EXPOSOME: CONNECTING THE DOTS FOR EFFECTIVE PREVENTION OF DISEASE

TNO innovation for life

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Our health is impacted by the environment we grow up, live, work, sport, sleep and relax in. **The combination of exposures during daily activities and over the lifetime constitutes a major risk factor for disease.** Many common disorders are closely linked to these exposures ranging from lifestyle factors, to chemical exposures, social interactions and stress. **All together such exposures have a huge health impact in society.** They contribute to the development and progression of diseases like cancer, respiratory and cardiovascular disease. **Many of these combined exposures can potentially be modified to prevent disease. However, the complex interrelations between exposures and effects are still a scientific challenge.** We often do not know why one person develops a disease and the other does not.

INTRODUCTION

The concept ‘exposome’ – the totality of exposures a person experiences during lifetime – will help to close this gap in knowledge. Better understanding will enable the development of effective personalized preventive measures in this area. The first exposome research has been carried out mostly in academic settings. Now the time is right for a transition from basic research to the first applications for health promotion. To facilitate applied exposome research, TNO has established an Exposome Program. This white paper describes TNO’s vision on the potential of the exposome for enhancing health. A potential that needs an alliance between academia, the private sector and end users to accomplish substantial health enhancements.

BOX 1: EXTERNAL RISK FACTORS – A SUBSTANTIAL CONTRIBUTOR TO HEALTH AND DISEASE

- External risk factors contribute to around 60% of attributable deaths and 40% of Disability-Adjusted-Life-Years (DALYs) worldwide.[1] External risk factors are the combination of behavioral, general and occupational environmental and metabolic risks. Importantly, these known risk factors only seem to explain perhaps roughly 50% of the modifiable risk of major chronic diseases. This indicates that much remains to be discovered.
- Environmental pollution is the largest environmental cause of disease and premature death in the world today. Diseases caused by pollution were responsible for an estimated 9 million premature deaths in 2015. This is 16% of all deaths worldwide.[2]
- Environmental chemical exposures including neurotoxicants, air pollution and endocrine disrupting chemicals, contribute costs that may exceed 10% of the global domestic product.[3]
- Exposure to particulate matter (PM10) is responsible for 4% of the burden of disease in the Netherlands. After smoking (13%) it is one of the major risk factors, with a similar magnitude as obesity and lack of physical activity.[4]
- 5% of the total burden of disease in the Netherlands is the result of work related exposure to substances. This burden consist of some 17.000 new cases and 2000 deaths annually, mainly due to (lung) cancer, COPD and asthma.

EXPOSOME: THE COUNTERPART OF THE GENOME

With the unraveling of the DNA code and the mapping of the genome, the expectation was that human diseases could be better explained. It was expected that more effective personalized treatments could be developed. Unfortunately, it is not that easy. Genetic predisposition is only part of the puzzle. It is estimated to account for about 10-30% of the disease burden.[5] Why does one person develop a disease and the other doesn't? Why do some patients benefit from a certain treatment or preventive measure while others don't? These questions can't be answered with genetic information only.

A wide variety of non-genetic factors in the environment we live in determine the likelihood and course of disease. These so-called exposures include e.g. chemical exposures in the work and urban environment, such as (air) pollution. But also lifestyle factors, such as diet or smoking and social interactions and stress. These external exposures have a substantial combined effect on health (see Box 1). These exposures are modifiable, unlike the genome at the level of its primary DNA sequence. Therefore external exposures have the potential for prevention. However, current insights in the association between these exposures and health are too limited for effective prevention. This is due to a lack of insight in how (combinations of) exposure patterns are related to health at the individual level. Moreover, each individual processes exposures in a different way depending on genetics but also external circumstances. This leads to variation in biological responses resulting in individual health outcomes. In other words: we don't know enough on where, when and why people are exposed. Therefore we don't know who will suffer from detrimental effects as a result. To overcome this knowledge gap, the total exposure to all risk factors during a person's life and how this is related to biological responses inside the human body is referred to as the exposome (see box 2). Gaining insight in the exposome and linking the exposome to health will provide new insights in how mixtures of risk factors are related to health at the individual level. This will in turn contribute to explaining the unattributable burden of disease.

BOX 2: WHAT IS THE EXPOSOME?

The exposome is the combination of all exposures from conception till death, and how our body deals with these exposures. The concept of the exposome was proposed in 2005 by cancer toxicologist Christopher Wild. He defined exposome as the 'totality of life-course environmental exposures (including lifestyle factors), from the prenatal period onwards'.[6] During the following years the definition of the exposome, and how to assess it, has been under discussion. Nowadays, the most common definitions comprise the total exposure during a person's life (external exposome) and how this is related to biological responses inside the body (internal exposome). See Figure 1.

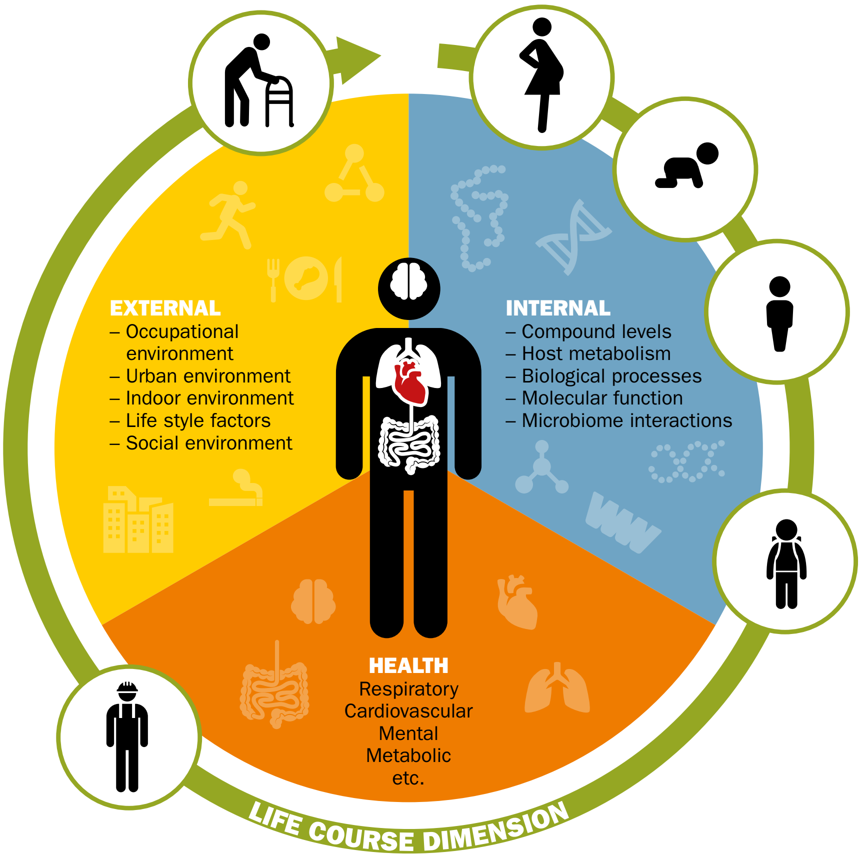

FIGURE 1: THE EXPOSOME: THE TOTALITY OF LIFE-COURSE EXTERNAL EXPOSURES AND BIOLOGICAL INTERNAL RESPONSES, FROM THE PRENATAL PERIOD UNTIL DEATH.

EXPOSOME – A PROMISING POTENTIAL

The promising potential of exposome is that it will provide the basis for evidence based health interventions. Both collective public health strategies as well as personalized intervention strategies. The basis of this potential is the insight at the individual level in the external and internal exposome and how these two interact with each other and relate to health.

CHALLENGING NEW FIELD OF RESEARCH

Although very appealing and promising, the exposome concept is challenging in many respects. The exposome is multifaceted and variable over time. Uncovering a person's exposome requires capturing the variety and dynamics of a multitude of exposures. This includes both external exposure profiles and biological responses, at the individual level over prolonged periods of time. After the conceptualization of the exposome in 2005, for several years, little progress was made because of this complexity. It was not until 2010 that exposome research has taken off. This is due to several advancing technologies that can contribute to uncovering the exposome that started to become more widely available. These advancing technologies are shown in Figure 2. The ultimate scientific challenge is to combine these technologies to achieve optimal insight in the exposome and its association with health. This requires multidisciplinary research.

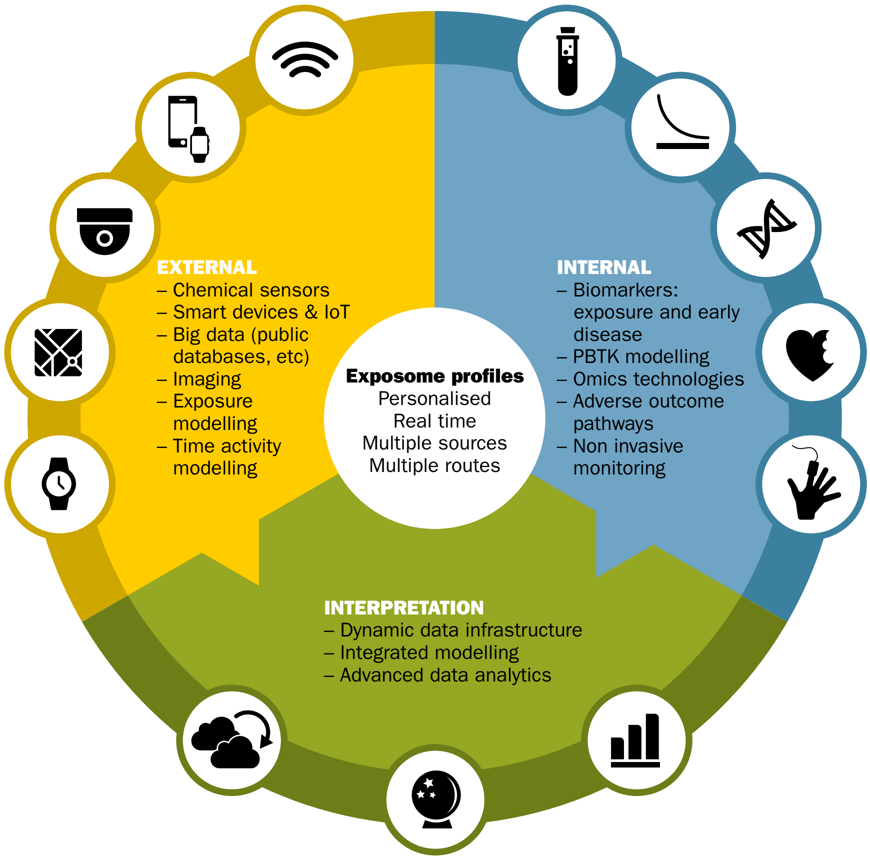

FIGURE 2: TECHNOLOGIES THAT CAN BE APPLIED TO ASSESS THE EXTERNAL AND INTERNAL EXPOSOME.

PBTK = Physiologically-based toxicokinetic; Omics = the collective characterization and quantification of pools of biological molecules that translate into the structure, function, and dynamics of an organism or organisms.

ASSESSING THE EXTERNAL EXPOSOME

Current external exposure assessment technology provides at best snapshots of single exposures. These snapshots are obtained by models or measurements and have limited resolution in time and space. In addition, data are often not available at the individual level. Better insights are needed in when, where, why (source, activity) and to which combinations of environmental factors people are exposed. To obtain those insights, one of the first essential steps is to acquire reliable data on exposure levels at a high time and space resolution and at the individual level. Lightweight, miniaturized and technically advanced low-cost sensors that provide real-time measurements with improved time and space resolutions are a key technology for assessing the external exposome. Sensors can be used to assess chemical exposures such as air or occupational, but also e.g. UV radiation, noise and physical activity.[7,8,9] Although the cost of sensors is decreasing while at the same time the quality is progressively improving, the reliability and specificity of low cost sensors compared to conventional exposure measurement techniques remains an issue.[9,10,11] Therefore, development of sensors with a higher reliability and specificity is a clear research need. At the same time, deployment of low cost sensors in large numbers (e.g. a sensor network) may improve the confidence due to many measurements rather than a few.[8,12] Methods are needed for deployment of sensors in large quantities as well as for referencing low cost sensors with higher uncertainty to more robust conventional monitors (in the field). Sensors will never be present all the time and everywhere. Therefore, exposure assessment will remain dependent on exposure and time-activity modelling.[9] Enrichment of exposure models with sensor data and insights will create opportunities for more accurate an detailed exposure estimates, also in situations where exposure sensors are not present. Collection of contextual data is essential for this. Time-activity data and other contextual data can also be obtained by smart data collection using technologies such as smart phones or smart watches, big data, imaging data, sensors for position or movement, beacons etc. Easier and cheaper monitoring of exposure and context at the same time is opening a wealth of new data for research and analysis. There is a need for methodology to integrate these different (sensor) data sources with exposure and time activity models into insights in personal exposure profiles.

ASSESSING THE INTERNAL EXPOSOME

The internal exposome will provide insights in whether a person will actually develop a health effect from one or multiple exposures and why. Several technologies are available and under development to measure the internal exposome. First, conventional biomonitoring approaches assessing levels of chemicals in blood, urine or hair, have been available for some time. Secondly, physiologically-based toxicokinetic (PBTK) modelling approaches are available to link external exposure to internal exposure. Thirdly, newer technologies involve omics, allowing for the detection, characterization and quantification of (ideally) all biomolecules and complete biological processes potentially affected by external exposures. Examples of biomolecules are DNA, mRNA, miRNA, metabolites, proteins and also the microbiome (mapping of all microorganisms within humans). Omics has promise to contribute to exposome studies, in particular when applied to easily accessible biological samples, taken at various moments in time. Omics may directly detect biomarkers of exposure, for example blood levels of various compounds and multiple metabolites. In addition, it can detect past exposures via so called ‘imprints’[5,12], for example in DNA methylation. Omics enables the study of several multiple exposures and related effects across a continuum from exposure, towards early health changes, and onwards to disease. As a consequence, omics can generate hypotheses regarding future development of exposure-associated disease and yield biomarkers to predict disease development. However, interpretation of omics data is a challenge. This is due to variability of omics responses within individuals, the limited insight in the specificity of the response per signal (e.g the biological meaning of changes in levels of one metabolite or protein) and different bioinformatics data analysis strategies applied that can yield different biological answers. Therefore, in addition to omics approaches, the internal exposome also can benefit from more focused approaches.

At present, the Adverse Outcome Pathways (AOPs) concept is under development. AOPs aim to formalize comprehensive amounts of mechanistic information to directly link exposure to clear health effects (adverse outcomes). In future, biomarkers derived from these pathways can be included into the exposome framework to map exposure or predict health effects.

Similar to assessment of the external exposome, assessment of the internal exposome currently is performed at defined 'static' moments in time. In many cases, it requires invasive collection of biomaterials (e.g. blood). Other approaches are needed to enable faster, real-time, less invasive read outs of omics and biomonitoring data. To accommodate this, new technologies are emerging, e.g.: smart phone based urine bio analyte detection[13], band-aids combined with lab on a chip approaches to continuously monitor blood biomarkers present in the interstitial fluid and exhaled breath constituents sensors[15].

BOX 3: KNOWLEDGE AGENDA'S

The unravelling of the exposome is currently part of several national and international knowledge agenda's: Dutch NWA-route Kwaliteit van de omgeving, Dutch Ministeries of SZW and VWS, EU program Health and Demographic Change US National Institutes of Environmental Health Sciences and US National Institute for Occupational Safety and Health.[16,17,18,19,20,21]

ADDITIONAL CHALLENGES

Uncovering a person's exposome will require capturing the dynamics and variety of exposure levels, which include both external exposure profiles and biological functions, over prolonged periods of time. This will generate enormous data flows. Consequently data infrastructures, data processing and advanced data analysis techniques for combining and analyzing exposome data are increasingly getting attention. Further development of models, in particular for combining multiple external exposure data with internal exposome data and models are needed.

Apart from technical challenges, the application of exposome technologies brings about other challenges as well. The use of wireless devices and storage of information on the internet leads to potential security concerns. Furthermore, privacy and ethical issues should be addressed when these technologies are applied for assessing external and internal exposure to environmental stressors. Issues of data ownership and data protection need to be clarified and structured to allow ubiquitous exposome monitoring to become an everyday reality.[9]

WINDOW OF OPPORTUNITY FOR PREVENTION

The exposome, at least considered in its totality, will continue to be an academic challenge over the coming decades. Worldwide significant progress is being made by different research groups in uncovering the various aspects of the exposome. The developed knowledge and technologies provide a range of opportunities for prevention (Figure 3):

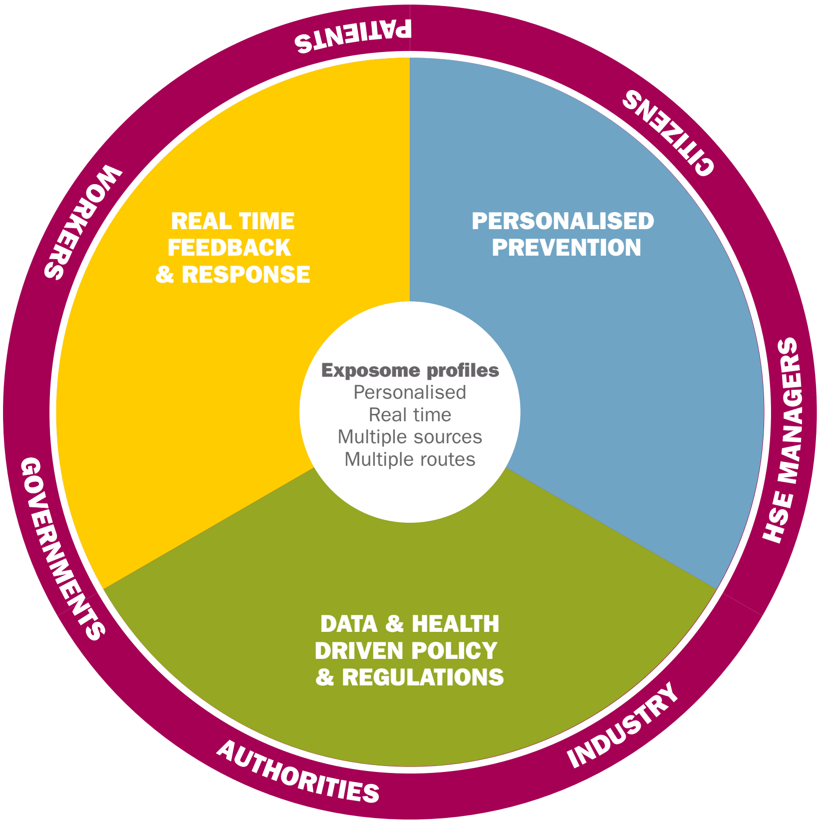

FIGURE 3: DEVELOPED KNOWLEDGE AND TECHNOLOGIES PROVIDE A RANGE OF OPPORTUNITIES FOR PREVENTION

DATA AND HEALTH DRIVEN POLICY, REGULATION AND PROCEDURES

Exposome research will lead to quantitative insights in which (aggregated) exposures and exposure routes contribute to health and how exposures may interact mechanistically. In addition, exposome technologies will provide insights in the determinants of exposure. For instance physical exposure sources but also how e.g. social factors or urban factors contribute to exposure. This improved data driven evidence will enable policy makers to develop better informed plans and policy. It will provide health and safety experts with the information to enhance procedures. And it will help regulators to establish more relevant guidance and limit values. In addition, the internal exposome will provide mechanistic data that can identify vulnerable subgroups. Identification of subgroups enables the definition of tailored procedures and regulations for groups with specific internal or external exposure profiles.

PERSONALISED PREVENTION

Exposome research will potentially benefit from the application of wearables, consumer devices and non-invasive technology to detect the external and internal exposome. These emerging technologies enable insights in the external and internal exposome at the individual level. This will create opportunities for personalized (self) management and E-health solutions which will give patients more individual control. In addition, also workers or citizens can become more involved in monitoring and managing their own exposures and health. For the development and validation of effective prevention at the personal level, behavioral sciences are of key importance.

REAL-TIME FEEDBACK AND RESPONSE

Exposome technologies will provide (near) real-time insights in external and ultimately also internal exposure patterns. With advances in connectivity and mobile devices, preventive tools can be developed that give automated immediate (real-time) feedback and instructions. For example about exposure reduction measures or health advice during situations with external or internal over-exposures. Real-time insights also offer several the potential of more immediate feedback on the effect of certain altered behavior or intervention on personal exposure (and on health impact).

Materializing these opportunities will contribute to a shift from curation to prevention. Exposome has the opportunity to contribute considerably to dealing with the challenges in the healthcare domain: increasing health care costs and shortage of medical staff. By providing the evidence base for algorithms behind eHealth, mHealth and worker and consumer health wearables it will contribute to the health tech industry. Global market forecasts identify considerable market potential for IoT opportunities in (public) health & safety applications (factories, worksites, cities) and in monitoring and managing illnesses by individuals.[22]

> "The ultimate scientific challenge is and will remain to combine these technologies to achieve optimal insight in the exposome and its association with health."

THE APPLIED EXPOSOME PROGRAM

GOAL

As outlined above, exposome knowledge and technologies will facilitate improved understanding of internal and external factors driving health. This can be the basis for collective public health and personalized intervention strategies. Our goal is to enable and stimulate prevention and promotion of health by adopting and developing exposome technologies. We believe this requires a focused approach and involvement of many disciplines. In order to support that we have established the Applied Exposome Program.

Together with partners we will work on:

INNOVATIVE TECHNIQUES FOR MEASUREMENT OF PERSONAL EXTERNAL AND INTERNAL EXPOSURES

We aim to develop innovative exposure measurement techniques, e.g. low cost, wearable, direct reading and/or non-invasive technologies. In order to enable the collection and interpretation of personal exposure measurements at a high resolution. Therefore we develop, optimize (incl. validation & calibration) and adapt sensor and other measurement techniques for measuring external exposure levels and internal markers. For instance, the development of a point of care biomarker assay for exposure to benzene (see box 5A), the development of interpretation techniques for personal passive sampling (see box 5B) and development and application of low cost particle counters (see box 5C).

MODELLING AND ADVANCED DATA ANALYTICS FOR ASSESSMENT OF THE EXPOSOME

We aim to develop data infrastructures, data processing tools and advanced data analysis techniques. These tools for combining and analyzing exposome data will enable insights in which exposures occur when, where and why and for whom. And it will provide insight in under which internal and external circumstances disease develops. We develop methodologies for integrating external exposures from different sources and through different exposure routes and for quantitative linkage of these external exposure (profiles) towards internal exposure and (early) health effects. For example the development of methods and data infrastructure for sensor model integration (box 5D) and integrated modelling of benzene (box 5E).

DEVELOPING GROUP BASED OR PERSONALIZED PREVENTIVE TOOLS MAKING USE OF EXPOSOME TECHNOLOGIES

We aim to develop preventive tools which transform exposome data into actionable feedback and advice. In order to optimize the impact of exposome technology and knowledge on prevention of disease. Given the relative immaturity of exposome research no example projects exist. However, TNO has a track record in personalized health which makes use of similar digital data streams and sense-reason-act principles for transforming these into actionable advice taking into account behavioral sciences. This history has led to valuable insights in ethics and privacy issues that come with the use of personalized data.[23]

Within our Exposome Program we will focus on high risk populations from the perspective of:

1) vulnerable populations, e.g. child health, chronic patients' health.
2) groups at risk for high exposure levels, e.g. occupational health, urban health.

COLLABORATIONS

At TNO we can contribute to these developments because of our multidisciplinary nature. It involves TNO experts ranging from sensor developers, exposure scientists, systems biologists to behavioral scientists. In addition, we initiate and stimulate public private partnerships that are much needed for taking this field further, towards applications. To achieve our ambitions, collaborations are needed with:

Academia: Large (multi-center) population and patient based studies are needed for obtaining quantitative insights in which (aggregated) exposures and exposure routes contribute to health and how exposures may interact mechanistically. These studies are mostly based in academic settings. TNO can contribute to these by developing technologies for external or internal exposome assessment, such as sensor development, non-invasive monitoring, modelling tools and data analytics tools. We have a strategic partnership with Utrecht University (see box 4).

In addition we are collaborating with other knowledge partners in current projects: RIVM, Haagse Hogeschool and University of Toronto (See Example projects)

The private sector: For the development of new exposome technologies collaborations with private partners that can take proof of concept technologies developed at/with TNO to market are needed, e.g. sensor developers, biomarker and analytical companies, computational modelling providers. In addition, continuity of developed preventive tools requires collaboration with e.g. app or health and safety software developers.

End-users: End-user involvement is essential for translating exposome knowledge and technologies into solutions such as procedures, prevention strategies and prevention tools. By collaborating with the end-users, their needs and perspective on capabilities, user friendliness etc. can be taken into account. End-users may include government, industrial Health Safety and Environment (HSE) experts but also citizens and patients and workers (organizations).

BOX 4: STRATEGIC PARTNERSHIP

Within the Exposome Program we have a partnership with Utrecht University (UU). Both UU and TNO work on exposome studies with the ultimate aim to develop effective public and personalized health strategies. TNO and UU have a track record in the required disciplines towards interdisciplinary exposome studies that complement each other. TNO has a strong focus on the development of novel tools to measure and model the exposome. UU together with the University Medical Center Utrecht (UMCU) have a strong focus on the application of these innovative exposome technologies in new and existing health studies among the general and patient populations and thereby obtaining novel insights in drivers of disease and disease progression. This collaboration will contribute to the common goal of developing effective public and personalized health strategies together with the private sector and end users.

Utrecht Exposome Hub
UU initiated an interdisciplinary hub on exposome studies in 2018. The hub connects excellent researchers from the faculties of medicine, veterinary medicine, science, geosciences, and social and behavioral Sciences. The Utrecht Exposome hub combines research on both the external exposome – focusing on sensoring, exposure modelling, and e- and mHealth applications – and on the internal exposome, focusing on microbiomics. By combining this research, it aims to develop successful prevention and intervention strategies in amongst others cardiovascular, mental, infectious, and immunological diseases. The Utrecht Exposome Hub stimulates productive and long lasting multidisciplinary collaborations with public and private stakeholders thereby creating shared value and, hence, societal and economic benefit. The position of exposome science within UU and the UMCU is further strengthened by the appointed of prof. dr. ir. Roel Vermeulen as Professor of Environmental Epidemiology and Exposome Science, in 2017.

TAKING THE NEXT STEP

In order to improve quality of life, a better understanding of the complex relationship between multifactorial environmental exposures and health effects is needed. Not only for health professionals, but also for individuals, like citizens, patients or workers. These individuals become increasingly aware of and are concerned about their own health status in relation to environmental factors. Exposome research will propel exposure and prevention science into the 21st century. However, several scientific challenges will remain for the years to come. Applied research on the translation of exposome knowledge and technology into solutions for health promotion is still in its infancy. We envisage further multidisciplinary and multi-partner oriented research in our program on Exposome.

WILL YOU JOIN US?

We are ready to further broaden our knowledge about the exposome: to develop techniques to measure the relation between the external exposome, internal exposome and disease and to develop practical applications that can give personalized health advice and reduce disease. To be able to do so, we would like to connect our knowledge and experience with academic, private and end-user partners. Will you join us and our strategic partners?

EXAMPLE PROJECTS

A. Point of care biomonitoring of industrial exposure to benzene

Because of its health effects there is a strong focus on benzene in personal monitoring programs in the (petro-)chemical industry. Biomonitoring is one of the established methods to assess worker exposure. Currently most commonly used biomonitoring methods are based on laboratory analyses of worker urines that generally have a turn-around time of several weeks and can be logistically challenging in certain parts of the world. In collaboration with industry TNO is developing a ‘point of care’ test for benzene metabolites in urine that can provide results within minutes to hours and can be performed at location. These results are more relevant for taking direct risk management measures and can prevent unnecessary (over)exposure to benzene.
In addition, point of care solutions provide the opportunity to collect more exposure measurements (at lower cost) creating insight in relevant exposure sources, locations and moments which can form the basis for better informed exposure management strategies.[24]

B. Passive sampling: a simple way to track personal exposure to a wide range of chemicals?

Capturing a wide range of exposures is challenging. Passive sampling is a technology that can potentially provide insight in the presence and concentrations of a wide range of chemicals during measurement times that range from a day to several months. Personal passive sampling devices have been developed elsewhere and include wristbands and broaches.[25,26] The advantages of these devices is that they are wearable, non-intrusive and able to gather information during many different activities (active, sleeping, swimming etc). At TNO we collaborate with the Institute for Risk Assessment Sciences (UU) and University of Toronto on investigating the application of these devices. Which components can be measured with passive sampling devices? What are the average exposure levels corresponding to a certain concentration in the device?

C. Low cost sensors for particulate matter: application studies and development

Recent technological developments have led to the availability of relatively low cost particulate matter (PM) sensors that mostly rely on optical particle counting. Due to the low cost of these devices, they have the potential to be more widely administered in exposure assessment and epidemiological studies. However, the field performance of these sensors have not been thoroughly tested. We have performed several pilot studies applying low cost sensors in field settings. For example with the EU HEALS consortium.19 In addition, with RIVM and the Haagse Hogeschool we are evaluating the use of low cost particle sensors for assessing dust exposure among construction workers. These studies will provide valuable insights in the application of low cost sensors for exposure assessment. In addition, technological advances are also being made for the next generation low cost particle sensors that will be able to measure particulate mass directly and that will enable characterization of particle composition. The optics department at TNO provides world class technical solutions for customer needs in the field of high performance compact optical systems in demanding environments.[27]

D. External exposures: methods and data-infrastructure for sensor-model integration

There is a need for technology that is able to accurately assess personal exposure profiles in both the general and work environment with the possibility to integrate both. To gain insight in when, where and why a person is exposed to which source and during which activity, methods are needed that can accurately estimate external exposure levels via different exposure routes during prolonged durations at the personal level resolved over space and time. Capturing these personal exposure profiles in (near) real-time can be achieved by applying accurate low cost sensors. TNO works, in collaboration with the Institute for Risk Assessment Sciences (UU), on the methodology for integrating exposure models and sensor enrichment to obtain personal exposure profiles relevant for health.

E. Integrated modelling, benzene as case study

As part of the internal exposome technology development, TNO and the Institute for Risk Assessment Sciences (UU) have started to work jointly on data modelling to integrate external exposure data with internal exposure and effect data (a.o. adverse outcome pathways). To do so, a data rich compound, benzene, was chosen for which both molecular data, internal and external exposure data and conventional epidemiological disease data are available. The technology developments involve the development of/adoption of PBTK models, the prioritization of modes of action and adverse outcome pathways of relevance to the effect (in this case Acute Myeloid Leukemia), the semi quantitative definition of these pathways and the full integration of the data within a computational model towards prediction of a health hazard and risk. This is benchmarked to the conventional epidemiological estimations.

REFERENCES

1 GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risk, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388(10053):1659-724.
2 Landrigan PJ, Fuller R, Acosta NJR et al. The Lancet Commission on pollution and health. Lancet 2017; doi: 10.1016/S0140-6736(17)32345-0. [Epub ahead of print].
3 Grandjean P, Bellanger M. Calculation of the disease burden associated with environmental chemical exposures: application of toxicological information in health economic estimation. Environ Health 2017;16(1):123.
4 https://www.gezondheidsraad.nl/nl/taak-werkwijze/werkterrein/gezonde-leefomgeving/gezondheidswinst-door-schonere-lucht.
5 Lichtenstein P, Holm NV, Verkasalo PK et al. Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343(2):78-85.
6 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):1847-50.(2005).
7 White RM, Paprotny I, Doering F, Cascio WE, Solomon PA, Gundel LA. Sensors and “apps” for community-based: Atmospheric monitoring. EM: Air and Waste Management Association’s Magazine for Environmental Managers 2012;May:36-40.
8 Snyder EG, Watkins TH, Solomon PA et al. The changing paradigm of air pollution monitoring. Environ Sci Technol 2013;47(20);11369-77.
9 Loh M, Sarigiannis D, Gotti A et al. How Sensors Might Help Define the External Exposome. Int J Environ Res Public Health 2017(4);434.
10 AIHA. The future of sensors: Protecting the Worker Health Through Sensor Technologies. 2016 Falls Church, VA.
11 Kumar P, Skouloudis AN, Bell M et al. Real-time sensors for indoor air monitoring and challenges ahead in deploying them to urban buildings. Sci Total Environ 2016;1:560-1.
12 Hoover MD, Debord DG. Turning Numbers into Knowledge: Sensors for Safety, Health, Well-being, and Productivity. Synergist (Akron) 2015;26(3):22-26.
13 Kanchi S, Sabela MI, Mdluli PS, Inamuddin, Bisetty, K. Smartphone based bioanalytical and diagnosis applications: A review. Biosens Bioelectron 2017’102:136-49.
14 http://cmt.lcnwebdesign1.co.uk/
15 http://www.fujitsu.com/global/about/resources/news/press-releases/2016/0418-01.html
16 https://wetenschapsagenda.nl/route/kwaliteit-van-de-omgeving/
17 Vrijheid M, Slama R, Robinson O et al. The human early-life exposome (HELIX): project rationale and design). Environ Health Perspect 2014;122(6):535-44.
18 Vineis P, Chadeau-Hyam M, Gmuender H et al. The exposome in practice: Design of the EXPOsOMICS project. Int J Hyg Environ Health 2017;220:142-51.
19 http://www.heals-eu.eu/
20 https://www.niehs.nih.gov/
21 https://www.cdc.gov/niosh/index.htm
22 Manyika J, Chui M, Bisson P, et al. The Internet of Things: mapping the value beyond the hype. McKinsey Global Institute. Available at: http://www.mckinsey.com/business-functions/business-technology/our-insights/the-internet-of-things-the-value-of-digitizing-the-physical-world.
23 Lieshout M van, Kraaij W, Molema H. Privacy in digital health a positive driver for innovation. TNO. Available at: http://publications.tno.nl/publication/34625774/ElYwxB/TNO-2017-privacy.pdf.
24 https://time.tno.nl/en/articles/this-is-how-we-trace-harmful-substances-even-faster/
25 O’Connell SG, Kincl LD, Anderson KA. Silicone wristbands as personal passive samplers. Environ Sci Technol 2014;48(6):3327-35.
26 Saini A, Okeme JO, Goosey E, Diamond ML. Calibration of two passive air samplers for monitoring phthalates and brominated flame-retardants in indoor air. Chemosphere 2015;137:166-73.
27 https://www.tno.nl/en/focus-areas/industry/expertise-groups/optics/

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