise annoyance. Environ Res. 2020;180:108850. https://doi.org/10.1016/j.envres.2019.108850
17. Andrianou XD, Makris KC. The framework of urban exposome: Application of the exposome concept in urban health studies. Sci Total Environ. 2018;636:963–967. https://doi.org/10.1016/j.scitotenv.2018.04.329
18. Senier L, Brown P, Shostak S, Hanna B. The socio-exposome: Advancing exposure science and environmental justice in a postgenomic era. Environ Sociol. 2017;3(2):107–121. https://doi.org/10.1080/23251042.2016.1220848
19. Cifuentes A. Foodomics, foodome and modern food analysis. TrAC Trends Anal Chem. 2017;96:1. https://doi.org/10.1016/j.trac.2017.09.001
20. Borzouie S. Application of metabolomics to measure the Alberta "Foodome". ERA https://doi.org/10.7939/R3891235D.
21. Hooton F, Menichetti G, Barabási AL. Exploring food contents in scientific literature with FoodMine. Sci Rep. 2020;10(1):16191. https://doi.org/10.1038/s41598-020-73105-0
22. Schymanski EL, Baker NC, Williams AJ, *et al.* Connecting environmental exposure and neurodegeneration using cheminformatics and high resolution mass spectrometry: Potential and challenges. Environ Sci Process Impacts. 2019;21(9):1426–1445. https://doi.org/10.1039/C9EM00068B
23. Vermeulen R, Schymanski EL, Barabási AL, Miller GW. The exposome and health: Where chemistry meets biology. Science. 2020;367(6476):392–396. https://doi.org/10.1126/science.aay3164
24. Karlsson O, Rocklöv J, Lehoux AP, *et al.* The human exposome and health in the Anthropocene. Int J Epidemiol. 2021;50(2):378–389. https://doi.org/10.1093/ije/dyaa231
25. Chiaia-Hernández AC, Günthardt BF, Frey MP, Hollender J. Unravelling contaminants in the Anthropocene using 2 statistical analysis of LC-HRMS non-target 3 screening data as recorded in lake sediments. Environ Sci Technol. 2017;51(21):12547–12556. https://doi.org/10.1021/acs.est.7b03357
26. Naffrechoux E, Cottin N, Pignol C, Arnaud F, Jenny JP, Perga ME. Historical profiles of PCB in dated sediment cores suggest recent lake contamination through the "halo effect". Environ Sci Technol. 2015;49(3):1303–1310. https://doi.org/10.1021/es5043996
27. Sabatier P, Mottes C, Cottin N, *et al.* Evidence of chlordecone resurrection by glyphosate in French West Indies. Environ Sci Technol. 2021;55(4):2296–2306. https://doi.org/10.1021/acs.est.0c05207
28. Hong S, Candelone JP, Patterson CC, Boutron CF. Greenland ice evidence of hemispheric lead pollution two millennia ago by greek and roman civilizations. Science. 1994;265(5180):1841–1843. https://doi.org/10.1126/science.265.5180.1841
29. Turner MC, Nieuwenhuijsen M, Anderson K, *et al.* Assessing the exposome with external measures: Commentary on the

state of the science and research recommendations. Annu Rev Public Health. 2017;38(1):215–239. https://doi.org/10.1146/annurev-publhealth-082516-012802
30. Egeland GM, Ponce R, Bloom NS, Knecht R, Loring S, Middaugh JP. Hair methylmercury levels of mummies of the Aleutian Islands, Alaska. Environ Res. 2009;109(3):281–286. https://doi.org/10.1016/j.envres.2008.11.004
31. Weyrich LS, Duchene S, Soubrier J, *et al.* Neanderthal behaviour, diet, and disease inferred from ancient DNA in dental calculus. Nature 2017;544(7650):357–361. https://doi.org/10.1038/nature21674
32. Shah SFH, Shah SHH, Ahmad L, Sherwani RAK, Aslam M. A study on various pollutants in water and their effect on blood of the consumers. Appl Water Sci. 2021;11(10):164. https://doi.org/10.1007/s13201-021-01498-y
33. Lin EZ, Esenther S, Mascelloni M, Irfan F, Godri Pollitt KJ. The fresh air wristband: A wearable air pollutant sampler. Environ Sci Technol Lett. 2020;7(5):308–314. https://doi.org/10.1021/acs.estlett.9b00800
34. Coggon D. Questionnaire based exposure assessment methods. Sci Total Environ. 1995;168(2):175–178. https://doi.org/10.1016/0048-9697(95)04621-7
35. De Souza YG, Greenspan JS. Biobanking past, present and future: Responsibilities and benefits. Aids. 2013;27(3):303–312. https://doi.org/10.1097/QAD.0b013e32835c1244
36. Kuwayama K, Miyaguchi H, Iwata YT, *et al.* Strong evidence of drug-facilitated crimes by hair analysis using LC–MS/MS after micro-segmentation. Forensic Toxicol. 2019;37(2):480–487. https://doi.org/10.1007/s11419-019-00472-3
37. Calafat AM, Ye X, Silva MJ, Kuklenyik Z, Needham LL. Human exposure assessment to environmental chemicals using biomonitoring. Int J Androl. 2006;29(1):166–171. https://doi.org/10.1111/j.1365-2605.2005.00570.x
38. Frye RE, Cakir J, Rose S, *et al.* Early life metal exposure dysregulates cellular bioenergetics in children with regressive autism spectrum disorder. Transl Psychiatry. 2020;10(1):1–12. https://doi.org/10.1038/s41398-020-00905-3
39. Rappaport SM, Barupal DK, Wishart D, Vineis P, Scalbert A. The blood exposome and its role in discovering causes of disease. Environ Health Perspect. 2014;122(8):769–774. https://doi.org/10.1289/ehp.1308015
40. Hsieh CY, Wang SL, Fadrowski JJ, Navas-Acien A, Kuo CC. Urinary concentration correction methods for arsenic, cadmium, and mercury: A systematic review of practice-based evidence. Curr Environ Health Rep. 2019;6(3):188–199. https://doi.org/10.1007/s40572-019-00242-8
41. Middleton DRS, Watts MJ, Polya DA. A comparative assessment of dilution correction methods for spot urinary analyte concentrations in a UK population exposed to arsenic in drinking water. Environ Int. 2019;130:104721. https://doi.org/10.1016/j.envint.2019.03.069
42. Haswell LE, Papadopoulou E, Newland N, Shepperd CJ, Lowe FJ. A cross-sectional analysis of candidate biomarkers of biological effect in smokers, never-smokers and ex-smokers. Biomarkers 2014;19(5):356–367. https://doi.org/10.3109/1354750X.2014.912354
43. Dickens JA, Miller BE, Edwards LD, *et al.*; Evaluation of COPD Longitudinally to Identify Surrogate Endpoints (ECLIPSE) Study Investigators. COPD association and repeatability of blood biomarkers in the ECLIPSE cohort. Respir Res. 2011;12(1):146. https://doi.org/10.1186/1465-9921-12-146
44. Xu MY, Wang P, Sun YJ, Yang L, Wu YJ. Identification of metabolite biomarkers in serum of rats exposed to chlorpyrifos and cadmium. Sci Rep. 2020;10(1):4999. https://doi.org/10.1038/s41598-020-61982-4
45. IBBL (Integrated BioBank of Luxembourg)—About Us. IBBL. Accessed April 21, 2021. https://www.ibbl.lu/about-ibbl/
46. Hammel SC, Phillips AL, Hoffman K, Stapleton HM. Evaluating the use of silicone wristbands to measure personal exposure to brominated flame retardants. Environ Sci Technol. 2018;52(20):11875–11885. https://doi.org/10.1021/acs.est.8b03755
47. Ruiz-Castell M, Kandala NB, Kuemmerle A, *et al.* Hypertension burden in Luxembourg: Individual risk factors and geographic variations, 2013 to 2015 European Health Examination Survey. Medicine (Baltimore). 2016;95(36):e4758. https://doi.org/10.1097/MD.0000000000004758
48. Samouda H, Ruiz-Castell M, Bocquet V, *et al.* Geographical variation of overweight, obesity and related risk factors: Findings from the European Health Examination Survey in Luxembourg, 2013–2015. PLoS ONE. 2018;13(6):e0197021. https://doi.org/10.1371/journal.pone.0197021
49. Booij K, Smedes F, Van Weerlee EM, Honkoop PJC. Environmental monitoring of hydrophobic organic contaminants: The case of mussels versus semipermeable membrane devices. Environ Sci Technol. 2006;40(12):3893–3900. https://doi.org/10.1021/es052492r
50. Reijnders PJH, Aguilar A, Borrell A. Pollution and marine mammals. In: WF Perrin, B Würsig, JGM Thewissen, eds. Encyclopedia of Marine Mammals. 2nd ed. Academic Press; 2009:890–898. https://doi.org/10.1016/B978-0-12-373553-9.00205-4
51. Perone A, Cocozza C, Cherubini P, *et al.* Oak tree-rings record spatial–temporal pollution trends from different sources in Terni (Central Italy). Environ Pollut. 2018;233:278–289. https://doi.org/10.1016/j.envpol.2017.10.062
52. Ruppert H, Wischow D, Rushmer T, Gestinger A, Jackson MD. Tree rings—A questionable indicator of heavy metal pollution in air or soil. Elsevier Sci. 2006;70(18):546. https://doi.org/10.1016/j.gca.2006.06.1007
53. Kylin H, Sjödin A. Accumulation of airborne hexachlorocyclohexanes and DDT in pine needles. Environ Sci Technol. 2003;37(11):2350–2355. https://doi.org/10.1021/es0201395
54. Ockenden WA, Steinnes E, Parker C, Jones KC. Observations on persistent organic pollutants in plants: Implications for their use as passive air samplers and for POP cycling. Environ Sci Technol. 1998;32(18):2721–2726. https://doi.org/10.1021/-es980150y
55. Koizumi A, Harada KH, Inoue K, *et al.* Past, present, and future of environmental specimen banks. Environ Health Prev Med. 2009;14(6):307–318. https://doi.org/10.1007/s12199-009-0101-1
56. Wang M, Carver JJ, Phelan VV, *et al.* Sharing and community curation of mass spectrometry data with GNPS. Nat Biotechnol. 2016;34(8):828–837. https://doi.org/10.1038/nbt.3597
57. Alygizakis NA, Oswald P, Thomaidis NS, *et al.* NORMAN digital sample freezing platform: A European virtual platform to exchange liquid chromatography high resolution-mass spectrometry data and screen suspects in "digitally frozen" environmental samples. TrAC Trends Anal Chem. 2019;115:129–137. https://doi.org/10.1016/j.trac.2019.04.008
58. Alygizakis NA, Samanipour S, Hollender J, *et al.* Exploring the potential of a global emerging contaminant early warning network through the use of retrospective suspect screening with high-resolution mass spectrometry. Environ Sci Technol. 2018;52(9):5135–5144. https://doi.org/10.1021/acs.est.8b00365
59. Nagl C, Spangl W. Sampling points for air quality. Public Health and Food Safety. 2019:104 (published online).

60. Bakand S, Hayes A. Toxicological considerations, toxicity assessment, and risk management of inhaled nanoparticles. IJMS. 2016;17(6):929. https://doi.org/10.3390/ijms17060929
61. Hissler C, Stille P, Krein A, *et al.* Identifying the origins of local atmospheric deposition in the steel industry basin of Luxembourg using the chemical and isotopic composition of the lichen *Xanthoria parietina*. Sci Total Environ. 2008;405(1–3): 338–344. https://doi.org/10.1016/j.scitotenv.2008.05.029
62. Mosley S Environmental history of air pollution and protection. In: Agnoletti M, Neri Serneri S, eds. The Basic Environmental History. Vol. 4. Environmental History. Springer International Publishing; 2014:143–165. https://doi.org/10.1007/978-3-319-09180-862.
63. Valenti C, Pozzi P, Busia A, *et al.* Respiratory illness and air pollution from the steel industry: The case of Piquiá de Baixo, Brazil (Preliminary report). Multidiscip Respir Med. 2016;11(1): 41. https://doi.org/10.1186/s40248-016-0077-9
64. Data Visualizations. Institute for Health Metrics and Evaluation. Accessed May 25, 2021. http://www.healthdata.org/results/data-visualizations
65. Number of Deaths by Risk Factor. Our World in Data. Accessed December 17, 2021. https://ourworldindata.org/grapher/number-of-deaths-by-risk-factor
66. State of Global Air. Accessed May 25, 2021. https://www.stateofglobalair.org/
67. Calderón-Garcidueñas L, Azzarelli B, Acuna H, *et al.* Air pollution and brain damage. Toxicol Pathol. 2002;30(3):373–389. https://doi.org/10.1080/01926230252929954
68. Moschet C, Anumol T, Lew BM, Bennett DH, Young TM. Household dust as a repository of chemical accumulation: New insights from a comprehensive high-resolution mass spectrometric study. Environ Sci Technol. 2018;52(5): 2878–2887. https://doi.org/10.1021/acs.est.7b05767
69. Han Q, Liu Y, Feng X, *et al.* Pollution effect assessment of industrial activities on potentially toxic metal distribution in windowsill dust and surface soil in central China. Sci Total Environ. 2021; 759(11):144023. https://doi.org/10.1016/j.scitotenv.2020.144023
70. Rostkowski P, Haglund P, Aalizadeh R, *et al.* The strength in numbers: Comprehensive characterization of house dust using complementary mass spectrometric techniques. Anal Bioanal Chem. 2019;411(10):1957–1977. https://doi.org/10.1007/s00216-019-01615-6
71. Butte W, Heinzow B. Pollutants in house dust as indicators of indoor contamination. Rev Environ Contam Toxicol. 2002;175: 1–46.
72. Melymuk L, Demirtepe H, Jílková SR. Indoor dust and associated chemical exposures. Curr Opin Environ Sci Health. 2020; 15:1–6. https://doi.org/10.1016/j.coesh.2020.01.005
73. Whitehead T, Metayer C, Buffler P, Rappaport SM. Estimating exposures to indoor contaminants using residential dust. J Expo Sci Environ Epidemiol. 2011;21(6):549–564. https://doi.org/10.1038/jes.2011.11
74. Ramírez N, Özel MZ, Lewis AC, Marcé RM, Borrull F, Hamilton JF. Exposure to nitrosamines in thirdhand tobacco smoke increases cancer risk in non-smokers. Environ Int. 2014;71: 139–147. https://doi.org/10.1016/j.envint.2014.06.012
75. Albergamo V, Schollée JE, Schymanski EL, *et al.* Nontarget screening reveals time trends of polar micropollutants in a riverbank filtration system. Environ Sci Technol. 2019;53(13): 7584–7594. https://doi.org/10.1021/acs.est.9b01750
76. Shiklomanov I. World fresh water resource. In: Gleick PH, ed. Water in Crisis. Oxford University Press; 1993:13–15.
77. EEA. *The European Environment: State and Outlook 2020: Knowledge for Transition to a Sustainable Europe*. Publications Office; 2019. Accessed July 5, 2021. https://data.europa.eu/doi/10.2800/96749
78. Cook PG. Introduction to Isotopes and Environmental Tracers as Indicators of Groundwater Flow. The Groundwater Project; 2020.
79. Jasechko S. Global isotope hydrogeology—review. Rev Geophys. 2019;57(3):835–965. https://doi.org/10.1029/2018RG000627
80. Cook PG, Böhlke JK. Determining timescales for groundwater flow and solute transport. In: PG Cook, AL Herczeg, eds. Environmental Tracers in Subsurface Hydrology. Springer US; 2000:1–30. https://doi.org/10.1007/978-1-4615-4557-6_1
81. Pidwirny M. *The Hydrologic Cycle*. Fundamentals of Physical Geography. 2nd ed. 2006. Accessed July 5, 2021. http://www.physicalgeography.net/fundamentals/8b.html
82. Suckow A. The age of groundwater—definitions, models and why we do not need this term. Appl Geochem. 2014;50: 222–230. https://doi.org/10.1016/j.apgeochem.2014.04.016
83. Freeze RA, Cherry JA. Groundwater. Prentice-Hall; 1979.
84. Gallé T, Koehler C, Plattes M, *et al.* Large-scale determination of micropollutant elimination from municipal wastewater by passive sampling gives new insights in governing parameters and degradation patterns. Water Res. 2019;160:380–393. https://doi.org/10.1016/j.watres.2019.05.009
85. Huizer M, ter Laak TL, de Voogt P, van Wezel AP. Wastewater-based epidemiology for illicit drugs: A critical review on global data. Water Res. 2021; 207:117789. https://doi.org/10.1016/j.watres.2021.117789
86. Lorenzo M, Picó Y. Wastewater-based epidemiology: Current status and future prospects. Curr Opin Environ Sci Health. 2019;9:77–84. https://doi.org/10.1016/j.coesh.2019.05.007
87. Bijlsma L, Botero-Coy AM, Rincón RJ, Peñuela GA, Hernández F. Estimation of illicit drug use in the main cities of Colombia by means of urban wastewater analysis. Sci Total Environ. 2016; 565:984–993. https://doi.org/10.1016/j.scitotenv.2016.05.078
88. Been F, Bastiaensen M, Lai FY, *et al.* Mining the chemical information on urban wastewater: Monitoring human exposure to phosphorus flame retardants and plasticizers. Environ Sci Technol. 2018;52(12):6996–7005. https://doi.org/10.1021/acs.est.8b01279
89. Sims N, Kasprzyk-Hordern B. Future perspectives of wastewater-based epidemiology: Monitoring infectious disease spread and resistance to the community level. Environ Int. 2020;139:105689. https://doi.org/10.1016/j.envint.2020.105689
90. Alygizakis N, Markou AN, Rousis NI, *et al.* Analytical methodologies for the detection of SARS-CoV-2 in wastewater: Protocols and future perspectives. Trends Analyt Chem. 2021;134: 116125. https://doi.org/10.1016/j.trac.2020.116125
91. Lundy L, Fatta-Kassinos D, Slobodnik J, *et al.* Making waves: Collaboration in the time of SARS-CoV-2—rapid development of an international co-operation and wastewater surveillance database to support public health decision-making. Water Res. 2021;199:117167. https://doi.org/10.1016/j.watres.2021.117167
92. Chiaia-Hernandez AC, Krauss M, Hollender J. Screening of lake sediments for emerging contaminants by liquid chromatography atmospheric pressure photoionization and electrospray ionization coupled to high resolution mass spectrometry. Environ Sci Technol. 2013;47(2):976–986. https://doi.org/10.1021/es303888v
93. Chiaia-Hernandez AC, Schymanski EL, Kumar P, Singer HP, Hollender J. Suspect and nontarget screening approaches to identify organic contaminant records in lake sediments. Anal Bioanal Chem. 2014;406(28):7323–7335. https://doi.org/10.1007/s00216-014-8166-0
94. Akoto O, Azuure AA, Adotey KD. Pesticide residues in water, sediment and fish from Tono Reservoir and their health risk

implications. SpringerPlus. 2016;5(1):1849. https://doi.org/10.1186/s40064-016-3544-z
95. Slobodnik J, Alexandrov B, Arabidze M, Guchmanidze A, Komorin V. Improving environmental monitoring in the Black Sea—Phase II (EMBLAS-II) ENPI/2013/313-169, UNDP Regional Bureau for Europe and the CIS. EMBLAS PROJECT. Published 2016. Accessed October 20, 2021. https://emblasproject.org/wp-content/uploads/2017/04/Joint-Black-Sea-Surveys-2016_16.pdf
96. US EPA O. Exposure Assessment Tools by Media—Water and Sediment. Published April 23, 2015. Accessed October 20, 2021. https://www.epa.gov/expobox/exposure-assessment-tools-media-water-and-sediment
97. Marx SK, Kamber BS, McGowan HA, Zawadzki A. Atmospheric pollutants in alpine peat bogs record a detailed chronology of industrial and agricultural development on the Australian continent. Environ Pollut. 2010;158(5):1615–1628. https://doi.org/10.1016/j.envpol.2009.12.009
98. Yang Q, Li Z, Lu X, Duan Q, Huang L, Bi J. A review of soil heavy metal pollution from industrial and agricultural regions in China: Pollution and risk assessment. Sci Total Environ. 2018;642:690–700. https://doi.org/10.1016/j.scitotenv.2018.06.068
99. Yuan J, Lu Y, Wang C, *et al.* Ecology of industrial pollution in China. Ecosyst Health Sustain. 2020;6(1):1779010. https://doi.org/10.1080/20964129.2020.1779010
100. Vehus T, Roberg-Larsen H, Waaler J, *et al.* Versatile, sensitive liquid chromatography mass spectrometry—Implementation of 10 μm OT columns suitable for small molecules, peptides and proteins. Sci Rep. 2016;6(1):37507. https://doi.org/10.1038/srep37507
101. Tchounwou PB, Yedjou CG, Patlolla AK, Sutton DJ. Heavy metal toxicity and the environment. In: A Luch, ed. Molecular, Clinical and Environmental Toxicology: Volume 3: Environmental Toxicology. Experientia Supplementum. Springer; 2012:133–164. https://doi.org/10.1007/978-3-7643-8340-4_6
102. Schofield K. The metal neurotoxins: An important role in current human neural epidemics? IJERPH. 2017;14(12):1511. https://doi.org/10.3390/ijerph14121511
103. Wani AL, Ara A, Usmani JA. Lead toxicity: A review. Interdiscip Toxicol. 2015;8(2):55–64. https://doi.org/10.1515/intox-2015-0009
104. Stone FGA, West R. Advances in Organometallic Chemistry. Vol. 41. Academic Press; 1997.
105. Harada M. Minamata disease: Methylmercury poisoning in Japan caused by environmental pollution. Crit Rev Toxicol. 1995;25(1):1–24. https://doi.org/10.3109/10408449509089885
106. Wilbur S, Wahlen R, Morton K. Organotin analysis by GC and LC ICP-MS. LC GC N Am 2004;22:33–33.
107. Rahman MM. Insecticide substitutes for DDT to control mosquitoes may be causes of several diseases. Environ Sci Pollut Res Int. 2013;20(4):2064–2069. https://doi.org/10.1007/s11356-012-1145-0
108. Richardson SD, Kimura SY. Water analysis: Emerging contaminants and current issues. Anal Chem. 2020;92(1):473–505. https://doi.org/10.1021/acs.analchem.9b05269
109. Chin-Chan M, Navarro-Yepes J, Quintanilla-Vega B. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. Front Cell Neurosci. 2015;9:124. https://doi.org/10.3389/fncel.2015.00124
110. Fiedler H, Kennedy T, Henry BJ. A critical review of a recommended analytical and classification approach for organic fluorinated compounds with an emphasis on per- and polyfluoroalkyl substances. Integr Environ Assess Manag. 2021;17(2):331–351. https://doi.org/10.1002/ieam.4352
111. Salgueiro-González N, Castiglioni S, Zuccato E, Turnes-Carou I, López-Mahía P, Muniategui-Lorenzo S. Recent advances in analytical methods for the determination of 4-alkylphenols and bisphenol A in solid environmental matrices: A critical review. Anal Chim Acta. 2018;1024:39–51. https://doi.org/10.1016/j.aca.2018.02.081
112. Tadeo JL. Analysis of Pesticides in Food and Environmental Samples. 2nd ed. CRC Press; 2019.
113. Lee HB. Review of analytical methods for the determination of nonylphenol and related compounds in environmental samples. Water Qual Res J. 1999;34(1):3–36. https://doi.org/10.2166/wqrj.1999.002
114. Tisler S, Pattison DI, Christensen JH. Correction of matrix effects for reliable non-target screening LC–ESI–MS analysis of wastewater. Anal Chem. 2021;93(24):8432–8441. https://doi.org/10.1021/acs.analchem.1c00357
115. Hollender J, Schymanski EL, Singer HP, Ferguson PL. Nontarget screening with high resolution mass spectrometry in the environment: Ready to go? Environ Sci Technol. 2017;51(20):11505–11512. https://doi.org/10.1021/acs.est.7b02184
116. Kruve A, Kaupmees K, Liigand J, Leito I. Negative electrospray ionization via deprotonation: Predicting the ionization efficiency. Anal Chem. 2014;86(10):4822–4830. https://doi.org/10.1021/ac404066v
117. Oss M, Kruve A, Herodes K, Leito I. Electrospray ionization efficiency scale of organic compounds. Anal Chem. 2010;82(7):2865–2872. https://doi.org/10.1021/ac902856t
118. Malm L, Palm E, Souihi A, Plassmann M, Liigand J, Kruve A. Guide to semi-quantitative non-targeted screening using LC/ESI/HRMS. Molecules. 2021;26(12):3524. https://doi.org/10.3390/molecules26123524
119. Sacher F, Ehmann M, Gabriel S, Graf C, Brauch HJ. Pharmaceutical residues in the river Rhine—results of a one-decade monitoring programme. J Environ Monit. 2008;10(5):664–670. https://doi.org/10.1039/B800701B
120. ISO (International Organization for Standardization)—Technical Committee ISO/TC 147. ISO/DIS 21253-1:2018(E)/Water quality Multi-compound class methods—Part 1: Criteria for the identification of target compounds by gas and liquid chromatography and mass spectrometry. Published online 2018.
121. Schymanski EL, Jeon J, Gulde R, *et al.* Identifying small molecules via high resolution mass spectrometry: Communicating confidence. Environ Sci Technol. 2014;48(4):2097–2098. https://doi.org/10.1021/es5002105
122. CAS REGISTRY. CAS. Accessed August 2, 2021. https://www.cas.org/cas-data/cas-registry
123. PubChem. PubChem. Accessed April 27, 2021. https://pubchem.ncbi.nlm.nih.gov/
124. Pence HE, Williams A. ChemSpider: An online chemical information resource. J Chem Educ. 2010;87(11):1123–1124. https://doi.org/10.1021/ed100697w
125. Wishart DS, Feunang YD, Marcu A, *et al.* HMDB 4.0: The human metabolome database for 2018. Nucleic Acids Res. 2018;46(D1):D608–D617. https://doi.org/10.1093/nar/gkx1089
126. Lowe CN, Williams AJ. Enabling high-throughput searches for multiple chemical data using the U.S.-EPA CompTox chemicals dashboard. J Chem Inf Model. 2021;61(2):565–570. https://doi.org/10.1021/acs.jcim.0c01273
127. Williams AJ, Grulke CM, Edwards J, *et al.* The CompTox chemistry dashboard: A community data resource for environmental chemistry. J Cheminform. 2017;9(1):61. https://doi.org/10.1186/s13321-017-0247-6
128. NORMAN Network. NORMAN Suspect List Exchange (NORMAN-SLE). Published 2021. Accessed April 22, 2021. https://www.norman-network.com/nds/SLE/

129. Barupal DK, Fiehn O. Generating the blood exposome database using a comprehensive text mining and database fusion approach. Environ Health Perspect. 2019;127(9):97008. https://doi.org/10.1289/EHP4713
130. Neveu V, Nicolas G, Salek RM, Wishart DS, Scalbert A. Exposome-Explorer 2.0: An update incorporating candidate dietary biomarkers and dietary associations with cancer risk. Nucleic Acids Res. 2020;48(D1):D908–D912. https://doi.org/10.1093/nar/gkz1009
131. Wishart D, Arndt D, Pon A, *et al.* T3DB: The toxic exposome database. Nucleic Acids Res. 2015;43(Database issue): D928–934. https://doi.org/10.1093/nar/gku1004
132. Zaslavsky L, Cheng T, Gindulyte A, *et al.* Discovering and summarizing relationships between chemicals, genes, proteins, and diseases in PubChem. Front Res Metr Anal. 2021. https://doi.org/10.3389/frma.2021.689059
133. Schymanski EL, Bolton EE, Kondic T, Thiessen P, Zhang J. PubChemLite for exposomics. Published online October 31, 2020. https://doi.org/10.5281/zenodo.4183801
134. MassBank of North America. Accessed May 17, 2021. https://mona.fiehnlab.ucdavis.edu/downloads
135. National Institute of Standards and Technology. NIST. Accessed May 26, 2021. https://www.nist.gov/
136. Guijas C, Montenegro-Burke JR, Domingo-Almenara X, *et al.* METLIN: A technology platform for identifying knowns and unknowns. Anal Chem. 2018;90(5):3156–3164. https://doi.org/10.1021/acs.analchem.7b04424
137. Horai H, Arita M, Kanaya S, *et al.* MassBank: A public repository for sharing mass spectral data for life sciences. J Mass Spectrom. 2010;45(7):703–714. https://doi.org/10.1002/jms.1777
138. MassBank—Consortium and its Contributors. MassBank/MassBank-Data: Release Version 2021.03. Zenodo; 2021. https://doi.org/10.5281/ZENODO.4563726
139. Blaženović I, Kind T, Sa MR, *et al.* Structure annotation of all mass spectra in untargeted metabolomics. Anal Chem. 2019;91(3):2155–2162. https://doi.org/10.1021/acs.analchem.8b04698
140. Wang L, Xing X, Chen L, *et al.* Peak annotation and verification engine for untargeted LC–MS metabolomics. Anal Chem. 2019;91(3):1838–1846. https://doi.org/10.1021/acs.analchem.8b03132
141. Helmus R, ter Laak TL, van Wezel AP, de Voogt P, Schymanski EL. patRoon: Open source software platform for environmental mass spectrometry based non-target screening. J Cheminform. 2021;13(1). https://doi.org/10.1186/:1.020-00477-w
142. Tautenhahn R, Patti GJ, Rinehart D, Siuzdak G. XCMS online: A web-based platform to process untargeted metabolomic data. Anal Chem. 2012;84(11):5035–5039. https://doi.org/10.1021/ac300698c
143. Tsugawa H, Ikeda K, Takahashi M, *et al.* A lipidome atlas in MS-DIAL 4. Nat Biotechnol. 2020;38(10):1159–1163. https://doi.org/10.1038/s41587-020-0531-2
144. Ruttkies C, Schymanski EL, Wolf S, Hollender J, Neumann S. MetFrag relaunched: Incorporating strategies beyond in silico fragmentation. J Cheminform. 2016;8(1):3. https://doi.org/10.1186/s13321-016-0115-9
145. Oberacher H, Sasse M, Antignac JP, *et al.* A European proposal for quality control and quality assurance of tandem mass spectral libraries. Environ Sci Eur. 2020;32(1):43. https://doi.org/10.1186/s12302-020-00314-9
146. Dührkop K, Shen H, Meusel M, Rousu J, Böcker S. Searching molecular structure databases with tandem mass spectra using CSI:FingerID. Proc Natl Acad Sci USA. 2015;112(41):12580–12585. https://doi.org/10.1073/pnas.1509788112
147. Cooper BT, Yan X, Simon Y, Tchekhovskoi DV, Mirokhin YA, Stein SE. Hybrid search: A method for identifying metabolites absent from tandem mass spectrometry libraries. Anal Chem. 2019;91(21):13924–13832. https://doi.org/10.1021/acs.analchem.9b03415
148. Uppal K, Walker DI, Liu K, Li S, Go YM, Jones DP. Computational metabolomics: A framework for the million metabolome. Chem Res Toxicol. 2016;29(12):1956–1975. https://doi.org/10.1021/acs.chemrestox.6b00179
149. Agache I, Miller R, Gern JE, *et al.* Emerging concepts and challenges in implementing the exposome paradigm in allergic diseases and asthma: A Practall document. Allergy 2019;74(3):449–463. https://doi.org/10.1111/all.13690
150. Bioconductor. Accessed May 18, 2021. https://www.bioconductor.org/help/faq/
151. Exposome Data Analysis. Accessed April 19, 2021. https://bioconductor.org/packages/release/bioc/vignettes/rexposome/inst/doc/exposome_data_analysis.html
152. Zhao F, Li L, Chen Y, *et al.* Risk-based chemical ranking and generating a prioritized human exposome database. Environ Health Perspect. 2021; 129(4):47014. https://doi.org/10.1289/EHP7722
153. Juarez PD, Matthews-Juarez P. Applying an exposome-wide (ExWAS) approach to cancer research. Front Oncol. 2018;8:313. https://doi.org/10.3389/fonc.2018.00313
154. Chadeau-Hyam M, Ebbels TMD, Brown IJ, *et al.* Metabolic profiling and the metabolome-wide association study: Significance level for biomarker identification. J Proteome Res. 2010;9(9):4620–4627. https://doi.org/10.1021/pr1003449
155. Walker DI, Pennell KD, Uppal K, *et al.* Pilot metabolome-wide association study of benzo(a)pyrene in serum from military personnel. J Occup Environ Med. 2016;58(8 Suppl 1):S44–52. https://doi.org/10.1097/JOM.0000000000000772
156. David A, Chaker J, Price EJ, *et al.* Towards a comprehensive characterisation of the human internal chemical exposome: Challenges and perspectives. Environ Int. 2021;156:106630. https://doi.org/10.1016/j.envint.2021.106630
157. Makuleke P, Ngole-Jeme VM. Soil heavy metal distribution with depth around a closed landfill and their uptake by datura stramonium. Appl Environ Soil Sci. 2020;2020:e8872475. https://doi.org/10.1155/2020/8872475
158. Pinho MGM, Mackenbach JD, den Braver NR, Beulens JJW, Brug J, Lakerveld J. Recent changes in the Dutch foodscape: Socioeconomic and urban–rural differences. Int J Behav Nutr Phys Act. 2020;17(1):43. https://doi.org/10.1186/s12966-020-00944-5
159. González A. GIS in environmental assessment: A review of current issues and future needs. J Environ Assess Policy Manag. 2012;14. https://doi.org/10.1142/S146433321250007X
160. ESFRI Announces new RIs for Roadmap 2021 | www.esfri.eu. Accessed August 3, 2021. https://www.esfri.eu/latest-esfri-news/new-ris-roadmap-2021