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Water in the Exposome

KWR

Bridging Science to Practice

Colophon

Water in the Exposome

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Managementsamenvatting

Waterexposoomonderzoek helpt de invloed van water op de gezondheid bloot te leggen

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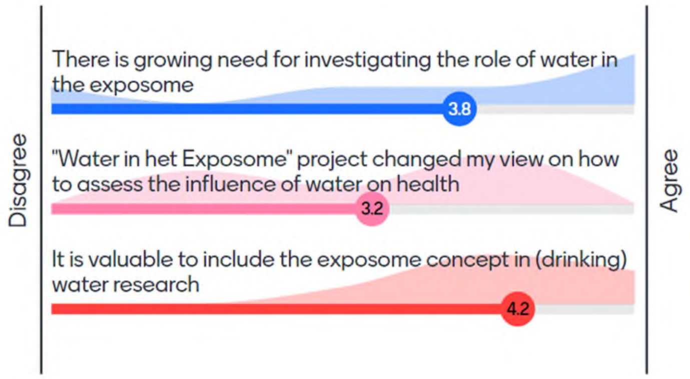
Water, essentieel voor het leven, speelt een rol in het exposoom – de som van alle externe blootstellingen en interne reacties daarop die de menselijke gezondheid kunnen beïnvloeden. Terwijl waterprofessionals drinkwatersystemen optimaliseren, blijft de relatieve blootstellingsimpact van kraanwater ongrijpbaar. Door principes van het exposoom-concept te implementeren, kunnen waterprofessionals de waterkwaliteit integraler interpreteren. Uitdagend is dat hierbij moet worden samengewerkt over (BTO-)disciplines heen. Het omarmen van inzichten uit exposoomonderzoek betekent een breder perspectief in de benadering van waterkwaliteit, wat gezondheid en duurzaamheid ten goede kan komen.



Meningen gepeild tijdens interactieve bijeenkomsten met exposoom-, drinkwater- en KWR-experts.

Belang: Wat betekent gebruik van het exposoom-concept voor gezondheid en de watersector?
Het exposoom wordt steeds meer beschouwd als een cruciaal raamwerk om gezondheid en ziekte te begrijpen. Het exposoom staat dan voor de levenslange blootstelling aan de som van verschillende niet-genetische factoren, en hun invloed op de gezondheid. Het exposoom is dus belangrijk, maar ons begrip van de volledige samenstelling en impact van het exposoom is beperkt, vooral binnen de context van de (drink)watersector. In dit onderzoek is verkend in hoeverre exposoomonderzoek kan worden uitgerold in de watersector. We hebben de raakpunten tussen exposoomonderzoek en de waterpraktijk verkend rond de mogelijke implicaties van het exposoom-concept voor onderzoek naar waterkwaliteit en gezondheid, en voor waterbeheerstrategieën.

Aanpak: Interactieve bijeenkomsten met exposoomdeskundigen en literatuuronderzoek
Om het conceptuele raamwerk van het exposoom en het nut ervan voor de watersector te verduidelijken, organiseerde KWR meerdere interactieve bijeenkomsten met exposoomexperts en drinkwaterexperts van waterbedrijven. Ook werd de nieuwste wetenschappelijke literatuur geraadpleegd en werden interacties met de exposoom-gemeenschap gefaciliteerd tijdens een internationale exposoomconferentie.

Resultaten: Toepassen exposoomconcept in drinkwatersector kan bijdragen aan gezondheid
De resultaten van dit onderzoek laten zien dat een integraal begrip van omgevingsinvloeden en biologische reacties gedurende het hele leven, waarbij de gezamenlijke bijdrage van alle

blootstellingsdomeinen aan chronische ziekten wordt erkend en tegelijkertijd de relatieve bijdrage van water wordt benadrukt van belang is voor het interpreteren van het totaal aan gezondheids-implicaties van het drinken van (Nederlands) drinkwater. Ons onderzoek laat ook zien dat er in het huidige exposoomonderzoek te weinig aandacht is voor de rol van drinkwater.
Een drinkwatersector die het exposoomconcept begrijpt en toepast, kan een bijdrage leveren aan een gezonde samenleving. Het exposoomconcept kan de drinkwatersector beter inzicht geven in de manier waarop de waterkwaliteit en -kwantiteit de menselijke blootstelling gedurende het hele leven kan beïnvloeden, en daarop acteren. Het integreren van verschillende disciplines zoals chemische veiligheid, biologische veiligheid, sociale wetenschappen en hydroinformatica, en betrokkenheid van belanghebbenden is cruciaal voor effectief exposoomonderzoek in de watersector. Deze interdisciplinaire aanpak zal studies gericht op verschillende gebieden faciliteren, zoals het holomicrobioom, op effecten gebaseerde methoden, mengseltoxiciteit, (op afvalwater gebaseerde) epidemiologie, sociale waarden van klanten en adaptief duurzaam waterbeheer.

Voortdurende allianties tussen onderzoeks-instellingen en de drinkwatersector zullen ons begrip van de rol van water als milieufactor die de menselijke gezondheid beïnvloedt verder verdiepen en bijdragen aan effectieve waterbeheerpraktijken.

Toepassing: Bevorder synergie en domeinoverschrijdende samenwerking
De implementatie van exposoomonderzoek in de (drink)watersector vereist gezamenlijke inspanningen en methodologische synergieën tussen disciplines. Stakeholders, waaronder universiteiten, overheidsinstellingen, bedrijven en stichtingen, worden opgeroepen om bij te dragen aan het verzamelen en analyseren van diverse soorten exposoomdata, in lijn met de ambities van de Nederlandse Topsector. Door onderzoeks-onderwerpen te prioriteren en domein-overschrijdende samenwerking tussen deskundigen te bevorderen, vertegenwoordigt dit rapport een belangrijke stap in de samenwerking tussen KWR, universiteiten en de Nederlands-Vlaamse drinkwatersector om ons begrip van de rol van (drinkwater)water in het exposoom te verdiepen.

Rapport
Dit onderzoek is beschreven in het rapport *Water in the Exposome* (BTO 2024.043) en het begeleidende rapport *Exposoomdenken: Risicoperceptie en ontwikkelingen* (BTO 2024.034)

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Summary

The exposome encompasses lifelong exposure to non-genetic factors like lifestyle, diet, socio-economic conditions, and environmental elements. It complements the human genome in explaining health and disease. Environmental risk factors, including pollution, contribute to a substantial part of global morbidity and mortality, with air pollution being a leading cause. However, our understanding of the exposome's full impact on health is still widely incomplete. The present report presents an integrated exploratory study gathering knowledge about exposome research and attempts to identify interfaces with various facets of (drinking) water practice.

To start, the exposome concept is explained in detail. The definition includes environmental influences and biological responses throughout life which highlights the exposome as being as fundamental to medicine and public health as, for example, the genome. Currently, research on the exposome is dispersed across traditional scientific fields, hindering a holistic understanding of its impact, including in the drinking water sector. All exposure domains contribute to chronic diseases and should be studied collectively. To this end, large exposome projects have recently been initiated in the European Union.

Current research and regulations do not yet fully address the complexity of environmental, biological, and social factors affecting human health. To protect current and future generations from the health impacts of environmental pollutants and other factors, a systematic and coherent effort is needed to devise relevant and complementary approaches. This involves recognizing and deeply exploring the connection between the external environment (e.g., air, water, food) and the internal environment within the body, where harmful chemicals can disrupt physiological processes.

An increasingly coordinated effort by various stakeholders (incl. universities, government agencies, companies, and foundations) to explore and understand the exposome is called for since it involves collecting diverse exposome data types and sources, leading to increased complexity. While recognizing that the complete exposome may never be fully characterized, the development of new risk assessment methods and synergistic dialogues across disciplinary realms hold promise in the investigation of the complex environment and can help steer science, regulation, and society into a healthier future.

In this report, the significance of the exposome concept for the drinking water practice is explored and an outlook is given on the possibilities to formulate new research or use tools from the exposome field. In addition, exposome research topics that are in line with the current BTO program are identified. Ultimately, exposome research topics were identified and prioritized for the (drinking) water sector, such as integrated assessment of relevant water contaminants and pathogens, identification of context-specific exposure factors contributing to health risks, standardization of data collection and analysis to help ascertain causal links, support methodological synergism between chemical and biological screening methods in waters and strengthen cross-domain experts cooperation.

Contents

How to read this report

In Chapter 1 the concept of ’human exposome’ is explained. The exposome encompasses the cumulative measure of (measurable) environmental influences and associated biological responses of humans throughout their lifespan, including exposures from the environment, diet, behavior, and endogenous processes. Chapter 2 explains the different domains that can be considered in exposome research, such as internal/external exposome, and categories of external exposome. In Chapter 3, methods are described to measure and quantify parts of the exposome. In Chapter 4 the link between exposome and drinking water is further explained, and its relevance to BTO program topics identified. A companion report on the societal aspects of ‘exposome thinking’ is also introduced. Chapter 5 provides an outlook. What can we learn and use from the exposome concept in the drinking water practice, and what research can be taken up? Chapter 6 concludes the report with overarching remarks and perspectives, summarizing key findings and offering insights for future directions.

1 What is the 'human exposome'?

In 2005, Christopher Wild coined the term "exposome" and laid the groundwork for the concept (Wild, 2005). In short, Dr. Wild proposed that the exposome "includes lifelong exposure to environmental factors (including lifestyle factors), from the prenatal stage". The exposome thus encompasses all non-genetic factors and associated biological responses throughout the life course that can influence our health. In this way, the exposome can be considered as the environmental complement to the human genome, when the latter fails to explain the majority of human disease. While the genome describes all genetic factors, the exposome describes all non-genetic factors that determine health and well-being, such as lifestyle, diet, socio-economic factors, and environmental factors, such as air pollution and chemicals in our environment.

The contribution of these non-genetic factors to morbidity and mortality is significant. The impact of environmental risk factors on health was highlighted by the Global Burden of Disease (GBD) project. Burden of disease from 84 metabolic, environmental, occupational and behavioral risk factors in 195 countries and territories (including risk factors related to water quality such as unsafe water, sanitation and handwashing) was estimated, showing that these modifiable risks contribute to about 60% of deaths worldwide (GBD, 2017). Using exposure-response associations, 9 million deaths per year (16% of all deaths worldwide) can be attributed to air, water and soil pollution alone (Landrigan *et al*., 2018). This makes pollution the biggest cause of disease and premature death in the world today, with air pollution as the leading cause. Vermeulen and colleagues (2020) emphasize that the true environmental impact on health is likely to be underestimated as many (un)known chemicals of concern have not yet been taken into account in this type of research and only less than half of the non-genetic risk burden has been explained, indicating the existence of unknown exposure factors contributing to morbidity and mortality. This underlines the relevance of exposome research to public health and highlights that important knowledge gaps regarding the actual impact of a wide variety of environmental factors on our health still exist.

After the conceptualization of the exposome, responses in science, medicine and other areas were initially slow to emerge despite its relevance (Rappaport and Smith, 2010). Miller & Jones (2014) argue that this is probably because the distinction with exposure assessment has not been overemphasized. In their view, the exposome should explicitly include how our bodies respond to environmental pressures, including epigenetic changes and mutations, as well as the complex chemistry that results from the biochemical reactions that sustain our life. Therefore, they formulated a refined definition of the exposome:

Exposome: The cumulative measure of environmental influences and associated biological responses throughout the lifespan, including exposures from the environment, diet, behavior, and endogenous processes.

Miller & Jones (2014), given its relevance to morbidity and mortality, emphasize that the exposome should be equivalent to the genome as the basis for contemporary medicine and public health. To adequately investigate this, it would theoretically be necessary to map the totality of the exposome (Rappaport & Smith, 2010). However, an obstacle to identifying key environmental influences is the fragmentation of research along traditional scientific fields. When epidemiologists investigate environmental risks, they tend to focus on a particular category of exposures such as air or water pollution, occupation, diet, stress and behavior, or types of infections. This division into classical silos leads to scientific separation and confuses the definition of "environmental exposure”. In fact, all these exposure categories can contribute to chronic disease and should be investigated collectively rather than separately (Rappaport & Smith, 2010). Exposome research represents a significant expansion of previous concepts, offering a more comprehensive understanding of the complex interactions between environmental exposures and health outcomes.

It follows that, despite extensive evidence showing that exposure to specific environmental factors and chemicals can lead to disease, current research approaches and regulatory policies fail to fully grasp and manage the environmental and chemical complexities of our world. A systematic and coherent approach is needed to better protect current and future generations against deleterious health effects of the increasing number of chemical pollutants and other environmental factors like pathogens or irradiation. To develop a more comprehensive picture of environmental exposure, it is important to recognize the difference and relationship between the external environment and the internal environment. The external environment refers to the makeup of all the elements outside of the human body, whereas the internal environment refers to the makeup of all the elements inside the human body. With respect to chemicals, for example, in the external environment, foreign chemicals that affect crucial physiological processes can enter the human body from various sources such as air, water or food. Once inside the body, the internal environment, these absorbed chemical compounds or pathogens with potentially harmful effects can trigger a range of biological effects, depending on the fraction that is free to interact with molecules, cells and tissues. The potential effects include inflammation, oxidative stress, lipid peroxidation, infections, and interference with intestinal flora and other key biological processes. The internal chemical environment fluctuates continuously throughout one’s life due to changes in external and internal influences, such as aging, infections, lifestyle, stress, psychosocial factors, and pre-existing diseases.

Taking an approach, where exposure, in the broadest sense, is not dissected into smaller components but rather considered holistically, undeniably leads to an increase in complexity. This approach combines a wide variety of types and sources of exposome data. This requires the application and development of new research approaches which also well align with the ambitions outlined in the One Health principle (Gao, 2021). The (scientific) literature on the exposome therefore refers to an agnostic approach, which means that although it will probably never be possible to comprehend the completeness of the exposome, the actual exposure throughout life can be estimated as closely as possible (Vermeulen *et al*., 2020).

2 Exposome domains

The human exposome consists of all exposures during a person's life. This definition includes exposures at different levels of resolution, from exposures at the individual level resulting from exogenous and endogenous processes, to exposures affecting entire populations (Niedzwiecki *et al*., 2019). This makes the exposome complex. For practical reasons, it can be divided into different parts.

The most fundamental distinction is that of the internal and external exposome (Figure 1; Wild, 2012). The internal exposome is understood to mean all internal processes in the body such as metabolism, endogenous hormones, body morphology, physical activity, intestinal flora, inflammation, lipid peroxidation, oxidative stress and aging. For example, the interplay between the human (epi)genome and the exposome also influence internal processes. These internal conditions will all affect the cellular environment and are described in different ways, for example as host factors or endogenous factors. Second, there is a wide range of specific external exposures, including radiation, infectious agents, chemical contaminants and environmental pollutants, diet, lifestyle factors (e.g. tobacco and alcohol use), occupation and medical procedures. The external exposome also encompasses the broader social, economic and psychological influences on the individual: social capital, education, financial status, psychological stress, urban and rural environment and climate. This so-called generic external exposome also includes the social determinants of health, and the environment in the earliest (prenatal) stages of life.

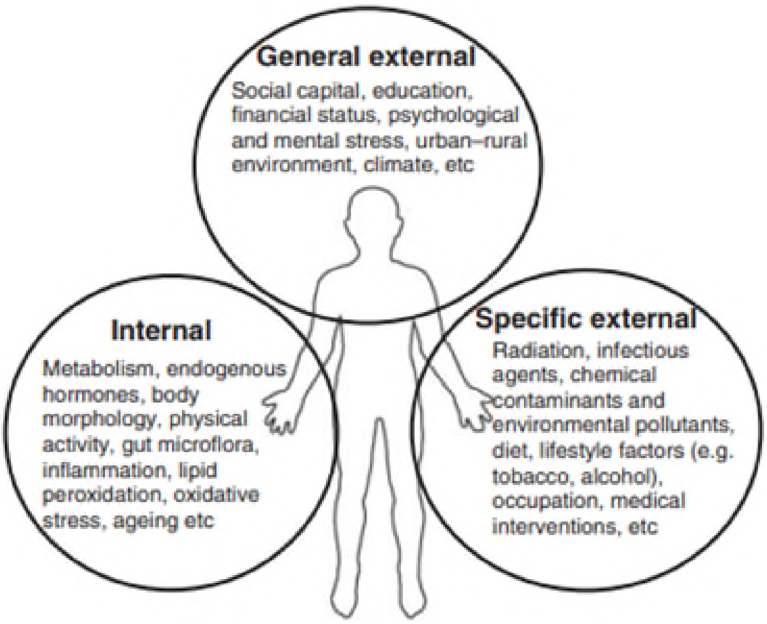

Figure 1. Three different domains of the exposome are schematically represented with some examples (not exhaustive) for each of these domains. Source: Wild, 2012.

The three domains described above overlap and it is sometimes difficult to classify a particular exposure in one domain or the other. Some exposure factors can fit both within the internal or specific external domain, depending on which biological response is being assessed. For example, exercise can lead to a better health condition, or an injury. Thus, the domains not only overlap, but can also be considered as intertwined, for example because the internal exposome may be at least partly a response to influences from the external exposome. The internal exposome can thus also provide an indication of the influence of the environment on health, considering that substances can be internalized from the environment. Considering the complexity of measuring the external exposome, characterizing the internal exposome may provide us with clues about the composition of the former. Mapping and systematically characterizing the internal exposome has only just begun. Identifying biological status indicators that exposure has occurred (biomarkers of exposure) and the surge of unique molecular patterns (molecular fingerprints) in the pathways leading to disease will strengthen our knowledge about non-genetic causes of disease, including exposures to chemicals and pathogens. The representation of cumulative biological responses, by means of measuring (mal)adaptations to external stress in humans and model species, is necessary for operationalizing the exposome concept (Miller & Jones, 2014). Biological responses are the physiological changes resulting from environmental exposures, such as metabolic changes (changes in the metabolome), protein modifications (changes in the proteome), DNA mutations and adducts (changes in the genome), epigenetic changes (reversible changes in the epigenome that influence gene expression) and disruptions to intestinal microbe populations (the microbiome). When it comes to external chemical exposure, the study of biological responses provides a better insight into mechanisms of toxicity and into the intra-/inter-individual variation in susceptibility to toxic effects of substances than a direct measure of internal chemical dose. Biological responses can sometimes even provide information about transient exposures that can no longer be measured directly. Although this type of research lies outside the scope of KWR's research activities, it remains relevant to stay up-to-date on the latest water-related insights from epidemiological studies, e.g., via collaborations and literature studies, for better understanding of processes and outcomes that are harder to explain elsewise.

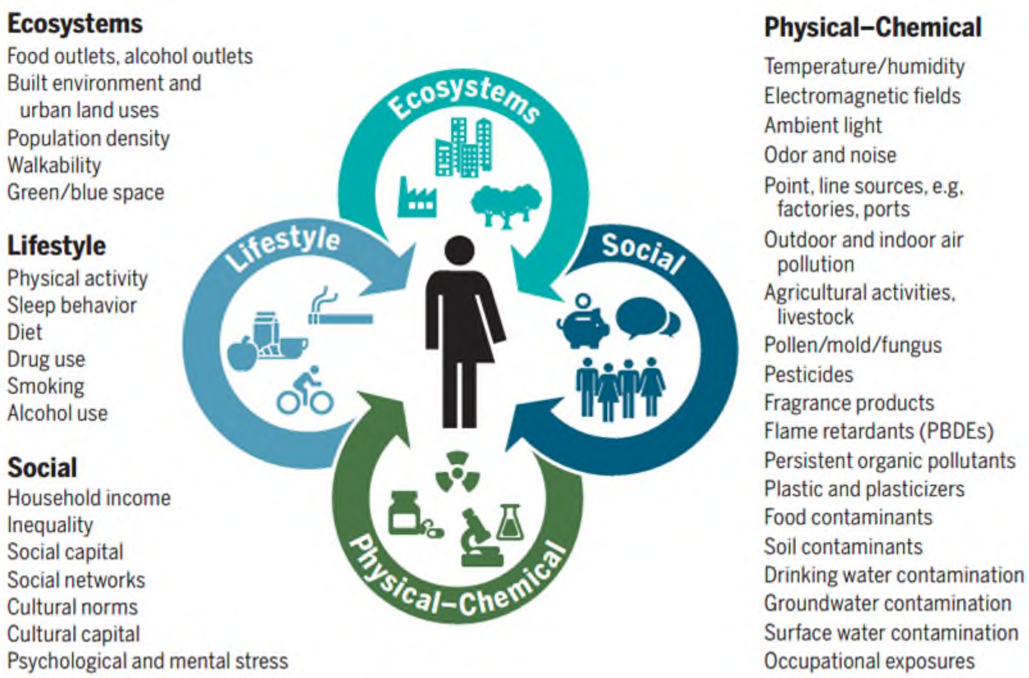

Figure 2. The external exposome is an integrated function of a person's interaction with its surroundings, such as ecosystems, social environments, physico-chemical exposures and its lifestyles. Source: Vermeulen *et al*., 2020.

In considering the categorization of determinants in exposome research, it is evident that while certain classifications have been made, such as those encompassing built environment or drinking water, the rigidity of these categories should be approached with some flexibility. Depending on the research objectives, more specific categories may need to be delineated to effectively capture relevant exposures. For instance, broader categories like socio-economic status, financial situation, and education, although integral, pose challenges as they often serve as intermediary variables influencing health determinants such as diet, access to healthcare, stress, and living environment quality.

The exceptional variety and dynamic nature of non-genetic factors makes it impossible to encapsulate the external exposome in a single domain or dimension (Figure 2). This creates a series of sampling and analytical challenges to capture and quantify as many different factors as possible (see Chapter 3). Therefore, there is currently no complete overview of all parts and processes of the exposome and the processes that influence it.

3 Exposome research tools and methods

In contrast to genome research, which now benefits from relatively cheap and accessible high-throughput sequencing technologies, characterizing the exposome currently poses a great challenge. The diversity of data (sources) (Table 1, Grady *et al.*, 2023) required for exposome research demands a multidisciplinary approach, using different research methods and approaches. This collection of approaches used to study the exposome is commonly referred to exposomics. In 2019, Zhang *et al*. (2021) argued in an international exposome workshop that both a top-down and bottom-up approach can be followed to help achieve a full mapping of the exposome (Figure 3). Despite the distinction and description of the 'top-down' and 'bottom-up' concept, it is not consensual and increasingly seen as outdated among the international community of exposome experts. Nonetheless, this conceptual framework was used to support the contextualization and identification of potential links to water research.

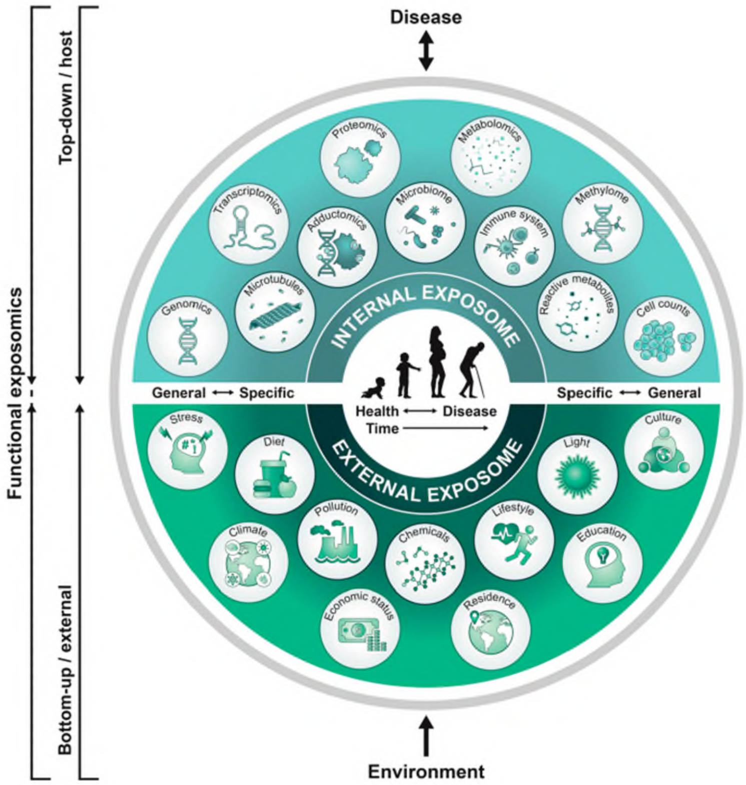

Figure 3. Functional exposomics approach to study the exposome. Source: Zhang *et al*., 2021.

In the 'top-down' approach, which starts from studying people and their health, molecular epidemiological studies focus on the relationship between internal or external exposure (e.g., small molecule biomarkers of exogenous compounds, protein adducts, reactive metabolites) and biological response profiles (e.g. metabolomics, gene expression, methylation) within the body using biospecimens (e.g., blood, faeces, urine, fat tissue). This approach can generate hypotheses about causal relationships between exposures and responses (including disease), but does not necessarily capture the direct, external measures of exposure (the external influence, such as contaminated water or air pollution). In the 'bottom-up' approach, which starts from studying external exposure factors, comprehensive data on external influences such as environmental exposure is collected through surveys, sensors, and analytical chemistry in environmental samples (external exposure) or in biospecimens. Identifying exposures can generate hypotheses about effects but does not (necessarily) assess that effect. Zhang *et al*. (2021) argue that functional exposome studies can bridge these two approaches. The functional exposome is a subset of the exposome that consists of biologically active exposures present in an individual. Measuring biologically active exposures requires specific tools that can characterize molecular interactions between an exposure and a functional biomolecule, such as DNA and proteins (Chung *et al*., 2021).

Table 1. Non-comprehensive list of exposome databases, according to the exposure data type and granularity. Source: Grady *et al.*, 2023.

Database	Type	Granularity
Public Health Exposome	External	County equivalents
Comparative Toxicogenomics Database	Internal	Individual
Human Early Life Exposome Study	External/Internal	Residential/individual
Geoscience and Health Cohort Consortium	External/Internal	Residential/individual
Southern Community Cohort Study	Internal	Individual
Toxic Exposome Database	Internal	Individual
Health and Environment-Wide Association Based on Large Population Surveys	Internal	Individual
EXPOsOMICS Project	External/Internal	Residential/individual
National Health and Nutrition Examination Survey	Internal	Individual
Exposome Explorer	Internal	Individual

3.1 Methods to assess external exposure

The external exposome is an integrated function of physical exposure, including what we eat , our experiences, and where we live and work. The chemical and microbiological exposome is an important and integral part of the exposome concept in drinking water. External exposures, also called stressors, are reflected in internal biological disturbances, and therefore exposures are not limited to chemicals and pathogens that enter the body, but also include chemicals produced by biological and other natural processes (Vermeulen *et al.*, 2020). External influences, including environmental exposures, are dynamic and vary greatly in magnitude over the lifespan of a human. When it comes to mapping the variety of external influences and environmental exposures that make up the entire external exposome, data from numerous sources and platforms must be integrated. Until recently, progress in understanding environmental exposures depended mainly on the availability of low-cost, high-throughput technologies for measuring exposure profiles (e.g., omics methodologies, high-resolution mass spectrometry techniques), which remain important tools and continue to be increasingly refined (Codrean *et al.*, 2023). Yet, developments in tools and approaches for monitoring exogenous exposures (e.g., remote sensing, global spatial positioning tracking) promise to enable rapid progress in this area (Niedzwiecki *et al*., 2019). A non-comprehensive list of diverse monitoring techniques relevant in early warning systems for drinking water sources is presented in Table 2.

Table 2. Non-comprehensive list of monitoring techniques relevant in early warning systems for drinking water sources. Source: Béen *et al.*, 2020.

Monitoring techniques	Name
Bioassays	iToxControl
	Microtox CTM
	CheckLight Online
	Algae Toximeter II
	Fluotox
	RobotLuminoTox (RTLx)
	DaphTox II
	Aqua-Tox-Control Daphnia
	Fish Toximeter II
	ToxProtect 64
	awaVision
	Bio-sensor
	Gymnotox
	Truitel TruitoSEM
	Intelligent Aquatic Biomonitor System (iABS)
	Aqua-Tox-Control
	MosselMonitor
	Biota Guard
Spectrometers	spectro::lyser
	The LiquID Station
	TruScan™ RM
	CBEx
	microPHAZIR™ RX
Event detection algorithms	CANARY
	ana::tool
	OptiEDS
	BlueBox™
	Event Monitor
Passive samplers	Silicone rubber
	Low density polyethylene
	POCIS
	Chemcatcher
	Styrenedivinylbenzene-reverse phase sulfonate (SDB-RPS)
	DGT
Other	FROG-5000
	FROG-4000

Measuring exposures in our environment can provide information about the sources and pathways of exposure, map the temporal variability of exposure, and provide estimates of historical exposures (Figure 3). Researchers use a variety of methods to quantify external exposures, from the population level (measurements, exposure modeling, geographic information systems, remote sensing) to the individual level (questionnaires, measurements). Recent technological advances have enabled more extensive measurements of environmental factors for population-level assessments (e.g., moving from large spatial scale assessments to hyperlocal maps) and individual level assessments (e.g., ecological instantaneous assessments, sensors, accelerometry and Global Positioning System tracking).

Over the past decade, several major technological advances have provided increasing information on external exposure over time and space. While many of those technologies are at an early technological readiness level, some technologies have been validated and demonstrated in relevant environments. It is therefore anticipated that many of these technologies can be widely applied in population studies in the near future, enabling better exposure assessment and linkage to both internal dose and associated biological responses (Niedzwiecki *et al*., 2019). An interesting timely example of such successful technological implementations is in wastewater-based epidemiology and surveillance, which is able to provide information of internal and external exposures at population level with a defined spatial and temporal scale (Aurich *et al.*, 2023, Cai *et al.*, 2023).

3.2 Methods to assess internal exposure

An important part of exposome research is linking exogenous (external) exposures to both the internal dose and the associated biological response (Figure 4).

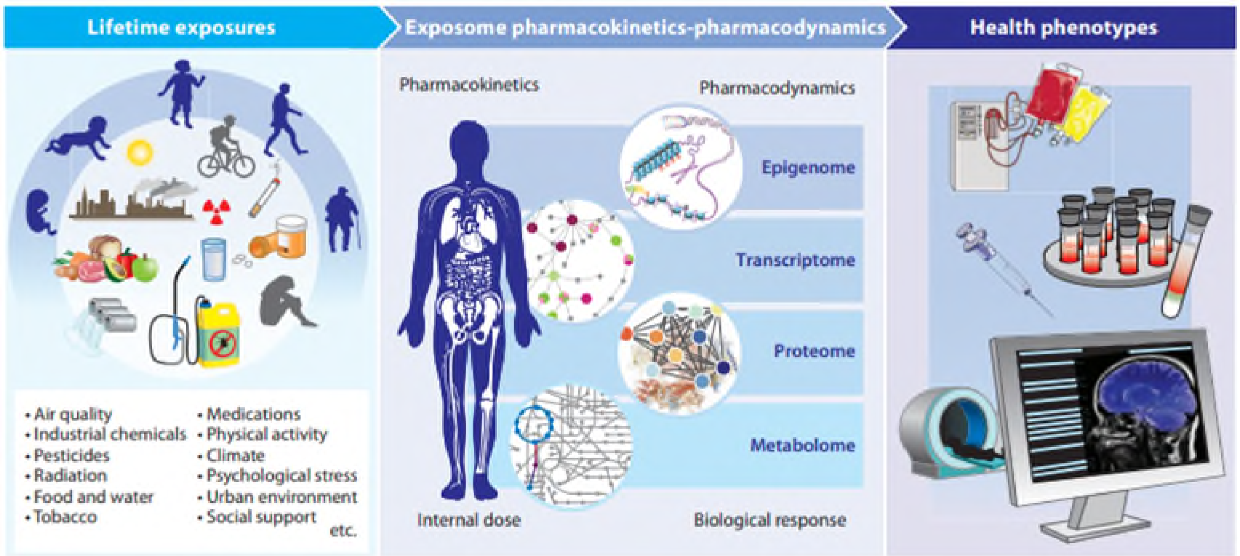

Figure 4. The exposome as an analytical framework linking exposures to health effects. The exposome attempts to measure, integrate and interpret the complex exposures faced throughout life. Furthermore, the exposure framework measures how these complex exposures affect our biological systems and relates them to health and disease outcomes. Source: Niedzwiecki *et al*., 2019.

When it comes to chemical exposure specifically, the internal dose is described based on toxicokinetics, and the biological response based on toxicodynamics. Exposure to natural and polluting substances in the environment can contribute to local and global changes in gene transcription, enzyme activity, changes in metabolism and protein synthesis/folding. As a result, micro- and macro-scale interactions occur between these systems, which can be characterized to study dose-response relationships. This can provide information about acute biological responses that may occur depending on the (degree of) exposure, and also whether long-term physiological changes due to environmental stressors that occurred years or decades earlier have been detected. Such biomarkers can be regarded as the 'memory' of exposures. From this perspective it is important to investigate the (expected) internal exposure contribution of water contaminants. This calls for new research on understanding and applying relevant methods, such as PBPK models, validated using concentrations measured in human biosamples (e.g., blood, urine). Additionally, as analytic platforms become increasingly high throughput / high content, characterization at the omics level becomes more accessible, and the application of the exposome framework can provide more insight into how the environment affects human health. The use of " omics" approaches (metabolomics, transcriptomics, proteomics, epigenomics) can help to better understand the role of exposures in human health, by enabling the measurement of biological responses at different scales and levels of detail (Figure 3 and Figure 4) (Pronk *et al*., 2021). The overall coordination of essential regulatory biochemical processes is through several regulatory mechanisms and signaling pathways. Disruptions in these processes due to exposures can be measured by changes occurring across connected nodes in a biological network. In particular, describing these types of complex networks requires transcending a single omics level and highlights the role of multi-omics approaches in exposome research. The availability of omics level data to assess biological responses offers new opportunities to understand environmental influences on human health. By integrating response measures from metabolomics, proteomics, transcriptomics and epigenomics, it is possible to understand at the systems biology level how exposures affect critical biochemical processes. When it comes to chemical exposures, such aggregated biological response patterns, combining toxicology and pharmacology with molecular and environmental epidemiology, may provide a new paradigm to delineate mechanisms underlying toxicological risks (Niedzwiecki *et al*., 2019).

3.3 Data science challenges in exposomics data

The collection of approaches used to study the exposome, i.e., exposomics, allows the generation of important exposome data. From a practical point of view, exposome data can be classified into two categories:

(i) exogenous data with heterogeneous measures of influences/stressors from outside the human body (including environmental exposures, behavioral and socio-economic factors), and
(ii) endogenous data with high-throughput molecular (omics) data essential for the characterization of internal doses and biological responses (including transcriptomics, proteomics, and metabolomics).

Exposome data are diverse in nature, and the strength and complexity of the correlations between the variables are different. Most omics data, and to a lesser extent exogenous exposure data, are of a high-dimensional nature, where the number of variables is large and can even exceed the number of observations ($p>n$), requiring the use of appropriate statistical modelling approaches to avoid misleading 'false positives' (Niedzwiecki *et al*., 2019, Chadeau-Hyam *et al.,* 2013, Agier *et al.,* 2016). Furthermore, the sheer magnitude of data also poses challenges in storage and assembly in aggregated databases. Data types need standardization and preprocessing methods (e.g., harmonization, noise abatement, feature selection, multicollinearity reduction) that also enable data integration (Grady *et al.*, 2023).

Water data serves various purposes, from real-time monitoring for early warnings to providing insights into seasonal and climate-related trends affecting water quantity and quality. However, extracting useful information from the complex water matrix poses a challenge, as does establishing the necessary data storage infrastructure and governance. Furthermore, acquiring good exposure data on a national scale with high spatial and temporal resolution currently presents an obstacle to implementing such a data structure. The implementation of (big) data science infrastructure in the water sector holds considerable promise, particularly in the analysis and interpretation of HRMS data. However, inferring causality remains a significant challenge, exacerbated by issues of data accessibility and transparency. Data sharing and statistical bias play pivotal roles in understanding the exposome, and the role of drinking water. Misclassifying exposure or health status related to drinking water can significantly bias findings, leading to erroneous conclusions. Moreover, underrepresentation of certain groups can introduce bias, whether due to varying dietary habits resulting in diverse exposures or factors like ethnicity or religious background affecting participation rates in cohort studies.

Transparency regarding chemicals in drinking water is increasingly demanded, while Non-Target Screening (NTS) methods are increasingly implemented. This approach generates vast amounts of data and introduces unknown variables, making it challenging to prioritize investigations. How to adequately communicate this complex information to consumers while also acknowledging embedded uncertainty in the data, analyses and conclusions upon them remains an active topic of discussion. For example, prematurely linking health-related data to exposures could foster skepticism about drinking water safety or erroneously sway the public's risk perception, underscoring the need for cautious data handling and ethical behavior. The ethical implications of exposome research are rarely discussed in the literature. In a recent systematic literature review on both the exposome and underlying research areas and approaches, Safarlou *et al*. (2023) mapped the ethical aspects relevant to exposome research. In it, they identify five prominent ethical themes in ethical discussions: the objectives of the exposome research, the standards, the tools, how it relates to the research participants, and the broader implications of its activity (e.g., informed consent, privacy). In addition, they provide some general principles for how future exposome research can make the best use of the overview of the ethical and bioethical aspects of individual-to-population scale research. Finally, they highlight three aspects of exposome research that are most in need of ethical and moral reflection: the usefulness of the findings, the epidemiological or clinical standards applicable to exposome research, and the disambiguation of unintended human bias and responsible action. From a drinking water practice perspective these appear as relevant elements to carefully consider further, for example in the expanding field of wastewater-based epidemiology and surveillance (Prichard *et al.*, 2014), and particularly in regards to how drinking water companies handle their unique societal role as drinking water providers and their trust relationship with the public.

3.4 Exposome thinking

People's reaction to gaining knowledge on the concept of the exposome can differ greatly. Especially since the exposome is a complex, novel concept that comes with many uncertainties. Currently, to our knowledge, there is no research describing this difference in public responses to the concept of the exposome, and how this response may affect risk communication. To capture this diversity of responses to the exposome and the different ideas that follow from them, we use the term 'exposome thinking'.

Exposome thinking: The response of an individual or group of individuals to gaining knowledge on the Exposome concept.

Each individual or group of individuals has their own form of exposome thinking. Individuals prioritize different aspects of the exposome and the knowledge available to them based on, among other things, the character of the information, their own personality, their socio-cultural environment and the political context (Brouwer *et al*., 2019). These priorities will affect the response and risk perception of people as regards the exposome, which in turn will affect the way in which people will act. What could a potential increase in the awareness and interest of (drinking water) customers for their personal exposome mean for drinking water companies? This question needs to be considered in the context of implementation of the revised Drinking Water Directive, which requires more transparency with regard to micro-contaminants in drinking water. A proposal for the implementation of this new obligation is currently under development within the Dutch drinking water sector, including discussions on future perspectives. These developments may require adjustments to (risk) communication, and therefore further research into the relationship between risk (perception), transparency and trust in drinking water and the drinking water companies. These questions are addressed in a companion report about ‘exposome thinking’ , set to be published concurrently with the present report. For additional information about this companion report, see Chapter 5.

4 Exposome research in the water sector

The exposome is an all-encompassing concept which can be conveniently divided into specific focus areas, for example, the 'drinking water-based human exposome'. The 'drinking water-based human exposome' explicitly attempts to holistically connect chemical and microbial exposure via drinking water-related activities (e.g., drinking, showering, cooking, swimming) (Vikesland & Raskin, 2016). Boelee *et al*. (2019) presents the drinking water supply systems as highly complex engineered microbiological ecosystems, the characteristics of which are influenced and determined by operational and environmental conditions (Figure 5) in ways that we currently do not fully understand. As analytical techniques improve (see Chapter 3), we can expect that more types of microorganisms (e.g., antibiotic-resistant bacteria) and other (in)organic contaminants (e.g., perfluorinated substances, pharmaceuticals) will be identified. New and emerging chemical contaminants of concern in water sources and drinking water are also becoming increasingly studied, followed by increasing attention from policy-makers (Valbonesi *et al*., 2021). One such example is persistent and mobile organic compounds (PMOCs) holding a great capacity to resist environmental degradation and bypass water treatment systems (Reemtsma *et al.*, 2016). The exposome concept provides a framework in which the external exposome via drinking water can be qualitatively and quantitatively compared with those of other environmental compartments (e.g., air, soil). The drinking water exposome can be considered at the level of the individual's exposure but is also shared by large (sub)populations, for example, those that use the same drinking water supply. This means that measuring the drinking water exposome provides insight into the exposure of, in many cases, large groups of individuals. This makes it possible, for example, to visualize differences between supply areas, provisioned with drinking water sourced from diverse locations or under particular management systems (Boelee *et al*., 2019). At the same time, the exposome concept shows that specific exposome factors in drinking water can be weighed against other exposome factors outside drinking water. In chemical and biological safety this means an emphasis on the combined influence of adverse influences on health and a means to prioritize abatement of these, given their relative influence.

Exposome methods for water-related research and drinking water practice

In the context of assessing (drinking) water quality and its influence on human health, effect-based methods (EBMs) emerge as promising tools which may provide useful contributions to exposome research. Unlike traditional methods focusing on a fixed number of measured chemicals, EBMs offer dynamic insights by assessing biological responses to complex environmental exposures. Utilizing an EBM battery with relevant bioassays can already provide an overall view of the water quality of a specific sample. This approach offers practical benefits, particularly when the risk associated with the sample is minimal or negligible. In such cases, employing EBMs can be advantageous over monitoring water quality based on numerous individual chemicals, streamlining the assessment process while maintaining effectiveness. While EBMs show promise, further research is needed to develop EBM batteries capable of addressing a broader spectrum of pertinent effects and find ways to integrate this information with epidemiological data. Presently, there's a significant emphasis on genotoxicity, but expanding the scope of EBMs will enhance their utility in comprehensively assessing water quality and water-based human exposure.

Analytical chemistry techniques, such as non-target HRMS screening, allow the measurement of drinking water samples and can be used to assess the full extent of potential external exposure to contaminants via this route in small scale population studies. In addition, dedicated targeted measurements can also be performed as to quantify priority water contaminants in drinking water. Modeling approaches based on targeted or non-target screening in combination with information on drinking water production and networks can potentially be used to model context-based exposures at the national level and supplement these exposure estimates in large-scale epidemiological studies. For example, wastewater influent monitoring is another useful tool for estimating internal exposure to chemical and microbiological contaminants, by measuring indicative endogenous biomarkers. Specific chemical information may also be integrated with drinking water (historical) measurements or clinical data, as to discern health disparities in consumers depending on drinking water sources (e.g., surface water, groundwater, private wells). A current example would be the higher concentrations of certain PFAS in surface water-derived drinking water compared to groundwater (Sadia *et al.*, 2023). Another example, is a major Danish epidemiological study providing evidence of an increased risk of birth defects of the eye from prenatal exposure to nitrate in the drinking water system (Stayner *et al.*, 2022).

Exposome in the Dutch Top Sector and drinking water Joint Research Program (BTO)

The exposome is a relatively novel concept, however much of underlying scientific research sustaining the resurgence of the Exposome field was already in place (e.g., epidemiology, genomics, multi-substance and multi-compartment external exposure). Several organizations and projects in the Netherlands and Europe focus on the human exposome, such as Utrecht University (https://www.uu.nl/en/research/life-sciences/collaborate/hubs/utrecht-exposome-hub), Dutch National Institute for Public Health and the Environment (https://athleteproject.eu/), Exposome-NL consortium (https://exposome.nl/), and European Human Exposome Network (https://www.humanexposome.eu/). In fact, one of the core ambitions of the Dutch 'Top Sector' on Life Sciences & Health, is that "*By 2040, the burden of disease as a result of an unhealthy lifestyle and unhealthy living environment will have decreased by 30%.*", in which exposome research is acknowledged as having a role to play (TKI, 2024). This ambition partially makes the basis for the country's Knowledge and Innovation Agendas (KIAs) that the top sectors have drawn up together with public and private partners. Therefore, it can be useful to identify which current research in the water sector may already be relevant under the Exposome umbrella. In order to identify topical overlaps between the Exposome and ongoing research at KWR Water Research Institute, the research lines under the Joint Research Program (BTO) of Dutch drinking water companies and Flemish Watergroep were evaluated in light of their potential relation and contributions to research on the human exposome via (drinking) water.

The process of identifying possibilities for exposome research in the research plans of the BTO 2024-2029 Theme Groups and the exploratory research "Water in the Exposome" is detailed in Table 5. The research areas within the BTO 2024-2029 Theme Group's six-year plans that could potentially intersect with the study of the human exposome, can be seen as "points of contact". These were signaled through an examination of the Research Lines together with BTO Theme Group coordinators as topical experts, leading to the identification of opportunities for research synergies within KWR and possibly with stakeholders. Feedback and insights were gathered from the BTO Theme Group Coordinators to confirm the identified "points of contact" and further enrich the analysis with highlights. Ultimately, the main goals of this analysis were to (1) signal topical overlaps between BTO projects and exposome research, (2) highlight ongoing or planned activities at KWR related to the human exposome, (3) help identify potential new research opportunities, and (4) facilitate discussions and future research synergies by further pulling together and integrating the exposome concept with water-based knowledge.

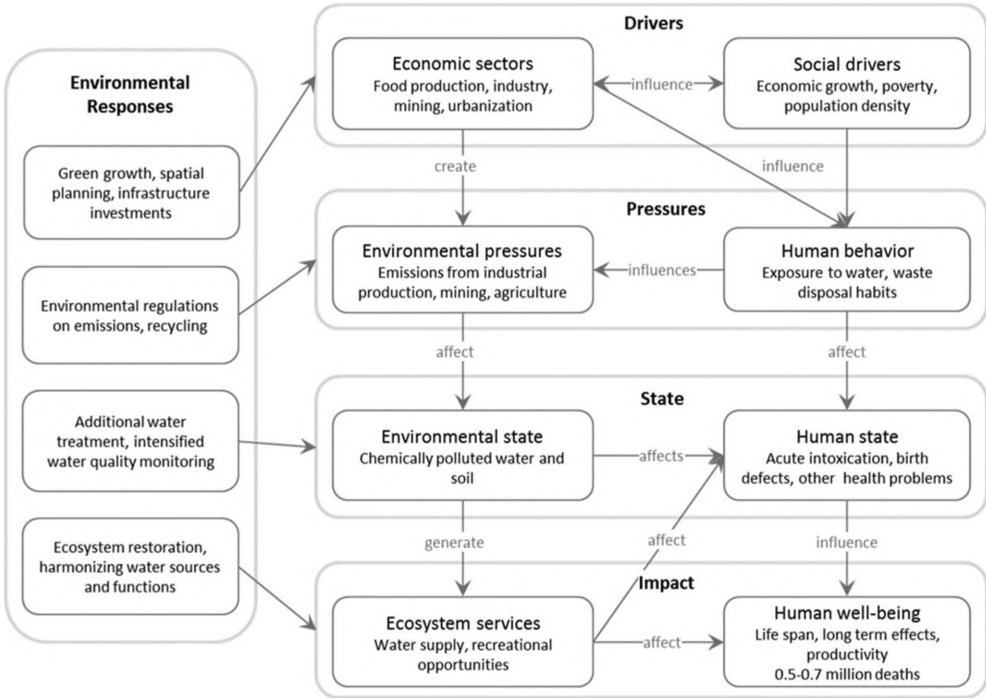

Figure 5. Drivers, Pressures, Impacts and Responses for the State of chemical water quality, with parallel tracks for environmental (left) and human (right) health. The health implications linked to water stem from both communicable and non-communicable diseases associated with water. These are exacerbated by the contamination of water with chemicals, solid waste (primarily plastics), pathogens, insects, and other carriers of disease. By adopting a systematic and holistic approach to water resource planning and management, with a focus on human health, we could potentially mitigate or prevent adverse health effects and amplify the health advantages. Source: Boelee *et al*., 2019.

It appears that the field of human exposome shares common ground with most of the BTO thematic research. The overlaps of relevant research questions are particularly noticeable within the themes of 'Biological Safety', 'Chemical Safety', and ' Sources, Water System and Nature'. For the remaining themes, the overlaps may be less evident and open to discussion. The 'Hydroinformatics' theme, on the other hand, presented the least number of obvious overlaps, although the increasing availability of different types of data on water quality/quantity and development of advanced digital tools (e.g., 'digital twins') may contribute to more integrated exposome research via the combination of models and real-time data. Interestingly, in line with the main goals of this exploratory project, an interesting study within the Theme Group 'Client' was developed in parallel, further supporting the utility of a topical overlap analysis. Consequently, a companion report about 'Exposome Thinking' was prepared (van Dooren *et al.*, 2024), set to be published concurrently with the current report. In short, the companion report on 'exposome thinking' explores the different forms of exposome thinking and risk perceptions among drinking water clients, based on client perspectives as identified by Brouwer, Pieron *et al*. (2019). Previous research by Brouwer *et al*. (2019) found that risk perception among drinking water clients that have the same client perspective is greatly similar. Thus, it is assumed that the same can be said for exposome thinking. In the companion report, 15 factors that can help understand how each client perspective will respond to gaining new knowledge on the exposome were identified. These factors, with future research, can be scored to assess the changes in perceptions and actions as a result of the exposome concept gaining attention. Within the report, scenario sketches of the response to the exposome concept are developed based on existing knowledge on the client perspectives. In addition, several social, technological and policy developments that could affect how the public responds to the exposome and how the exposome concept might influence current developments were explored. These developments include the introduction of the newly revised EU Drinking Water Directive and the rise of Big Tech, for example through the use of wearable health devices, such as smart watches. Finally, additional research topics to study the societal developments related to the exposome concept are proposed.

KWR has established a robust and extensive water research capacity and portfolio that spans decades. A large part of this is developed within the context of the joint research programme of Dutch and Flemisch water companies (BTO; https://www.kwrwater.nl/en/samenwerkingen/joint-research-programme-with-the-water-utilities/). Originally conducted without the explicit label of 'exposome research', a reassessment of the programme's thematic strategies and consultations with theme group coordinators revealed that KWR's historical and ongoing water-focused research inherently contributes to the exposome field. Despite water receiving limited attention in exposome research circles, its undeniable role in lifetime exposure to contaminants underscores its significance. For example, although for some contaminants, drinking water is the main exposure route, it is in many instances a far healthier alternative for other drinks and beverages. In the BTO and together with water companies, KWR has generated unique knowledge crucial to understanding the cumulative impact of environmental influences and associated biological responses throughout an individual's lifespan. Recognizing its strategic position in knowledge generation and exchange, KWR is poised to actively contribute to the water-focused exposome domain.

Currently, KWR's water research activities and strategy fits more with the approach that starts from studying external exposure factors, such as water contaminants, than with the approach in exposome research which starts from studying people and their health (see Chapter 3, Figure 3). Nevertheless, the ongoing work on bioassays and its ambitions for functional genomics (Pronk *et al*., 2021) could help bridge the two approaches via contributing to (new) functional exposome studies. In addition, wastewater-based epidemiology and surveillance of endogenous chemical and biological markers enables to perform analysis of exposure and public health on a population level (Medema *et al.*, 2020, Choi *et al.*, 2018, Steenbeek *et al.*, 2020). KWR occupies, as a water knowledge institute, a research niche that adds value to the science surrounding the aggregated and cumulative measurement of environmental influences, and can contribute to the broader exposome research community. The water sector's research activities can be (partly) integrated with human exposome research, particularly through schemes like *Topconsortia voor Kennis en Innovatie* (TKI), BTO 2024-2029, and WiCE (https://www.kwrwater.nl/en/samenwerkingen/collectief-onderzoek-water-circulaire-economie/). For example, the developments of networks and research infrastructures for environmental exposure assessment are closely followed, such as EIRENE-NL, a consortium led by Utrecht University (https://www.onderzoeksfaciliteiten.nl/node/3850). Future dialogues and research opportunities will delve into how the water sector perceives and strategically integrates its research within the broader context of the human exposome. Potential new focus areas, based on a water topical overlap analysis (Table 5), for water research related to the human exposome can include temporal dynamics for cumulative effects on health, customer socioeconomics for exposome profiling, water distribution and asset management for mapping urban influences, life course water-based epidemiology for exposome associations with lifetime exposures (NTS vs. exposure mapping), public health strategies for preventing and mitigating the impact of health issues, data science for data integration and analysis (chemistry, toxicology, clinical), psychobehavioral trend analysis towards the water sector regarding water quality and quantity (e.g., increased bottle consumption due to social and news media), and integration of quantitative microbial risk assessments (QMRA) and chemical risk assessment in drinking water.

Table 5. Identified topical overlaps between exposome research and research activities according to the 2024-2029 BTO 6-year plans (Hummelen, 2023). 'Research line', 'Research questions' and 'Questions/examples, were replicated in this table if considered relevant for exposome research. 'Topical Overlap' indicates the percentage of research topics in the BTO theme which have been identified as being directly or indirectly associated with exposome research.

Theme Group	Topical overlap	Research line	Research questions	Questions/examples	TG Coordinator's highlights
Biological Safety	100%	Biological activity	Which factors influence unwanted regrowth in the pipeline network and how do you control them? (distribution + indoor installation)	• Risk (management) of opportunistic pathogens • Prevent exceedances (bacteria of the coli group (coliforms), Aeromonas)	• What are differences in the water quality from different abstract points, treatment options (e.g., shifts in microbial communities)? • What are microbial background exposure-specific health effects in a diverse population? • How do microbiomes in all parts of our food system combine to form a single large network, known as a 'holomicrobiome', relate to the microbiome related to the water cycle?
		Biological pollution	How can faecal contamination in surface water, alternative sources and sources of contamination be efficiently monitored and characterized?	• Efficient pathogen monitoring in surface water • Faecal contamination in alternative sources (concentrations, variation) (wastewater, rainwater, ...)	
			How can pathogen removal by soil passage be better predicted, verified, and controlled in practice?	• Measures to manage risk • Reduction measurements based on risk-based monitoring	
			How can contamination of the pipeline network be prevented, detected, and corrected? (distribution and indoor installation)	• How does the risk of infection through distribution relate to the limit value for clean water?	
			How can the risk calculation in the Analysis of	• Risk calculation for negative pathogen samples	

			Microbiological Safety of Drinking Water (AMVD) be improved?		
		Methods	Which new, rapid and/or continuous methods can be developed, tested and implemented to determine, monitor and monitor microbiological water quality?	• New Methods (e.g., Crispr-Cas) • Rapid methods (molecular, sensors) • Continuous methods (e.g., passive sampling, sensors) • Quantitative Methods (e.g., qPCR, DDPCR) • Informative methods (e.g., metagenomics, proteomics)	
		New threats and opportunities for Biological Activity and Biological Pollution	How relevant is drinking water compared to other AMR exposure routes in the future?	• How relevant is drinking water compared to other AMR exposure routes?	
			Microbes of Emerging Concern	• What is the potential risk compared to known pathogens?	
			Climate change and social developments	• Effect of temperature, low discharge, energy transition and the like on infection risk and biological stability	
Chemical Safety	100%		Analytical Chemistry	• How do we ensure that we respond effectively and efficiently to new developments and that our analytical methods are fast, accurate and sufficient to detect new priority emerging contaminants in relevant matrices? • How can we make monitoring/signaling strategies more efficient and resilient in order to more accurately identify the increasing pressure on water quality?	• What substances are present and emitted to (drinking) water, surface/sub soil, air, and what are (differences in) consumer exposure patterns?(water stress at abstraction points) • What is the effect of exposure to chemicals when exposure to other factors occurs at the same time?
			Forensic chemistry research	• Where can action be taken to best limit the spread of chemical pollution in surface and groundwater?	

			Toxicological risk assessment	• What are relevant human exposures to chemical substances via (drinking) water, and which substances are given priority? • What is the influence of chemicals in drinking water on human health (and, where relevant for water companies, on the environment)? • What is the influence of (new) water quality policy on drinking water practice? • How do state-of-the-art risk assessment methodologies fit into the assessment of drinking water safety?	• What is the influence of mitigation options on exposure patterns?
Clients	67%	Diversity	The further development and further application of the customer perspectives		• Which clear links to topics, such as, ‘transparency and trust’ can be identified and assessed?
		Digitization	Strengthening insight into the relationship between transparency and trust		
Distribution	67%	Water quality during the drinking water supply	Chemical water quality in the pipe network	• How can chemical changes in the drinking water composition – due to internal and external factors – be understood, monitored, and possibly prevented during the drinking water supply?	• Which safety elements in the distribution system (permeation, pipe materials, biofilm) are relevant to human exposome? • Are sediments a relevant piece of the puzzle to understand the influence of water distribution networks to the human exposome?
			Microbiological water quality and heating in the pipe network	• How can changes in microbiological water quality – due to internal and external factors – be understood, monitored, and possibly prevented during the drinking water supply?	
			Sediments	• How can sediment and brown water in the drinking water network be understood, monitored, and possibly prevented?	
		Design of a future-proof pipe network	Principles for target structures	• How can the different objectives of the water company, the influences from the environment, and the uncertainties in the future development	

				of both be weighed against each other in a valuable way in the (re)design of new or existing distribution networks?	
		Asset management for drinking water supply	Line condition	• How can the condition of the pipeline network be mapped out with greater certainty and detail?	
			Asset Decision Making	• How can the various objectives of the water company be weighed against each other in a valuable way in the prioritization of construction, maintenance, replacement, and operation of the various components of the pipeline network?	
Sources, Water System and Nature	64%	Resources now and in the future	Quality sources	• Improved predictability of groundwater and surface water quality and consequences for raw water quality through the use of new techniques for data collection and analysis (big data, AI, catchment area sensoring, biomonitoring) • New source quality threats in view	• Can predictability of potential threats be achieved by linking environmental conditions and changes in legislation? • Drinking water companies are diversifying their sources; what are implications on purification effort and exposure of humans to contaminants?
			Mining technology and management	• Methodology for AMVD calculations for groundwater extraction and deep infiltration	
			Functioning wells in the water system	• Methods and effectiveness diversification sources (groundwater and surface water) in the picture, source strategy	
		Water system and nature (recovery)	Effects of climate change, sea level rise and adaptation measures on resources and nature	• Insight into changes in withdrawals from other users (increase in use of groundwater?)	
			Water transition: challenges and opportunities	• Better insight into quantity and quality effects of (large-scale) replenishment of the groundwater system by water managers and industry	

				• What is the impact of increasing water circularity? insight into changing dynamics of water supply and demand.	
		Strategic issues	Knowledge base National and International policy programs (WFD, Natura2000, forest strategy, etc.)	• Meaning of the WFD for the drinking water sector, what and how better after 2027?	
			Closing water chain (reuse effluent)	• Insight into the effect of large-scale reuse on the water system and drinking water supply	
Water in the Circular Economy	60%	Water in the Circular Economy	Transition and normative knowledge development	• Explore potential future scenarios for the water-energy-raw materials system, considering both likely and unlikely outcomes, and investigate strategies for system change beyond mere optimization. • Examine adaptive transition pathways from the existing system to a sustainable, circular economy, focusing on the timing and sequence of actions required for a successful transition. • Address the challenge of balancing climate impact and diverse social values in decision-making processes, particularly in investment decisions within the water sector.	• How to shape research as to provide stakeholders with possible paths for action? • How to accelerate co-creation and collaboration in early research for the greater impact and better transition solutions? • How to prevent possible negative impact of the integration of water and energy on the health of water consumers? • Can model-based exposome maps (e.g., insight in water quality flows) be used effectively to assessment of circularity, sustainability and robustness?
			Climate-neutral water and energy supply and sustainable coexistence of water and energy functions	• Developing and influencing appropriate legal frameworks and policy implementation practice in collaboration with local and regional authorities. • Monitoring policy choices on a national and regional scale with regard to water and energy in order to identify possible effects on (drinking)	

				water consumption at an early stage and to quantify them as much as possible.	
			Model-based systems thinking for assessment of circularity, sustainability, and robustness	• Insight into the distribution between water demand and water supply at provincial level, with refinement during the seasons and across the regions. Water quantity and water quality flows are captured in calculation software that quickly provides insight into various scenarios and measures.	
Treatment	40%	Water quality in relation to purification	Organic micros (incl. PFAS)	• New purification processes for the removal/degradation of PFAS (ARP, ion exchange, new developments)	• What are the effects of different treatment steps on the exposome/human health?
			Disinfection	• Securing and monitoring membrane systems (AMVD, use of qPCR, sensoring) • LED UV development	
		Circularity, sustainability, alternative sources	Alternative sources	• How can drinking water be produced sustainably from alternative sources (brackish water, seawater, effluent WWTP, or a combination of sources)? • Assessing chemical/microbiological safety at alternative sources (such as effluent WWTP)	
			Use of residual materials: elaboration of iron sludge	• Use of iron pellets (deposit directly in drinking water treatment or as fertilizer), for example for dephosphating anaerobic water (groundwater, bank filtrate) • Acidifying iron sludge (continued Hercauwer), use in drinking water purification	
Area-Oriented Management and Transitions	33%	Responding to the environment in transition (System)	Transdisciplinary building blocks for area-oriented drinking water goals	• In what way (via which tools) can the strategic drinking water importance be made transparent for environmental partners?	• How can the human exposome be considered in area-oriented drinking water goals?

Hydroinformatics	25%	Digital twins	integral view from source to tap and complete water system	• Linking models/digital twins and/or their information flows in an integral image • How to visualize this, make (autonomous or not) decisions and communicate • Linking external data streams	• How might the availability of data on water quality aspects through digital twins contribute to our understanding of the exposome?

5 A water perspective on the next steps in exposome research

Innovative methods are needed to study the interplay of exposure factors in the exposome, and to understand the effects on health and disease. There are multiple approaches to data acquisition, integration and knowledge generation in the extensive exposure and health studies required for exposome research, including questionnaires, mobile sensors for air quality and noise, UV exposure, physical exercise, and smartphone apps to aid in the collection of dietary data. Yet, subsequent steps are needed to convert the findings into policy in order to protect the population against the negative effects of exposures (Bruinen de Bruin *et al.*, 2022; EEA, 2021). Measures are steadily being trialed and implemented throughout the globe, Europe and the Netherlands to bring about the positive contributions of exposome research insights via careful urban planning, increased exposure to greenspace (e.g., parks, gardens, nature reserves) and bluespace (e.g., lakes, rivers, fountains), facilitation of social and cultural interaction in urban centers, promotion of active lifestyle outdoors and healthy dietary options (e.g., soft drinks vs. high quality drinking water). Exposome research promises to become an important part of (personalized) medicine and public health, in alignment with Dutch policy goals and EU's strategic ambitions towards a toxic-free environment. KWR initiated dedicated discussions on the next steps in exposome research from a water perspective, in collaboration with water utility companies, the national authority on health and the environment, and with academic experts. This chapter presents research topics and challenges that followed from these dedicated discussions.

Mapping the external exposome

The rate, volume and diversity of exogenous stress factors entering our environment continue to increase (EEA, 2020, EC, 2021). An eminently important exogenous factor on human health is the complex, multifaceted and concurrent chemical exposures (Vineis *et al*., 2020). However, a sizable proportion of diseases are caused by unknown exposure factors. After all, the non-genetic component exceeds the population-wide contribution of heredity to disease and death (Vermeulen *et al*. 2020). In the development of research methods for mapping the exposome, special attention is therefore paid to the application of mass spectrometry for gaining insight into the chemical exposome consisting of large and, particularly, small molecules, with an emphasis on the application of high-resolution mass spectrometry (HRMS) and non-target analyses to identify previously unknown and complex chemical exposures (Zhang *et al*., 2021, Escher *et al*., 2017). Small molecule imaging by HRMS is an important approach for measuring both external and internal exposures, by measuring exogenous molecules in environmental matrices, including water, and both exogenous and endogenous molecules in human tissue. However, it must be considered that the chemical exposome contains a huge diversity of substances with very different properties. For example, it spans a breadth of water solubility and octanol-water partition coefficients (K_{ow}) of many orders of magnitude and includes ionizable substances and metals. In view of the diversity of research methods and resulting data, regulators are currently extending their computational and high-throughput approaches to account for the ever-increasing number of anthropogenic substances.

Linking environmental exposures and biological responses

Computational and high-throughput approaches provide an important foundation for establishing molecular links that can elucidate the relationships between environmental exposure and biological responses (Niedzwiecki *et al*., 2019; Zhang *et al*., 2021). However, challenges remain to exploit the full potential of exposome research to better understand the health effects of exposure to complex chemical mixtures and other types of exposures (see Chapter 3).

Exposome research challenges

The following main challenges have been identified and also discussed in more detail in key publications by Vermeulen *et al*. (2020) and Zhang *et al*. (2021):

(i) Additional efforts are needed to combine gas and liquid chromatography analytical approaches, but also for example inductively coupled plasma (ICP) and hydrophilic interaction liquid chromatography (HILIC) mass spectrometry, for comprehensive exposomics measurements. Such integration and standardization also includes sample extraction protocols leading to better sensitivity and increasing the efficiency in measuring a variety of exogenous substances (e.g., PMOCs).

(ii) The screening of exogenous and endogenous chemicals and their biological effects via human tissue, blood and urine, need to be improved with higher throughputs and lower costs. In the context of wastewater-based epidemiology, these screenings would provide a substantial scaling advantage where one sample would relate to hundreds or thousands of individuals in a community, instead of a single person.

(iii) Major investments in mass spectrometry infrastructure will be required to support human exposome studies on a scale at least comparable to that of the Human Genome Project. This should be done in conjunction with activities to support method standardization. The EIRENE consortium aims to fill the gap in the European infrastructural landscape and to pioneer the first EU infrastructure on human exposome. This will contribute to increasing the scale and scope of the studies to a level that provides the necessary statistical power to characterize the influence of chemical (mixture) exposures.

(iv) The further development and support of cheminformatic and bioinformatic tools, including network theory and network medicine, is needed to elucidate the constellation of the chemical environment and its biological consequences. This also includes the development of open scientific workflows and extensive public exposome databases in combination with spectral libraries of known and known-unknown substances.

(v) Adequate protection against the occurrence of false positives should be ensured by insisting on replication in independent studies and using methods to establish causation, such as Mendelian randomization, sibling comparisons, and exposure negatives and negative control outcomes.

(vi) Strengthening communication between scientists in different disciplines in combination with the development of interdisciplinary exposome centers is essential to meet the challenges by this emerging scientific transdiscipline.

Drinking water exposome research

Consumption of water is a primary necessity of life, and people constantly come into contact with water via sanitation and food. This elevates the critical need to understand its contribution on the exposome. Besides providing the water sector practitioners an opportunity to optimize their drinking water production and distribution operations, it would also offer clients the opportunity to consider their options more fairly. Yet, the relative contribution of drinking water on the exposome remains unknown. Thus, it is important to explore how models, techniques and insights from the exposomics field can be used to better understand the balance between positive and potential negative impacts on health from drinking water or alternatives (e.g., chlorine-free tap water, bottled water, sugary drinks) (Tosun *et al.*, 2020). From a water-focused perspective, drinking water risk assessment sustained on the exposome concept can provide several key insights and research opportunities with potential relevance to the water sector. Based on the present report and discussions with stakeholders and academic experts, some of these insights and opportunities are listed in more detail below:

(i) At the intersection of water research and exposome, lies the opportunity to illuminate the complexities of drinking water exposures and their implications for human health. Studies may aid in pinpointing vulnerabilities, particularly in anticipation of future challenges that could intensify pressures on both the quantity and quality of drinking water sources.

(ii) The exposome concept suggests that the factors of influence of drinking water extend beyond exposure to water contaminants but should also incorporate genetic and other internal factors, which interact with the exposome, as well as exposure factors. Further research is required to identify the most relevant factors and facilitate implementation in water quality practice and policy, which likely extends over the long term.

(iii) The exposome concept shows that actual health risk is dependent on frequency, length and type of exposure, building the exposure history that makes up the exposome. The response in humans is more than the internal calculated chemical dose as a measure and includes cumulative biological responses and lifestyle. Future research is necessary for the implementation of this approach in water quality practice and policy, which is expected to be a long-term endeavor.

(iv) In risk assessment of drinking water, although further research and evidence is needed, the exposome concept suggests that exposures ‘add up’ and that these should be considered in an integrative manner as to better ascertain the (in)dependance of effects and the prioritization of risk factors. Food, air, and many other factors contribute to explaining the health burden. This is an important realization when interpreting health risks via (drinking) water. For chemical safety for instance, it is important to get a feel for the compounding effect or risks of ‘all’ chemical traces in environmental matrices that humans come into contact with. Future research is essential to facilitate the implementation of this initiative, a priority that the water sector may consider focusing on in the short to medium term.

(v) Exposure via drinking water may be a small contribution to the total human exposome, consisting of many factors of influence. However, for some factors it may be the *only* or *permanent* influence. These include water-borne pathogens as well as unique chemical contaminants specific to water, which may be prioritized for immediate attention. Additionally, it is important to consider the lower control over exposure through drinking water compared to food, where individuals have greater autonomy in their choices. Due to this flexibility, higher contaminant levels may be tolerated in food than drinking water. due to this flexibility, the fact that drinking water serves as a proxy for other exposure routes should not be overlooked. Environmental waters, including drinking water sources, can contaminate food through various pathways, linking exposure routes such as soil, water, and possibly even air via precipitation.

(vi) The exposome concept provides the drinking water sector with a goal, which is to have a holistic and less fragmented view on the influence of drinking water quality and quantity on health. Ways to achieve this goal is through dialogue, cross-domain cooperation, standardized collection of diverse data types (internal and external exposome) coherently and systematically, to translate reliable findings into science-based water regulation. Within the BTO, communication among stakeholders, key research efforts, and investments in better organizing water databases and data capabilities can be coordinated.

(vii) To study the influence of chemical water quality on human health, non-targeted (NTS) and effect-based methods (EBMs) can be put to practice to complement fixed numbers of measured target chemicals. In coordination with epidemiological studies, EBMs may help bridge the gap between exposure assessment and health outcomes. On one hand, identifying biological responses to complex environmental exposures, offers insights into the overall impact on human health. On the other hand, EBMs pinpoint specific exposome components contributing to observed effects, elucidating underlying mechanisms and pathways of exposure-related health outcomes. Further research is necessary to pinpoint EBM batteries capable of addressing a broader spectrum of the most important health effects, expanding on the current emphasis on genotoxicity.

(viii) For drinking water, the analytical chemistry methods to measure chemicals at low detection limits are continuously improved. This includes non-target screening and the integration with hazard-assessment based on quantitative structure-activity relationships (QSARs), which is currently being addressed in BTO thematic research. Also, the analytical (functional) genomics methods for measuring waterborne pathogens and their effects on health are continuously being improved. Furthermore, significant research investments are currently being made in microbiological holistic concepts, in parallel with the exposome (the totality of exposures), such as the holomicrobiome (the totality of microbiomes).

(ix) From a precautions position, the presence of contaminants in drinking water could potentially be largely avoided if the sources of contaminants are also restrained, for example, via stricter discharge permits or restrictions in the marketing of certain chemicals. This kind of action requires a wide and coordinated effort from various stakeholders which may have competing interests. While water-based legislation and regulations hinge on political will and feasibility, research efforts contribute crucial pieces to the overarching puzzle. Exposome research can support policymakers to better understand the health effects of exposure to complex chemical mixtures and other types of exposures, to identify those (policy) measures that most effectively protect human health.

(x) Epidemiological research can help contextualizing health risks by identifying or determining how drinking water may contribute to certain health outcomes or stress factors within a population.

(xi) The exposome can be considered on various levels. The external exposures via drinking water can complement information on internal exposures and may potentially be linked to ‘drivers’ of water-related exposome via environmental forensics investigations (e.g., industry, urban centers, agriculture). Research is needed to support this endeavor and anticipated to yield results in the mid- or long-term.

6 Conclusion

The exposome concept provides the drinking water sector with a goal, which is to have a holistic and less fragmented view on the influence of drinking water quality and quantity on the human exposome. Mapping the human exposome is an enormous undertaking requiring the engagement of stakeholders across the board. The water sector is facing unprecedented challenges and is under increasing pressure due to stress on and scarcity of water resources. A good understanding of how (drinking) water contributes to the totality of exposures of human individuals and populations in their lifetime is necessary to prioritize measures in practice and policy to safeguard the production of safe and healthy drinking water. Therefore, cross-collaboration among knowledge fields is crucial to gain a comprehensive perspective on how the water sector may act and substantially contribute to public health by ensuring the safety of water, preventing water-related health issues and promoting good health. Exploring exposome research in the water sector requires a thoughtful integration of various disciplines, including biological safety, chemical safety, hydroinformatics, client research, stakeholder engagement, and water in the circular economy. This interdisciplinary approach may encompass studies focused on chemical mixtures, the holomicrobiome, effect-based methods, wastewater-based epidemiology, advanced analytical methods, water distribution networks, data harmonization, social values, and adaptive sustainable transitions. The present report represents a unique initiative in the drinking water sector that has encouraged researchers to look beyond their specific disciplines, foster valuable knowledge networks, and explore co-creation with stakeholders. Ongoing collaborations between KWR Water Research Institute, universities, and the Dutch-Belgium drinking water sector will deepen our understanding of the role of (drinking) water within the exposome while envisioning proactive measures to sustain water quality and promote a healthier future.

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