EXPOSOMICS

Environmental Health: Past, Present, and Future

Linda S. BIRNBAUM

Ph.D., Scientist Emeritus and Former Director, National Institute of Environmental Health Sciences and National Toxicology Program, Scholar in Residence, Nicholas School of the Environment, Duke University

Abstract

People have long been interested in the relationship between their health and their environment. The last thirty years have shown that it is necessary to have a holistic and multi-factorial approach to environmental health and to grasp the way in which these problems affect populations differently according to social and economic criteria. The 21st century must also call for new multidisciplinary research approaches that include all types of exposure, at various doses, from the fetus to senior citizens, and over the long term. What are the current challenges in environmental health research?
Keywords: Environmental Health, Toxicology, Exposure, Exposomics

Résumé

Santé Environnementale : passé, présent, futur

Depuis longtemps les hommes se sont intéressés à la relation entre leur santé et leur environnement. Ces trente dernières années ont montré qu'il est nécessaire d'avoir une approche holistique et plurifactorielle de la santé environnementale et de saisir la manière dont ces problématiques affectent différemment les populations en fonction aussi de critères sociaux et économiques. Le XXIe siècle doit aussi voir apparaître de nouvelles approches d'une recherche multidisciplinaire englobant tous les types d'exposition, aux différents dosages, du fœtus au grand âge, et sur la longue durée. Quels sont les défis actuels en santé environnementale ?
Mots-clés : *santé environnementale, toxicologie, exposition, exposomique*

Our environment, our health, our life

Realization of the role of the environment on health is at least 2000 years old, dating back to concern about lead poisoning, or plumbism, in the Roman empire. In 1786, Benjamin Franklin concluded that occupationally related "colic" in a group of typesetters was caused by lead. Taking the handle off the water pump following the investigations of John Snow ended the cholera epidemic in London in 1854. One hundred years later, the London Fog of 1952 was due to air pollution and an air inversion. Rachel Carson's book Silent Spring, published in 1962, launched the modern environmental movement. Since that time, there have been a series of significant findings linking environmental exposures to adverse effects on human health (Table 1).

According to the WHO (1989), "Environmental health comprises those aspects of human health, including quality of life, that are determined by physical, biological, social, and psychosocial factors in the environment. It also refers to the theory and practice of assessing, correcting, controlling and preventing those factors in the environment that can potentially affect adversely the health of present and future generations." Environmental health addresses all human health-related aspects of both the natural and the built environment. This includes the quality of air, water and land, as well as noise, housing, waste and physical factors, vector control and environmental justice. There is an increasing gap between rich and poor in environmental health, and rapid urbanization is driving river and ocean pollution and degradation. The environmental burden of disease is greatest in countries that have the lowest global national incomes and the largest populations. In fact, more than 12% of all global deaths are linked to the environment, and the majority are associated with non-communicable diseases, such as obesity, type 2 diabetes, cardiovascular disease, asthma and cancer. Fewer deaths are caused by contagious diseases, even in the least developed countries.

Our health is determined not only by our genes, but also by our environment. Our environment is not just synthetic chemicals such as pesticides, consumer and personal care products, combustion and drugs, but also our diet, microbiomes, infectious agents, lifestyle and stress. Air pollution is the greatest cause of global environmental deaths, followed by water pollution, then occupational exposure and soil pollution (Landrigan et al, 2018)[1]. Pollution can impact every organ and tissue in the human body.

A key focus that has emerged for environmental health is susceptibility across the lifespan – that is, that people are more sensitive to environmental threats during times of rapid development and differentiation such as *in utero*, childhood, adolescence, pregnancy, and aging. Another focus concerns complex chronic diseases and combined environmental exposures. Health disparities can greatly impact not only exposure but susceptibility, and there are constantly emerging novel environmental threats. Newer research areas concentrate on epigenetics and stem cells, the microbiome and exposome, developing predictive methods and high throughput screening, and

[1] The Lancet Commission on pollution and health.Landrigan PJ, Fuller R, Acosta NJR, Adeyi O, Arnold R, Basu NN, Baldé AB, Bertollini R, Bose-O'Reilly S, Boufford JI, Breysse PN, Chiles T, Mahidol C, Coll-Seck AM, Cropper ML, Fobil J, Fuster V, Greenstone M, Haines A, Hanrahan D, Hunter D, Khare M, Krupnick A, Lanphear B, Lohani B, Martin K, Mathiasen KV, McTeer MA, Murray CJL, Ndahimananjara JD, Perera F, Potočnik J, Preker AS, Ramesh J, Rockström J, Salinas C, Samson LD, Sandilya K, Sly PD, Smith KR, Steiner A, Stewart RB, Suk WA, van Schayck OCP, Yadama GN, Yumkella K, Zhong M.Lancet. 2018 Feb 3;391(10119):462-512. doi: 10.1016/S0140-6736(17)32345-0. Epub 2017 Oct 19.PMID: 29056410

highlight the requirement to engage with communities. It is essential that research is translated from data to knowledge to action.

The need to transform toxicology and exposure science in the 21st century

There is a need to transform toxicology and exposure science in the 21st century. Why would we focus on 20th century methods more than 2 decades into the 21st? Environmental health research must move on from its previous approaches of assuming that chemicals act by overwhelming the body's defenses at high doses, and understand that chemicals act by disrupting control of developmental processes at low doses. We must focus more on studying the long-term impacts of both acute and chronic exposures, especially in the fetus and in children. And we must move from studying one chemical at a time into the reality that we are always exposed to mixtures. These new approaches require multidisciplinary approaches and teams.

We understand that certain chemicals are particularly bad actors. Compounds with broad pollution exposure such as bisphenols, phthalates, flame retardants, PFAS, pesticides, mercury, lead, cadmium, arsenic and PCBs cause a wide variety of health effects. The same is true of air pollution, a complex mixture of gases, volatiles and particles that is associated with coughing and wheezing, bronchitis and COPD[2], altered lung development, asthma, increased blood pressure and arteriosclerosis, heart attacks, ischemic heart disease and strokes. Air pollution is also associated with cancer of the lung, nasopharynx and larynx, diabetes, liver and kidney damage, decrease in birth weight, autism, IQ deficits, and neurodegenerative disorders including ALS (*amyotrophic lateral sclerosis*), Alzheimer's disease and schizophrenia. Indoor air exposure associated with household air pollution is associated with millions of deaths each year, especially in young children and women who are burning biofuels for cooking and heating. Household products also significantly contribute to both indoor and outdoor air pollution.

The WHO has defined an endocrine-disrupting chemical as an exogenous substance or mixture that alters the function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations. The endocrine system is extremely complex and context dependent, with multiple points of regulation for finely tuned responses. It naturally operates at low doses and effects can be organizational, as in development (and therefore irreversible), or activational, as in maintaining our basic physiology. Exposures to endocrine disruptors are ubiquitous and involve agricultural chemicals, industrial chemicals and byproducts, waste products, pharmaceutical products, and personal care and consumer products. Many of these have effects at low doses, especially in reproduction and development. Often the internal dose (or "body burden") in experimental animals is within the range of general population exposure. Effects include all kinds of toxicities, including impacts on the immune system, heart and brain. What is clear is that early life exposure can have long-lasting effects because at this time, organs are forming, gene expression programs are being established, epigenetic reprogramming occurs, and the effects are permanent. It has also become clear over the past several decades that early life exposure can lead to latent effects, not only in the directly exposed fetus/child but in following generations.

2 COPD for *Chronic obstructive pulmonary disease*

EXPOSOMICS and other new approaches

There are key questions which need to be addressed. Some external exposures can be monitored by environmental sensors, and biomonitoring can be used to assess internal exposure. Effects from environmental exposures may vary depending on the timing of exposure – acute vs. chronic, critical developmental windows, ongoing vs. past, and the exposure route (inhalation, ingestion, dermal absorption). Chemical mixtures are now a reality, and evidence is building that an additivity approach is appropriate to studying effects at environmental levels. The complexity of mixtures can be approached by either a top-down or a bottom-up approach, or by using the actual mixture of concern. Their complexity is mind-boggling, especially if non-chemical stressors are included in the analysis (as they should be). The exposome, first described by Chris Wild in 2005[3], is the total exposure from pre-conception until death. The exposome includes stressors, sources, location, time, route, distribution, and targets. New technologies are being developed including personal sensors that can monitor diet, physical activity, psychosocial stress and addictive substances, analysis of chemical exposures, and biological response indicators. Integrated tools and technologies are under development. External exposures can be evaluated by questionnaires, pictures, GIS imaging, and personal sensors such as smart phones and wristbands. Targeted analysis for hundreds of chemicals is carried out using a variety of chemical and bioassay approaches. However, the study of the exposome has revealed that there are thousands of knowns and unknowns. Agnostic approaches involve highly technical methods involving mass spectrometry and other chromatographic analyses. Biomonitoring is usually based on blood/serum/plasma and urine, but other available biospecimens such as breast milk, semen and skin biopsies can also be used. Today, high-throughput approaches look at other parts of the exposome such as the metabolome and proteome, as well as synthetic chemical exposures.

There are several other recent approaches to environmental health that are being used extensively. The first is systematic review, which has been used in clinical medicine for a long time but was only applied to environmental health around a decade ago. Systematic reviews are literature-based evaluations involving a predefined, multi-step process, critical assessment, and address a specific question. The evidence integration process involves looking at not only human data (which is almost completely observational in the case of environmental exposures), but also animal data obtained both in the wild and in experimental contexts, and mechanistic information. This process results in a hazard conclusion in which all the steps are transparent, but still involves scientific judgement. The second approach has been in development for over 20 years but is known today as NAMs, or New Approach Methodologies. Because there are tens if not hundreds of thousands of chemicals, there is no way of conducting toxicology, or epidemiological, studies on them all. NAMs involves both computational approaches and high-throughput *in vitro* tests which may lead to the development of predictive models of response. They can be used to identify targets, pathways or networks linked to adverse outcomes. Challenges to the use of NAMs include the general acceptance of animal models for human health risk assessment, different regulatory requirements from different agencies, the need to cover a huge chemical space, the difficulty of procuring standards, and overcoming regulatory and institutional inertia. Key characteristics (KCs) represent the third, relatively new approach to assessing environmental health effects. Key characteristics involve common patterns of response. "The best thing we have going for us is our intelligence, especially pattern recognition, sharpened over eons of evolution" (Neil deGrasse Tyson, 2015)[4]. The recognition that common KCs of toxicants cause

3 Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology; Wild CP. Cancer Epidemiol Biomarkers Prev. 2005 Aug;14(8):1847-50. doi: 10.1158/1055-9965.EPI-05-0456.PMID: 16103423

4 Tyson, Neil de Grasse (2015), Cosmos: A Spacetime Odyssey-transcripts (Episode 3), When Knowledge Conquered Fear .

various diseases leading to a more holistic view, leads us to anticipate that in the future, the role and importance of mechanistic understanding in hazard identification will increase. There will be fewer traditional animal studies. Mechanistic and other relevant information will play a bigger role in identifying potential carcinogens and environmental chemicals targeting other diseases. There will be more mining and data analysis from data repositories. The new approaches will need to remain scientifically sound but take less time. KCs provide an effective way to organize mechanistic information. With all the new approaches, advanced tools can facilitate the process, but expert judgement remains critical.

The existential threat of our time is climate change, which has led to a great increase in billion-dollar weather and climate disasters. There are more fires and heat waves, more droughts but also more flooding. The increase in temperatures has led to shifts in agriculture and vector locations, as well as direct impacts on allergies, food security and mental health. There are observable impacts of climate change on health at this time and it is projected that the impacts will increase in severity. The health effects of climate change are associated with other social and environmental determinants of health. We all know that actions to reduce greenhouse gas emissions have the potential to greatly reduce morbidity and mortality, especially by reducing the air pollution resulting from fossil fuel combustion. Pope Francis stated in 2015 that "climate change is a global problem with grave implications: environmental, social, economic, political and for the distribution of goods. It represents one of the primary challenges facing humanity in our day."

Let us all understand that the health benefits of meeting climate goals far outweigh the costs. These benefits include the improvement of environmental and public health.

Some Major Environmental Health Findings, 1967-2015

1967	ASBESTOS linked to mesothelioma
1972	HERB NEEDLEMAN demonstrates problems with low level lead
1975	DES (diethylstilbesterol) linked to cancer
1985	2nd HAND SMOKE linked to cancer
1989	1^{s} Genetically Modified Mouse
1993	Harvard 6 CITIES STUDY
1994	BRCA 1 (breast cancer gene 1) cloned
1995	Prostate Cancer Suppressor Gene Cloned
1996	Developmental Neurotoxicity of PCBs
1997	Methyl Mercury in Seafood linked to Developmental Delays
1999	Aflatoxin causes Liver Cancer
2000	Air Pollution linked to All-Cause Mortality
2001	Dust Mites Cause Asthma
2002	Ozone Causes Asthma
2002	Dietary Supplements alter Fetal Epigenome
2004	<10ppm Benzene reduces blood cell counts
2005	Artificial Light Suppresses melatonin
2006	PON1 Metabolizes OP Pesticides
2007	Hexavalent Chromium causes Cancer
2008	Growing concern for BPA
2009	Exposome Sensors Research Takes Off
2009	Personal Sensors for Toxicants
2010	Climate Change causes Human Health Effects
2010	Deepwater Horizon Oil Spill and Environmental Disaster Research
2015	Brominated Flame Retardants cause cancer in rodents
2015	Cell and Tissue Epigenome Mapped