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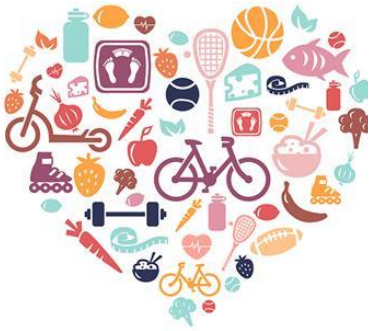
The Exposome, A Scientific Challenge



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Summary

- *The notion of exposome is understood as the totality of human environmental exposures from conception onwards.*
- *While the exposome theory has raised high expectations throughout society, its practical application remains limited.*
- *With regard to chemical exposure, the notions of multiple exposures and the time span of exposures are increasingly being considered in research and risk assessment activities.*
- *In order to fully identify and analyse exposures and their associated health implications, we need to standardise procedures and allocate a significant amount of logistical and financial resources.*

Mr. Cédric Villani, MP, President of the Office

While some conditions have a clear genetic origin, others, such as most forms of cancer, have no known cause. This observation prompted Christopher Wild, former Director of the International Agency for Research on Cancer (IARC), to investigate their origins in the wider environment, and to introduce the concept of the exposome back in 2005.

The exposome is defined as a complement to the genome and is understood as "the totality of exposures that individuals may experience over their lifetime."[1] There are several environmental factors that can influence a person's state of health: food, air, water, UV radiation, noise pollution, psycho-emotional environment, lifestyle, socio-economic conditions, etc.

The exposome concept considers them as a whole, rather than looking at the individual effects of each factor on an organism. Some factors may act together, others may act against each other. The time factor (duration of exposure, exposure window) may also be a determining factor.

The fact that this concept has been included in the French Public Health Code [2] demonstrates the legislator's desire to protect the general public by taking into account all the factors that may have negative impacts on human health, in accordance with the "right to live in a balanced and healthy environment."[3]

The fourth National Environmental Health Plan (Plan national santé-environnement – PNSE4), which is currently undergoing public consultation, includes proposals to increase knowledge of the exposome through the establishment of a Green Data Hub and to help structure and strengthen environmental health research through a Priority Research Programme (PRP).[4]

A holistic approach to environmental health

Environmental health is a scientific field that focuses on how environmental factors can influence human health; this includes occupational exposures. The specific nature of the exposome concept involves considering all the factors as a whole and assessing their effects over time.[5]

- **A wide-ranging concept**

Christopher Wild's theory suggests that, from the prenatal period onwards, everything that is not derived from the genome should be considered as part of the exposome.[6] This concept takes into account a wide range of environmental factors: chemical (pollutants), physical (UV), psycho-emotional (stress), social (close environment) and lifestyle (nutrition and sport).

It is difficult to fully understand an exposome defined in this way. This is why its assessment is usually limited in scope - the chemical exposome, for example - or indirect, based on the measurement of internal factors, such as elements found in the blood.

- **Health-environment interactions**

Although the idea that the environment can influence one's health was first suggested as early as the 5th century BC,[7] it remains largely unexplored. It has also been linked to a number of "non-communicable diseases"[8] (cardiovascular, diabetes, cancers, asthma, etc.), the origins of which are not yet fully understood. This is a major public health issue, as 90% of deaths in the EU are thought to be due to non-communicable

diseases,[9] and it is estimated that environmental factors in the broad sense are responsible for 70-80% of these diseases.[10]

There are well known cases of health-environment interactions, such as nutritional imbalance and the development of metabolic diseases or the effects of endocrine disruptors on the reproductive system. Environmental factors can have different effects, depending on their nature.

In a "One Health" approach, which combines human, animal and environmental health, the exposome needs to be better characterised by monitoring ecosystems, which would enable us to better assess the effects of climate change on human health.

- **The need to identify and understand the effects of multiple exposures**

There are examples of proven synergy between environmental factors: the risk of lung cancer associated with exposure to radon is multiplied by 25 for smokers.[11] This example underlines the need for a multi-disciplinary approach.

An evolving methodology

With this unprecedented need to assess all exposures, we are faced with a methodological challenge, which can only be overcome by adopting a multi-disciplinary approach that combines life sciences, analytical chemistry, statistics, human sciences, data science, technology and connected devices. Different types of studies, already used in environmental health or developed in the specific context of the exposome, can be used to characterise it more effectively.

- **Toxicology, the basis of environmental health**

Toxicology involves the study of the adverse effects of chemical, biological or physical substances on living organisms. It is an experimental approach that involves exposure under controlled conditions with a control group, which enables us to identify causal relationships between a substance and its effects on the exposed organism. However, these experimental causal relationships cannot always be transposed to humans.

This discipline is the basis for assessing the risks associated with chemical molecules, which is governed by the European REACH regulation.[12] However, the traditional practice of toxicology consists of examining the effect of individual substances, without considering the possible additive or synergistic effects of certain substances.

- **Modelling: QSAR and AOP**

Since conventional toxicology procedures are time-consuming and costly, particularly in terms of human and animal life spans, it is impossible to fully assess the effects of molecules to which an individual may be exposed during his or her lifetime. A number of computer-based approaches have been developed in order to speed up this process.

QSAR (*quantitative structure-activity relationship*) modelling consists of deducing the biological effects of molecules from their chemical structure. The AOP (*adverse outcome pathways*) approach is designed to break down the biological effects of molecules to better identify the mechanistic processes involved.

These approaches allow us to combine exposures, by adding up the effects of molecules with similar structures or action mechanisms, and to identify the main risk factors for a set of molecules.[13]

- **Cohort studies**

Epidemiological cohort studies can identify statistical associations between health conditions and environmental factors. Their statistical soundness depends on the number of participants and the number of factors assessed.[14] Their observational nature[15] limits them to identifying correlations, but cross-checking these results with those from experiments can be used to draw conclusions.[16] In some cases (studying industrial accidents, occupational exposure and certain methodological approaches), epidemiological studies can provide evidence of causal relationships.

Cohorts may include individuals representing the larger population or a group of people with the same health condition, together with a control group. A cohort study can last from a few years to several decades, and can even extend over a number of generations, studying the descendants of those who were involved in the study at the beginning.

The environmental factors assessed can be external – based on questionnaires,[17] direct measurements or modelling (radiation levels or air pollution) – or internal – based on direct measurements (measuring contaminant levels in the blood, analysing gut microbiota, etc.).[18]

Cohorts are very expensive to set up and are often developed through partnerships between research institutes and health agencies. Several large-scale projects are being organised across Europe, with nine new projects set to be launched this year as part of the *European Human Exposome Network*.[19]

- **The EWAS *(environment-wide association studies)***

The EWAS concept is modelled on the GWAS (genome-wide association study) methodology, which consists of analysing the genome of a large number of individuals affected by the same health condition and identifying common variations that may be responsible for it.[20] While GWAS establishes links between the genome and health, the EWAS aims to uncover correlations between diseases and the environment.

These cohort studies are conducted with a large number of environmental factors, and therefore a large

number of participants. While thousands or tens of thousands of participants may provide enough data to identify the most important risk factors, weaker signals and synergistic effects require cohorts involving several hundred thousand people, or even more.[21]

One of the first studies of this type, conducted by researchers at Stanford University in 2010 involving 266 environmental factors and several cohorts of several thousand people, identified an association between type 2 diabetes and pollutants (PCBs) and pesticide compounds.[22]

The EWAS method presents a number of difficulties, such as the variability of environmental factors in terms of time and space, whereas the genetic data are stable. Previous studies have not been able to obtain the required level of information from existing environmental databases, which are not designed for such studies. This demonstrates the great need for standardised approaches.[23]

What avenues do we need to explore?

- **The need for improved exposome measurements**

More detailed information on the environment of the study participants would help us to better understand the exposome. The development of "mobile sensors or detectors capable of measuring environmental contaminants",[24] which are affordable and can collect real-time data for high-speed analysis,[25] will help to achieve this. There is also a need to develop analytical infrastructures that can thoroughly characterise biological samples.

Smart phones provide an opportunity to create interactive interfaces with study participants. They can also be used as a direct (noise) or indirect measurement tool (by identifying an individual's location, we can assess their risk of exposure to a factor for which the level of risk is mapped, such as geological risks, like radon or[26] air pollution).

- **The need for more information on how health factors are influenced by environmental factors**

Developments in the biomedical fields of "omics"[27] have made it possible to better characterise the biological response to any given factor. These technologies can therefore be used to establish links between exposure and health effects by identifying possible mechanisms.[28] There is also a need to support the study of under-researched health impacts, such as immunity, neuro-behaviour and metabolism.

By cross-checking studies on large population samples, we can establish correlations between health and the environment using mass data science and artificial intelligence. *However, since these associations may be subject to bias, they need to be treated with caution and confirmed by mechanistic studies.*

A Green Data Hub[29] has been set up to provide access to health-related environmental databases, which will prove extremely valuable if it can improve access to and the use of under-used resources. But linking up with the Health Data Hub may not prove beneficial as the data is too vague and may be biased. Above all, this combination will provide working hypotheses to be explored.

How can this research be used?

- **Is it possible to make predictions based on exposures?**

A number of researchers are working to develop environmental risk scores or exposome risk scores,[30] similar to polygenic risk scores, based on existing genome-health interactions. While these scores cannot provide a definitive predictive value, they could be used for educational purposes, particularly for patients with asthma or heart disease.

- **Studying risk factors to prevent disease**

The advantage of better understanding the exposome of representative samples of the population (or categories of the population) lies primarily in identifying risk factors and therefore in the resulting preventive actions that will benefit the entire population.

This work could be used to introduce monitoring for environmental factors that have not previously been monitored, or to improve such monitoring.

Technologies that allow real-time monitoring of air pollutants would be of great interest for public health, as they would allow us to better characterise chronic exposure to certain pollutants. As the Opecst pointed out at the end of the public hearing on the prevention and management of industrial risks,[31] the use of such tools would also help to identify the pollutants emitted during industrial disasters. [32] They can also be complemented by better knowledge of individual indoor air quality, another of the PNSE4's priorities.

Disease prevention also means using the exposome concept in risk prevention. With regard to the chemical exposome, the ANSES and its European counterpart, the EFSA, are working to identify the main sources of risk within chemical mixtures and to assess the effects of similar molecules.

Limitations

The biggest limitations are linked to the methodology used, which is different for each study, and which, amongst other things, makes it impossible to cross-check the results of each study. The different types of exposure[33] experienced by each individual are also a limiting factor, both in terms of better understanding the actual level of exposure and in developing public health policies, which are designed to protect everyone, even though each individual's exposome is different.

- **Timing**

The long time frame (an entire lifetime, including the foetal period) is a major limitation when it comes to measuring the exposome. Back in 2010, researchers recommended focusing on critical exposure windows, periods when organisms are more sensitive to environmental factors.[34] Furthermore/an other issue is the fact that, a health effect is unlikely to occur in conjunction with exposure to an environmental factor. Some have an effect during the developmental stages, but these effects may only become apparent later on in life, and may even be passed on to the next generation.[35]

It is therefore important to be able to study large cohorts whose environmental factors are clearly identified, starting in the foetus.

- **Genome-environment interactions**

It is possible that a number of environmental factors interact with genetic factors, which makes it difficult to use information about the exposome on an individual basis. The development of environmental health study methodology will enable us/researchers to produce Genome-Environment-Wide Interactions Studies (GEWIS).[36]

Studying environment-genome-health interactions involves using epigenetics to examine the links between the environment and the genome. This can be achieved using techniques to assess whether a compound alters the epigenome, for epigenetic changes that are strongly associated with health effects.

- **The costs involved**

Research laboratories simply cannot afford the costs associated with cohort studies, which involve sampling and analysing hundreds of thousands of people.[37]

The high costs involved make it difficult to acquire sufficient knowledge about the exposome. This scientific field requires significant investment, as stated in the report on cohorts for health research by the General Inspectorates of Social Affairs (Igas) and the General Inspectorates of Education, Sport and Research (Igésr).[38]

Establishing a specific framework for research institutes and national health agencies would allow us to make better use of the research findings and to improve our analysis and storage facilities, which are not yet available on such a large scale in France, thus reducing costs.

Findings and recommendations

The exposome concept is part of the "One Health" global health concept. While the concept itself is well understood, the way in which it is measured, and thus the possibility of establishing environment-health associations, remains limited due to the difficulties involved in putting it into practice.

This is partly due to the high costs associated with using such a methodology, as well as the lack of available funds.[39] It would therefore be extremely beneficial to set up a research infrastructure for both research institutes and health agencies. It would be responsible for providing logistical, human and financial resources for monitoring prospective cohorts, not only on representative samples of the population but also on vulnerable populations. This data can then be made available to the various research organisations as part of an open science approach.

There is also a need to develop an infrastructure dedicated to investigating the chemical exposome and to strengthen modern toxicology by combining experimental and computer-based aspects and by including other disciplines such as epigenetics and critical health impacts, including immunity, neuro-development and metabolism.

Finally, improving knowledge about the exposome will hopefully influence European regulations for assessing the risks associated with chemical substances.[40]

The Office's websites:
http://www.assemblee-nationale.fr/commissions/opecst-index.asp
http://www.senat.fr/opecst/

Persons consulted

- Mr. Robert Barouki, toxicologist, biochemistry professor and member of the Scientific Council of the Office;

- Mr. Rémy Slama, environmental epidemiologist and co-director of the Aviesan multi-thematic Public Health Institute;

- Mr. Gérard Lasfargues, Deputy Director General of the Science for Expertise Unit and Mr. Matthieu Schuler, Director of Risk Assessment at the French National Agency for Food, Environmental and Occupational Health Safety (the ANSES);

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- Ms. Stéphanie Combes, Director of the Health Data Hub.

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[14] A larger number of participants gives the study greater statistical validity. The number of participants should be increased as the number of factors to be assessed increases.

[15] *Cohort studies consist of monitoring the participants' environmental factors without suggesting or imposing any changes in their habits, as it would be unethical to ask a group to place themselves in specific conditions which are suspected to have a negative impact on their health.*

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