Minireview

Understanding exposures and latent disease risk within the National Institute of Environmental Health Sciences Superfund Research Program

Sara M Amolegbe, Danielle J Carlin, Heather F Henry, Michelle L Heacock, Brittany A Trottier and William A Suk

Superfund Research Program, National Institute of Environmental Health Sciences (NIEHS), National Institutes of Health (NIH), Department of Health and Human Services (DHHS), Research Triangle Park, NC 27560, USA
Corresponding author: Sara M Amolegbe. Email: sara.amolegbe@nih.gov

Impact Statement

This article provides an overview of the National Institute of Environmental Health Sciences (NIEHS) Superfund Basic Research and Training Program (SRP) and describes how the program is well-positioned to use multidisciplinary approaches to study the effects of exposures and later-life diseases. By explaining how the SRP is working to address this challenge of linking exposures and later-life diseases, the minireview provides an outline of needs and next steps to advance this field and improve our understanding of how exposures contribute to disease, especially when there is a lag between exposures and disease onset.

Abstract

Understanding the health effects of exposures when there is a lag between exposure and the onset of disease is an important and challenging topic in environmental health research. The National Institute of Environmental Health Sciences (NIEHS) Superfund Basic Research and Training Program (SRP) is a National Institutes of Health (NIH) grant program that uses a multidisciplinary approach to support biomedical and environmental science and engineering research. Because of the multidisciplinary nature of the program, SRP grantees are well-positioned to study exposure and latent disease risk across humans, animal models, and various life stages. SRP-funded scientists are working to address the challenge of connecting exposures that occur early in life and prior to conception with diseases that manifest much later, including developing new tools and approaches to predict how chemicals may affect long-term health. Here, we highlight research from the SRP focused on understanding the health effects of exposures with a lag between exposure and the onset of the disease as well as provide future directions for addressing knowledge gaps for this highly complex and challenging topic. Advancing the knowledge of latency to disease will require a multidisciplinary approach to research, the need for data sharing and integration, and new tools and computation approaches to make better predications about the timing of disease onset. A better understanding of exposures that may contribute to later-life diseases is essential to supporting the implementation of prevention and intervention strategies to reduce or modulate exposures to reduce disease burden.

Keywords: Disease latency, developmental origins of disease, early-life exposures, environmental health

Experimental Biology and Medicine **2022; 247: 529–537. DOI: 10.1177/15353702221079620**

Introduction

Diseases are often detected or diagnosed in early to late adulthood, but the origins of these diseases may be a result of exposures occurring much earlier in life or even before life begins. Understanding the health effects of exposures and resultant later onset of disease is an important and challenging issue.

A large body of epidemiologic, clinical, and basic mechanistic research supports the developmental origins of health and disease (DOHaD) paradigm. DOHaD refers to the hypothesis that the diseases of adulthood can be influenced by exposures before birth and during critical periods of early fetal and childhood growth and development.[1] Sometimes, these risks include exposures to an individual's parents before conception and can also carry over into future generations.[2]

The DOHaD paradigm originally focused on nutrition but has since expanded to include the effects of environmental chemical exposures on early-life development and subsequent development of disease across the lifespan.[3–5] For example, in addition to changes in diet and lifestyle, a subclass of endocrine-disrupting chemicals (EDCs) in the environment can contribute to obesity, type 2 diabetes, and non-alcoholic fatty liver disease. These chemicals might predispose some individuals to gain weight despite their efforts to limit caloric intake and increase levels of physical activity.[6,7] Research has also shown that carcinogens

readily cross the placenta, which could provide evidence of potential early stage chemical carcinogenesis in children.[8] Furthermore, other studies link early-life exposures to environmental chemicals and risk for immune-related diseases and lung dysfunction later in life.[9] These concepts have wide implications for understanding the causes, and for developing potential prevention strategies, for a wide range of non-communicable diseases.[10]

Development during the fetal and infancy stage is characterized by rapid growth and maturation of organs and systems. Variation in environmental exposures and/or the quality or quantity of nutrients consumed by parents before conception and mothers during pregnancy, as well as infants during the first year of life, can lead to enduring and significant effects on development that may lead to later-life health consequences. These effects, or "programming," persist long after an initial exposure, predisposing the individual to disease in later life, and thus represent an important risk factor for a variety of non-communicable diseases, such as heart disease and cancer.[11] There is also compelling evidence that exposures to parents before conception can affect their child's lifetime health.[12]

Early-life programming and transcriptional regulation supports the need to understand epigenetic mechanisms as a determinant in disease predisposition.[13] With epigenetic techniques, researchers have been able to examine changes in DNA, which can affect gene expression, to explore new potential mechanisms and develop new clinical and cohort studies to determine how people respond to early-life exposures.[1] Epigenetic modifications such as DNA methylation, histone modifications, and expression of non-coding RNAs are involved in the mediation of early-life environmental exposures and may impact health later in the life course. For example, researchers have linked DNA methylation to metabolic health measures and future metabolic health status. These studies suggest that DNA methylation may mediate the effects of early-life exposures on later-life risk of obesity and obesity-related diseases.[5]

Researchers are also exploring how mechanisms at different life stages of exposure translate to differences in disease outcomes, as well as other factors that may impact resilience and disease vulnerability. This includes the influence and effects of social inequalities and social and behavioral factors on environmental health risks. Also of interest is the role of the microbiome and how changes in gut microbiota early in life can impact windows of susceptibility and later-life disease.[1,14,15] Another mechanism that is gaining attention is environmentally induced somatic mosaicism. Exposures during critical windows of development can affect a person's normal tissue development but may also explain tissue-specific effects of hazards in the adult organism due to genetic mosaicism.[16] In addition, transgenerational inheritance is a promising avenue of research that is under active investigation. Some health effects appear to be transmitted to offspring, suggesting that these epigenetic effects persist across generations.[17–19] Scientists are beginning to understand epigenetic inheritance or the mechanisms by which non-genetic information is transmitted to and deciphered by subsequent generations. A better understanding of how and when epigenetic inheritance occurs will advance the understanding of how organisms cope with changing environments and diseases that may be influenced by a parent's environment.[18]

Unlike models of infectious disease, in which individuals remain healthy until they contract a disease, non-communicable diseases can develop gradually over the life course.[4] In addition, responses to similar environmental challenges vary substantially between people, even in individuals who are genetically identical.[4] However, the mechanisms by which environmental insults can have long-term and later-life effects are relatively unclear; one challenge stems from translating studies in single cells to whole humans. Further exploring toxicant-mediated disruptions to epigenetic programming and how these effects may be transmitted across generations is essential for the implementation of initiatives aimed at reducing non-communicable diseases.[20]

The Superfund Research Program

The National Institute of Environmental Health Sciences (NIEHS) Superfund Basic Research and Training Program (SRP) is a National Institutes of Health (NIH) grant program that uses a multidisciplinary approach to support biomedical and environmental science and engineering research and to train the next generation of environmental health scientists. Since its inception in 1987, the SRP has supported researchers to better understand how exposures to hazardous substances in the environment affect health and disease[21] and to determine sustainable ways to prevent exposure and remediate these substances.[22,23] Moreover, a key goal of the SRP is to use basic research findings to understand the mechanisms by which exposure to contaminants leads to human disease and why some individuals may be resilient to exposures and less susceptible to disease than others.

Because of the multidisciplinary nature of the program, SRP grantees are well-positioned to study exposure and latent disease risk. More specifically, SRP-funded scientists are working to address the challenge of connecting exposures that occur early in life and prior to conception with diseases that manifest much later, including developing new tools and approaches to predict how chemicals may affect long-term health and how they may interact with each other to exacerbate effects. SRP scientists collaborate across disciplines and contribute their domain expertise to answer specific questions that are part of a larger problem that a single discipline could not answer alone, leveraging a systems approach to integrate research and data to tackle critical complex research questions.[24] SRP researchers are addressing these questions from their vantage point of expertise and looking across model organisms, life stages, and developing tools to make better predictions. Some of these SRP-funded research studies are highlighted in Figure 1.

This minireview highlights research from the SRP focused on understanding the health effects of exposures when there is a lag between exposure and the onset of the disease and provides future directions for addressing knowledge gaps for this complex and challenging topic.

Looking across cells, animal models, and humans

SRP researchers have used a combination of *in vitro* and *in vivo* models as well as long-standing cohort studies to evaluate the effects of a variety of environmental exposures and later-life health effects. For example, SRP researchers have assessed the effects of flame retardants on later-life fat

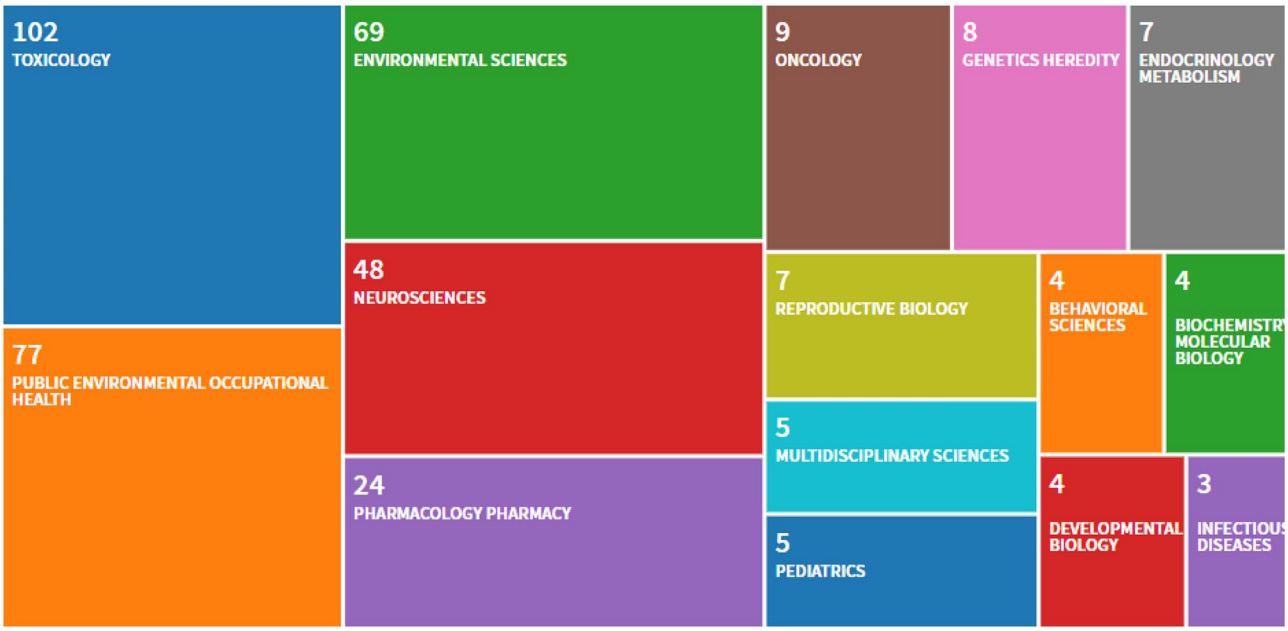

Figure 1. Web of Science research categories Treemap created in Clarivate Analytics' Web of Science. The journal landscape Treemap displays a set of 215 publications from SRP-funded studies related to exposures and latent disease risk, categorized by Web of Science Research Areas. Web of Science classifies the journals it indexes into approximately 250 subject categories. Journals can be assigned to multiple Categories (at least one, up to six). Publications are indexed with the Category assigned the parent Journal and therefore may have more than one Category assigned. The visualization shows how these SRP-funded studies have spanned a variety of disciplines and addressed questions in multiple fields. (A color version of this figure is available in the online journal.)

accumulation and obesity across various organisms. They have characterized how brominated and organophosphate flame retardants in indoor dust increase fat accumulation in mouse cells.[25] These findings were confirmed in studies of humans, where researchers found that higher serum levels of chemicals in flame retardants were associated with increased formation of fat cells and fat accumulation and higher body mass index.[26] In addition, using the zebrafish model, they showed how exposure to these hazardous compounds favors the development of fat cells over bone cells,[27] which indicates that these changes early in life may contribute to degenerative bone diseases in adulthood.

SRP researchers have also used the mouse model to elucidate the relationship between arsenic exposure and later-life health outcomes. For example, they found that early-life exposure to arsenic permanently altered airway structure and function in mice, which could potentially lead to problems in the lungs later in life including chronic cough and obstructive or restrictive lung disease.[28] SRP researchers have also found that prenatal and early-life exposure to arsenic disrupted normal metabolism and elevated the risk for fatty liver disease in mice maintained on a high-fat diet. According to the investigators, individuals exposed to arsenic during key developmental periods while on a Western-style diet may be at increased risk for metabolic disease later in life.[29]

Another example, and as part of a study of populations in Massachusetts and Rhode Island, SRP grantees linked early-life exposure to tetrachloroethylene (PCE) in drinking water with increased risk of cancer, epilepsy, visual dysfunction, and mental illness later in life.[30–32] They found that "risky" behaviors, particularly drug use, were more frequent among adults who were exposed to higher levels of PCE in the womb and in early childhood.[33] The team also uncovered that prenatal exposure to both alcohol and PCE may combine to increase the risk of using multiple illicit drugs as a teenager.[34]

SRP researchers also revealed associations between early-life per- and polyfluoroalkyl substance (PFAS) exposure and immune dysfunction and metabolic abnormalities.[35,36] For instance, they have identified associations between PFAS exposures and impaired glycemic status in metabolically vulnerable pregnant women, which may enhance the risk of development gestational diabetes and could lead to metabolic-related outcomes in their newborns.[36] They also found that childhood PFAS exposure may be associated with elevated serum lipid concentrations, which may be a risk factor for development of cardiovascular disease and hyperlipidemia later in life.[37] They are currently identifying pathways by which exposure to PFAS contributes to obesity and weakened immune systems. They found evidence that PFAS disrupts metabolism by altering the regulation of hormones that help control energy storage and body composition.[38]

In mice, SRP researchers have provided evidence for a link between inflammation-related signaling and the development of asbestos-induced malignant mesothelioma, providing a potential early mechanistic sign of mesothelioma.[39] Using serum samples from human studies, researchers also identified serum lipid biomarkers for mesothelioma and asbestos exposure, an approach that may promote early detection and treatment.[40] By examining DNA mutations in mesothelioma patients with a family history of cancer, they identified genetic factors associated with higher incidence of asbestos-induced malignant mesothelioma. This suggests the utility of genetic testing for some patients for the purpose of early detection of cancers and clinical intervention.[41] Although the link between asbestos exposure and

mesothelioma is well-documented,[42–44] SRP grantees are exploring ways to detect the disease earlier in the disease progression and/or predict whether a person may be more susceptibility to the disease later in life.

SRP grantees are also assessing how exposure to lead, arsenic, manganese, and cadmium alone or in mixtures during development alters signaling molecules in the brain to accelerate cognitive aging, which may lead to cognitive decline.[45] They previously found that lead induces a response in neural stem cells that is dependent on NRF2, the master transcriptional factor for the oxidative stress response, and identified a potential mechanism linking lead exposure with neural stem cell function and neurodevelopment in children.[46] SRP grantees have also found that increased progression of Parkinsonism was associated with cumulative manganese exposure.[47]

After an epidemiological study was released showing an association between in utero *N*-nitrosodimethylamine (NDMA) exposure and childhood cancer, an SRP Center was established to further explore and address the problem of NDMA exposure in Massachusetts. They are using mouse studies to identify mutational fingerprints of NDMA that could serve as a clue as to how NDMA contributes to cancer. They are also studying very early cellular responses to NDMA exposure, including changes in gene expression and cell signaling, to gain a better mechanistic understanding of disease causation.[48]

Looking across life stages: arsenic as a case study

In addition to evaluating exposures across various models and organisms, some SRP researchers have also initiated longitudinal cohort studies to assess the health effects of environmental exposures across the lifespan. A primary example of this work includes the Health Effects of Arsenic Longitudinal Study (HEALS) and its ancillary studies to follow a population in Bangladesh that has been exposed to varying concentrations of arsenic through contaminated well water.[49] The cohort was first established in 2000 with 12,000 participants,[50] and since has expanded to include over 35,000 people. Their work has been instrumental in associating long-term and early-life arsenic exposure with numerous diseases across the life course. For example, they have demonstrated an association between higher arsenic exposure and chronic disease mortality, including cardiovascular disease.[51,52] They found that arsenic exposure increased the risk of heart disease and shed light on how arsenic exposure was associated with QT interval prolongation, or irregular electrical activity of the heart, which has been associated with increased risk of cardiovascular mortality.[53,54] They also revealed that exposure to arsenic in early life can lead to increased blood pressure in adolescence.[55] These researchers have also made important discoveries linking early-life exposure to arsenic with decreased intellectual function and motor function in adolescence.[56,57] These findings were mirrored in a population in the United States where higher arsenic exposure was associated with lower intelligence quotient (IQ).[58]

Another SRP-funded cohort focused on elucidating the effects of early-life exposure to arsenic in a group of people in northern Chile who were exposed to high levels of arsenic in drinking water before a water treatment plant was installed. Even 25 years after a major decrease in arsenic exposure, they reported that population mortality rates remained elevated compared to the unexposed group.[59] They found an association between prenatal and childhood arsenic exposure and signs and symptoms of lung disease in adults, such as decreases in lung capacity and increases in chronic cough and bronchitis.[60] Researchers also uncovered an association between early-life arsenic exposure and type 2 diabetes and hypertension in adults.[61,62] Early-life arsenic exposure was also found to be associated with cancer in specific kidney and ureter cells as well as lung and bladder cancer in adults.[63,64]

Researchers are also exploring mechanisms by which exposure to arsenic early in development affects health throughout life and have found evidence that these later-life health effects may be tied to changes in the epigenome.[65,66] Through studies in newborn cord blood and placenta cells, investigators have shown how arsenic exposure results in epigenetic changes that can disrupt the endocrine system. This would not only explain differences in birth outcomes among children but may also be linked to onset of later-life diseases and dysfunctions.[67,68]

Making better predictions

To close the gap in understanding later-life diseases resulting from early-life exposures, researchers and decision-makers need better tools and strategies to predict how different hazardous exposures may harm human health. One approach to help risk assessors predict the toxicity of chemicals is based on understanding key characteristics of chemicals that lead to toxicity. The key characteristics framework, which was work funded by the SRP, helps identify and summarize the potential health risks of different chemicals based on mechanistic data and prioritize them for further study.[69] So far, researchers have identified key characteristics shared by chemicals that cause cancer, are toxic to male and female reproduction, and are EDCs.[69–73] They are currently working on additional key characteristics of neurotoxicants, cardiovascular toxicants, and hepatotoxicants.[74] By understanding key characteristics of chemicals as a basis for searching, organizing, and evaluating mechanistic evidence to support hazard identification, scientists are one step closer to identifying chemicals that may lead to disease earlier on in the disease progression.

SRP researchers are also developing experimental and computational approaches to model environmental chemicals to predict their long-term adverse effects based on short-term experiments. For example, through the Carcinogenome Project, researchers developed a framework to predict long-term cancer risk from short-term chemical exposure data. This fast, cost-effective method uses gene expression profiling, which measures the activity of a thousand or more genes to capture what is happening in a cell. It then applies computer modeling to predict the ability of the chemicals to initiate a cascade of cellular events that can lead to cancer.[75]

Other models are being developed to predict the toxicity of complex polycyclic aromatic hydrocarbon (PAH) mixtures. Using zebrafish, researchers screen PAH mixtures for

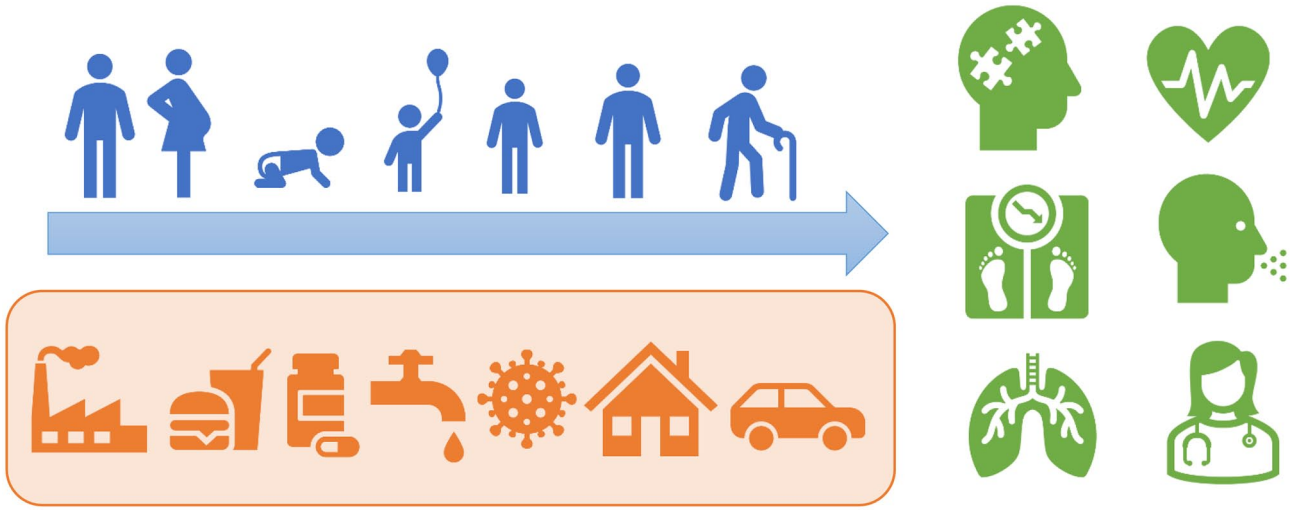

Figure 2. Understanding the health effects of exposures when there is a lag between exposure and the onset of disease is an important and challenging issue in environmental health. (A color version of this figure is available in the online journal.)

toxicity based on their chemical structure and bioactivity, including changes at the molecular, organ, and organism levels, to predict how early-life exposures affect long-term brain development and behavior.[76] Through this work, they have found that zebrafish exposed to PAHs as embryos had impaired behavior as larvae and decreased learning and memory function as adults.[77] In addition, studies are focusing on identifying how exposure to even more complex mixtures (e.g. PAHs and pesticides) early in life affects brain and metabolic outcomes later. Researchers have identified critical windows of neurodevelopment that were sensitive to harmful exposures and revealed important differences between exposure to individual PAH chemicals compared to realistic mixtures.[78] Researchers have also reported that rats exposed to pesticides shortly after birth had altered metabolism that may contribute to obesity and other metabolic outcomes in adulthood.[79–81]

Moving forward

Improving what researchers know about the association between early-life exposures and later-life effects in humans will require a multidisciplinary approach that integrates mechanistic, human, and animal studies. Future research could include animal studies that address mechanistic hypotheses integrated with studies of human populations that address exposures, molecular alterations, and latent disease outcomes.[66] Cohort studies could test hypotheses based on mechanisms proposed by animal and cell-based studies.[1] Multidisciplinary teams can work to share data and enhance integration of mechanistic data across fields of science and model organisms. Incorporating data on exposures and disease risk from different disciplines that are addressing similar questions can provide a broader understanding and uncover the answers to these complex research questions.[82]

More research is needed to explore how mechanisms at different life stages of exposure translate to differences in disease outcomes. This includes further advancing fields related to identifying critical windows of development and environmentally induced somatic mosaicism, the role of the microbiome in disease, and a better understanding of additive or synergistic effects of multiple exposures and how differences in exposure routes can impact disease susceptibility. Developing and expanding computational tools and machine learning approaches could improve what grantees know about chemical bioactivity, explore the potential combined effects of mixtures, and predict risk based on data from studies investigating effects later in life. Developing tools that integrate geospatial data can also provide an effective way to visualize how environmental factors, as well as other social stressors, contribute to community vulnerability to contaminants and potential health effects.[83]

Expanding knowledge about how different chemical characteristics can lead to changes in the body will provide mechanistic information that may help to predict potential health effects later in life. In addition to understanding chemical characteristics, it is also important to understand key characteristics, or hallmarks, of disease and aging to consider when predicting potential health effects. As researchers explore key hallmarks of aging, which represent the common denominators that occur with aging, it is important to integrate data on exposures that may help to explain why older adults may be more or less susceptible to health effects.[84,85] Hallmarks of aging that change throughout life relate to a combination of genetics and environmental factors, such as an individual's lifestyle and exposure history.[84] By utilizing the concept of the hallmarks of aging in studies, and linking these changes to hallmarks associated with disease, researchers may be able to better study factors contributing to disease latency.

Although a significant amount of research has been conducted to investigate sensitive windows of exposure early in life and later-life diseases, more research is needed that focuses on exposures that occur during all life stages of exposure, including adolescence and early adulthood (Figure 2). Specifically, most SRP and other environmental health studies on exposures and latent disease risk focus on prenatal and childhood exposures, but there is more to learn about

adult exposures. Exposures during adulthood can also lead to diseases after a long latency period, so focusing on adolescents and adults, including more vulnerable time periods such as puberty, pregnancy, and menopause, and following them for long periods of time, may reveal new insights into latent disease risk.

When looking at historical data to predict exposures, cohort studies may also inadvertently lead to sampling bias, where the data collected could be more likely to leave out traditionally marginalized groups who may be underrepresented in the available health and mortality records. For example, a study assessing itemized asbestos exposure profiles for a community in 1930 using Ancestry.com and other publicly accessible databases highlights how historic cohort studies likely underestimate the impact of asbestos exposure on minority populations.[86] Involving communities early in the research process or initiating community-based participatory research studies that closely involve the community may provide a better window into what people are exposed to and help prevent some forms of sampling bias.

Connecting exposures to later-life disease requires a better estimate of exposures and a more detailed understanding of a person's exposome, or the totality of exposures throughout life. The exposome concept was first coined by Chris Wild in 2005 to encompass the totality of human environmental exposures from conception onwards, complementing the genome.[87] Exposome studies use different methods to collect a large number of exposures, such as through self-reported questionnaires, exposure biomarkers, geographic information, personal sensors, and other exposure technologies.[88] The fact that people have different habits, physically move, and are exposed to a variety of different chemicals in their everyday life makes it difficult to estimate a lifetime of exposures unless researchers have more accurate information to assess previous exposures based on biological factors. To be able to link exposures to later-life effects, researchers need to be able to better characterize exposures and develop untargeted methods to assess potential exposures and their associated effects on the body. For example, SRP researchers have developed an untargeted approach to measure DNA adducts in neonatal blood spots from a population-based case–control study of childhood leukemia to identify risk factors for childhood leukemia.[89] NIEHS researchers are also using shed teeth to better reconstruct lifetime exposures to a variety of chemicals from the prenatal period through childhood, which helps to associate exposures during critical windows with latent diseases.[90] For example, one study showed that essential and toxic elements are regulated differently in children with autism spectrum disorder, revealing a potential sensitive biomarker for early diagnosis.[91] These techniques are now being applied to study and predict neurodegenerative diseases that occur later in life, including amyotrophic lateral sclerosis and Parkinson's disease.[92] Although they have demonstrated a broad range of chemical metabolites can be measured in a tooth, there are still many unidentified metabolites.[90,93]

Large cohort studies are a rich source of data but are also expensive to maintain and can take several years to yield data for analysis. As a result, data from these existing resources should be shared and leveraged when possible to make the most use of these large and expensive longitudinal studies. SRP supports the NIEHS Human Health Exposure Analysis Resource (HHEAR) initiative, which is comprised of a consortium of NIH-funded researchers with access to high-quality analytical capabilities and exposure assessment services.[94] The SRP has supported the HHEAR laboratory at the Icahn School of Medicine at Mount Sinai to provide state-of-the-art services for analyzing biological and environmental samples including untargeted analysis of samples such as blood, urine, stool, saliva, teeth, and hair to help link exposures and health outcomes. A second supported lab at Duke University focused on untargeted and targeted analyses to comprehensively measure chemicals in air samplers, silicone wristbands, and environmental media, including water, soil, sediment, and dust, with the goal of associating health outcomes to their environmental sources.[95,96]

Together, these approaches can give a more comprehensive picture of what humans are exposed to throughout their lives and help strengthen the evidence linking exposures and disease. More research on the origins of disease also plays an important role in establishing factors that play a role in disease outcomes and developing early prevention and intervention strategies to combat these factors earlier in the disease progression.[97]

Conclusions

The complexity of exposures and underlying biology, and the complex interplay between the two, contributes to the challenge of understanding the connection between exposures and disease, especially when there is a lag between the exposure and disease onset. It requires a significant investment of time, effort, and resources. This together with the limitations of epidemiological studies and across model organisms necessitates a multidisciplinary approach so that data and research findings can be evaluated from across mechanistic, animal, and human studies. The SRP is well-poised to address research questions related to latency of disease because of its broad array of multidisciplinary projects investigating across various models and life stages and by supporting investigators that take a systems approach to their research. Advancing the field of latency to disease will also require sharing and integrating research information and the development of high-throughput, computational, and machine learning approaches to make better predications of the onset of disease. In addition, a major limitation to the studies presented in this review has been that they only establish association and not causality between early-life exposure and latency of disease. This notion indicates the need for more studies that can reliably extrapolate cellular and tissue effects from environmental exposures and identify and use early biomarkers to predict disease across all life stages. More importantly, a better understanding of the basis of exposures that may contribute to later-life diseases is essential to supporting the implementation of prevention and intervention strategies to reduce or modulate exposures to reduce disease burden.

AUTHORS' CONTRIBUTIONS

W.A.S., S.M.A., and D.J.C. conceived of the main conceptual ideas for the manuscript; all authors participated in the development of an outline and contributed studies and examples to the minireview; S.M.A. wrote the manuscript with support from D.J.C.; all authors reviewed and approved the final version of the manuscript.

ACKNOWLEDGEMENTS

The authors thank Dr Elizabeth Martin for reviewing the manuscript and providing feedback on its content. The authors also thank Dr Lesley Skalla for creating the Web of Science research categories Treemap from SRP-funded publications.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID ID


Danielle J Carlin https://orcid.org/0000-0002-7578-858X

REFERENCES

1. Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. *Nutr Rev* 2017;**75**:951–70
2. National Institute of Environmental Health Sciences. *Developmental origins of health and disease*, 2019, https://www.niehs.nih.gov/research/supported/health/developmental/index.cfm
3. Haugen AC, Schug TT, Collman G, Heindel JJ. Evolution of DOHaD: the impact of environmental health sciences. *J Dev Orig Health Dis* 2015;**6**:55–64
4. Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and public health implications. *Am J Clin Nutr* 2011;**94**:1754S–8S
5. Bianco-Miotto T, Craig JM, Gasser YP, van Dijk SJ, Ozanne SE. Epigenetics and DOHaD: from basics to birth and beyond. *J Dev Orig Health Dis* 2017;**8**:513–9
6. Heindel JJ, Newbold R, Schug TT. Endocrine disruptors and obesity. *Nat Rev Endocrinol* 2015;**11**:653–61
7. Heindel JJ, Blumberg B, Cave M, Machtinger R, Mantovani A, Mendez MA, Nadal A, Palanza P, Panzica G, Sargis R, Vandenberg LN, Vom Saal F. Metabolism disrupting chemicals and metabolic disorders. *Reprod Toxicol* 2017;**68**:3–33
8. Henshaw DL, Suk WA. Diet, transplacental carcinogenesis, and risk to children. *BMJ* 2015;**351**:h4636
9. Cao J, Xu X, Hylkema MN, Zeng EY, Sly PD, Suk WA, Bergman Å, Huo X. Early-life exposure to widespread environmental toxicants and health risk: a focus on the immune and respiratory systems. *Ann Glob Health* 2016;**82**:119–31
10. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiol Rev* 2014;**94**:1027–76
11. Langley-Evans SC. Nutrition in early life and the programming of adult disease: a review. *J Hum Nutr Diet* 2015;**28**:1–14
12. Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, Barker M, Saffery R, Yajnik CS, Eckert JJ, Hanson MA, Forrester T, Gluckman PD, Godfrey KM. Origins of lifetime health around the time of conception: causes and consequences. *Lancet* 2018;**391**:1842–52
13. Bale TL, Baram TZ, Brown AS, Goldstein JM, Insel TR, McCarthy MM, Nemeroff CB, Reyes TM, Simerly RB, Susser ES, Nestler EJ. Early life programming and neurodevelopmental disorders. *Biol Psychiatry* 2010;**68**:314–9
14. Al Nabhani Z, Eberl G. Imprinting of the immune system by the microbiota early in life. *Mucosal Immunol* 2020;**13**:183–9
15. Guo F, Cai D, Li Y, Gu H, Qu H, Zong Q, Bao W, Chen A, Liu HY. How early-life gut microbiota alteration sets trajectories for health and inflammatory bowel disease? *Front Nutr* 2021;**8**:690073
16. Miles B, Tadi P. Genetics, somatic mutation. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing, 2021, https://www.ncbi.nlm.nih.gov/books/NBK557896/
17. Harris A, Seckl J. Glucocorticoids, prenatal stress and the programming of disease. *Horm Behav* 2011;**59**:279–89
18. Burton NO, Greer EL. Multigenerational epigenetic inheritance: transmitting information across generations. *Semin Cell Dev Biol*. Epub ahead of print August 2021. DOI: 10.1016/j.semcdb.2021.08.006
19. Xavier MJ, Roman SD, Aitken RJ, Nixon B. Transgenerational inheritance: how impacts to the epigenetic and genetic information of parents affect offspring health. *Hum Reprod Update* 2019;**25**:518–40
20. Vickers MH. Early life nutrition, epigenetics and programming of later life disease. *Nutrients* 2014;**6**:2165–78
21. National Institute of Environmental Health Sciences. About SRP: superfund research program, 2021, https://www.niehs.nih.gov/research/supported/centers/srp/about/index.cfm
22. Henry HF, Suk WA. Sustainable exposure prevention through innovative detection and remediation technologies from the NIEHS Superfund Research Program. *Rev Environ Health* 2017;**32**:35–44
23. Landrigan PJ, Wright RO, Cordero JF, Eaton DL, Goldstein BD, Hennig B, Maier RM, Ozonoff DM, Smith MT, Tukey RH. The NIEHS superfund research program: 25 years of translational research for public health. *Environ Health Perspect* 2015;**123**:909–18
24. Suk WA, Heacock M, Carlin DJ, Henry HF, Trottier BA, Lopez AR, Amolegbe SM. Greater than the sum of its parts: focusing SRP research through a systems approach lens. *Rev Environ Health* 2020;**36**:451–7
25. Kassotis CD, Hoffman K, Stapleton HM. Characterization of adipogenic activity of house dust extracts and semi-volatile indoor contaminants in 3T3-L1 cells. *Environ Sci Technol* 2017;**51**:8735–45
26. Kassotis CD, Kollitz EM, Hoffman K, Sosa JA, Stapleton HM. Thyroid receptor antagonism as a contributory mechanism for adipogenesis induced by environmental mixtures in 3T3-L1 cells. *Sci Total Environ* 2019;**666**:431–44
27. Macaulay LJ, Chernick M, Chen A, Hinton DE, Bailey JM, Kullman SW, Levin ED, Stapleton HM. Exposure to a PBDE/OH-BDE mixture alters juvenile zebrafish (***Danio rerio***) development. *Environ Toxicol Chem* 2017;**36**:36–48
28. Lantz RC, Chau B, Sarihan P, Witten ML, Pivniouk VI, Chen GJ. In utero and postnatal exposure to arsenic alters pulmonary structure and function. *Toxicol Appl Pharmacol* 2009;**235**:105–13
29. Ditzel EJ, Nguyen T, Parker P, Camenisch TD. Effects of arsenite exposure during fetal development on energy metabolism and susceptibility to diet-induced fatty liver disease in male mice. *Environ Health Perspect* 2016;**124**:201–9
30. Aschengrau A, Winter MR, Vieira VM, Webster TF, Janulewicz PA, Gallagher LG, Weinberg J, Ozonoff DM. Long-term health effects of early life exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study. *Environ Health* 2015;**14**:36
31. Getz KD, Janulewicz PA, Rowe S, Weinberg JM, Winter MR, Martin BR, Vieira VM, White RF, Aschengrau A. Prenatal and early childhood exposure to tetrachloroethylene and adult vision. *Environ Health Perspect* 2012;**120**:1327–32
32. Aschengrau A, Weinberg JM, Janulewicz PA, Romano ME, Gallagher LG, Winter MR, Martin BR, Vieira VM, Webster TF, White RF, Ozonoff DM. Occurrence of mental illness following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study. *Environ Health* 2012;**11**:2

33. Aschengrau A, Weinberg JM, Janulewicz PA, Romano ME, Gallagher LG, Winter MR, Martin BR, Vieira VM, Webster TF, White RF, Ozonoff DM. Affinity for risky behaviors following prenatal and early childhood exposure to tetrachloroethylene (PCE)-contaminated drinking water: a retrospective cohort study. *Environ Health* 2011;**10**:102
34. Gallagher LG, Webster TF, Aschengrau A. Exploring associations between prenatal solvent exposures and teenage drug and alcohol use: a retrospective cohort study. *Environ Health* 2017;**16**:26
35. DeWitt JC, Blossom SJ, Schaider LA. Exposure to per-fluoroalkyl and polyfluoroalkyl substances leads to immunotoxicity: epidemiological and toxicological evidence. *J Expo Sci Environ Epidemiol* 2019;**29**:148–56
36. Jensen RC, Glintborg D, Timmermann CAG, Nielsen F, Kyhl HB, Andersen HR, Grandjean P, Jensen TK, Andersen M. Perfluoroalkyl substances and glycemic status in pregnant Danish women: the Odense child cohort. *Environ Int* 2018;**116**:101–7
37. Blomberg AJ, Shih YH, Messerlian C, Jørgensen LH, Weihe P, Grandjean P. Early-life associations between per- and polyfluoroalkyl substances and serum lipids in a longitudinal birth cohort. *Environ Res* 2021;**200**:111400
38. Shelly C, Grandjean P, Oulhote Y, Plomgaard P, Frikke-Schmidt R, Nielsen F, Zmirou-Navier D, Weihe P, Valvi D. Early life exposures to perfluoroalkyl substances in relation to adipokine hormone levels at birth and during childhood. *J Clin Endocrinol Metab* 2019;**104**:5338–48
39. Kadariya Y, Menges CW, Talarchek J, Cai KQ, Klein-Szanto AJ, Pietrofesa RA, Christofidou-Solomidou M, Cheung M, Mossman BT, Shukla A, Testa JR. Inflammation-related IL1β/IL1R signaling promotes the development of asbestos-induced malignant mesothelioma. *Cancer Prev Res (Phila)* 2016;**9**:406–14
40. Xu R, Mesaros C, Weng L, Snyder NW, Vachani A, Blair IA, Hwang WT. Comparison of statistical methods for detection of serum lipid biomarkers for mesothelioma and asbestos exposure. *Biomark Med* 2017;**11**:547–56
41. Ohar JA, Cheung M, Talarchek J, Howard SE, Howard TD, Hesdorffer M, Peng H, Rauscher FJ, Testa JR. Germline BAP1 mutational landscape of asbestos-exposed malignant mesothelioma patients with family history of cancer. *Cancer Res* 2016;**76**:206–15
42. Ferrante D, Mirabelli D, Tunesi S, Terracini B, Magnani C. Pleural mesothelioma and occupational and non-occupational asbestos exposure: a case-control study with quantitative risk assessment. *Occup Environ Med* 2016;**73**:147–53
43. Lacourt A, Gramond C, Rolland P, Ducamp S, Audignon S, Astoul P, Chamming's S, Gilg Soit Ilg A, Rinaldo M, Raherison C, Galateau-Salle F, Imbernon E, Pairon JC, Goldberg M, Brochard P. Occupational and non-occupational attributable risk of asbestos exposure for malignant pleural mesothelioma. *Thorax* 2014;**69**:532–9
44. Bourdès V, Boffetta P, Pisani P. Environmental exposure to asbestos and risk of pleural mesothelioma: review and meta-analysis. *Eur J Epidemiol* 2000;**16**:411–7
45. NIH. EV miRs in cognitive function decline associated with early life metal exposure, 2021, https://grantome.com/grant/NIH/P42-ES030990-02-5598
46. Wagner PJ, Park HR, Wang Z, Kirchner R, Wei Y, Su L, Stanfield K, Guilarte TR, Wright RO, Christiani DC, Lu Q. In vitro effects of lead on gene expression in neural stem cells and associations between up-regulated genes and cognitive scores in children. *Environ Health Perspect* 2017;**125**:721–9
47. Racette BA, Searles Nielsen S, Criswell SR, Sheppard L, Seixas N, Warden MN, Checkoway H. Dose-dependent progression of parkinsonism in manganese-exposed welders. *Neurology* 2017;**88**:344–51
48. Engelward BP. Implications of an epidemiological study showing an association between in utero NDMA exposure and childhood cancer. *Environ Mol Mutagen* 2021;**62**:288–92
49. NIEHS Superfund Research Program. SRP researchers tackle arsenic from many angles, 2021, https://www.niehs.nih.gov/research/supported/centers/srp/phi/archives/biomedical/HEALS/index.cfm
50. Ahsan H, Chen Y, Parvez F, Argos M, Hussain AI, Momotaj H, Levy D, van Geen A, Howe G, Graziano J. Health Effects of Arsenic Longitudinal Study (HEALS): description of a multidisciplinary epidemiologic investigation. *J Expo Sci Environ Epidemiol* 2006;**16**:191–205
51. Argos M, Kalra T, Rathouz PJ, Chen Y, Pierce B, Parvez F, Islam T, Ahmed A, Rakibuz-Zaman M, Hasan R, Sarwar G, Slavkovich V, van Geen A, Graziano J, Ahsan H. Arsenic exposure from drinking water, and all-cause and chronic-disease mortalities in Bangladesh (HEALS): a prospective cohort study. *Lancet* 2010;**376**:252–8
52. Chen Y, Graziano JH, Parvez F, Liu M, Slavkovich V, Kalra T, Argos M, Islam T, Ahmed A, Rakibuz-Zaman M, Hasan R, Sarwar G, Levy D, van Geen A, Ahsan H. Arsenic exposure from drinking water and mortality from cardiovascular disease in Bangladesh: prospective cohort study. *BMJ* 2011;**342**:d2431
53. Chen Y, Wu F, Liu M, Parvez F, Slavkovich V, Eunus M, Ahmed A, Argos M, Islam T, Rakibuz-Zaman M, Hasan R, Sarwar G, Levy D, Graziano J, Ahsan H. A prospective study of arsenic exposure, arsenic methylation capacity, and risk of cardiovascular disease in Bangladesh. *Environ Health Perspect* 2013;**121**:832–8
54. Chen Y, Wu F, Parvez F, Ahmed A, Eunus M, McClintock TR, Patwary TI, Islam T, Ghosal AK, Islam S, Hasan R, Levy D, Sarwar G, Slavkovich V, van Geen A, Graziano JH, Ahsan H. Arsenic exposure from drinking water and QT-interval prolongation: results from the Health Effects of Arsenic Longitudinal Study. *Environ Health Perspect* 2013;**121**:427–32
55. Chen Y, Wu F, Liu X, Parvez F, LoIacono NJ, Gibson EA, Kioumourtzoglou MA, Levy D, Shahriar H, Uddin MN, Islam T, Lomax A, Saxena R, Sanchez T, Santiago D, Ellis T, Ahsan H, Wasserman GA, Graziano JH. Early life and adolescent arsenic exposure from drinking water and blood pressure in adolescence. *Environ Res* 2019;**178**:108681
56. Wasserman GA, Liu X, Parvez F, Chen Y, Factor-Litvak P, LoIacono NJ, Levy D, Shahriar H, Uddin MN, Islam T, Lomax A, Saxena R, Gibson EA, Kioumourtzoglou MA, Balac O, Sanchez T, Kline JK, Santiago D, Ellis T, van Geen A, Graziano JH. A cross-sectional study of water arsenic exposure and intellectual function in adolescence in Araihazar, Bangladesh. *Environ Int* 2018;**118**:304–13
57. Parvez F, Wasserman GA, Factor-Litvak P, Liu X, Slavkovich V, Siddique AB, Sultana R, Sultana R, Islam T, Levy D, Mey JL, van Geen A, Khan K, Kline J, Ahsan H, Graziano JH. Arsenic exposure and motor function among children in Bangladesh. *Environ Health Perspect* 2011;**119**:1665–70
58. Wasserman GA, Liu X, Loiacono NJ, Kline J, Factor-Litvak P, van Geen A, Mey JL, Levy D, Abramson R, Schwartz A, Graziano JH. A cross-sectional study of well water arsenic and child IQ in Maine schoolchildren. *Environ Health* 2014;**13**:23
59. Marshall G, Ferreccio C, Yuan Y, Bates MN, Steinmaus C, Selvin S, Liaw J, Smith AH. Fifty-year study of lung and bladder cancer mortality in Chile related to arsenic in drinking water. *J Natl Cancer Inst* 2007;**99**:920–8
60. Steinmaus C, Ferreccio C, Acevedo J, Balmes JR, Liaw J, Troncoso P, Dauphiné DC, Nardone A, Smith AH. High risks of lung disease associated with early-life and moderate lifetime arsenic exposure in northern Chile. *Toxicol Appl Pharmacol* 2016;**313**:10–5
61. Castriota F, Acevedo J, Ferreccio C, Smith AH, Liaw J, Smith MT, Steinmaus C. Obesity and increased susceptibility to arsenic-related type 2 diabetes in Northern Chile. *Environ Res* 2018;**167**:248–54
62. Hall EM, Acevedo J, López FG, Cortés S, Ferreccio C, Smith AH, Steinmaus CM. Hypertension among adults exposed to drinking water arsenic in Northern Chile. *Environ Res* 2017;**153**:99–105
63. Ferreccio C, Smith AH, Durán V, Barlaro T, Benítez H, Valdés R, Aguirre JJ, Moore LE, Acevedo J, Vásquez MI, Pérez L, Yuan Y, Liaw J, Cantor KP, Steinmaus C. Case-control study of arsenic in drinking water and kidney cancer in uniquely exposed Northern Chile. *Am J Epidemiol* 2013;**178**:813–8
64. Ferreccio C, Yuan Y, Calle J, Benítez H, Parra RL, Acevedo J, Smith AH, Liaw J, Steinmaus C. Arsenic, tobacco smoke, and occupation: associations of multiple agents with lung and bladder cancer. *Epidemiology* 2013;**24**:898–905
65. Bailey K, Fry RC. Long-term health consequences of prenatal arsenic exposure: links to the genome and the epigenome. *Rev Environ Health* 2014;**29**:9–12
66. Bailey KA, Smith AH, Tokar EJ, Graziano JH, Kim KW, Navasumrit P, Ruchirawat M, Thiantanawat A, Suk WA, Fry RC. Mechanisms

underlying latent disease risk associated with early-life arsenic exposure: current research trends and scientific gaps. *Environ Health Perspect* 2016;**124**:170–5

67. Meakin CJ, Martin EM, Szilagyi JT, Nylander-French LA, Fry RC. Inorganic arsenic as an endocrine disruptor: modulation of the glucocorticoid receptor pathway in placental cells via CpG methylation. *Chem Res Toxicol* 2019;**32**:493–9
68. Rojas D, Rager JE, Smeester L, Bailey KA, Drobná Z, Rubio-Andrade M, Stýblo M, García-Vargas G, Fry RC. Prenatal arsenic exposure and the epigenome: identifying sites of 5-methylcytosine alterations that predict functional changes in gene expression in newborn cord blood and subsequent birth outcomes. *Toxicol Sci* 2015;**143**:97–106
69. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect* 2016;**124**:713–21
70. Arzuaga X, Smith MT, Gibbons CF, Skakkebæk NE, Yost EE, Beverly BEJ, Hotchkiss AK, Hauser R, Pagani RL, Schrader SM, Zeise L, Prins GS. Proposed key characteristics of male reproductive toxicants as an approach for organizing and evaluating mechanistic evidence in human health hazard assessments. *Environ Health Perspect* 2019;**127**:65001
71. La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, Patisaul HB, Guyton KZ, Kortenkamp A, Cogliano VJ, Woodruff TJ, Rieswijk L, Sone H, Korach KS, Gore AC, Zeise L, Zoeller RT. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nat Rev Endocrinol* 2020;**16**:45–57
72. Luderer U, Eskenazi B, Hauser R, Korach KS, McHale CM, Moran F, Rieswijk L, Solomon G, Udagawa O, Zhang L, Zlatnik M, Zeise L, Smith MT. Proposed key characteristics of female reproductive toxicants as an approach for organizing and evaluating mechanistic data in hazard assessment. *Environ Health Perspect* 2019;**127**:75001
73. Smith MT, Guyton KZ, Kleinstreuer N, Borrel A, Cardenas A, Chiu WA, Felsher DW, Gibbons CF, Goodson WH 3rd, Houck KA, Kane AB, La Merrill MA, Lebrec H, Lowe L, McHale CM, Minocherhomji S, Rieswijk L, Sandy MS, Sone H, Wang A, Zhang L, Zeise L, Fielden M. The key characteristics of carcinogens: relationship to the hallmarks of cancer, relevant biomarkers, and assays to measure them. *Cancer Epidemiol Biomarkers Prev* 2020;**29**:1887–903
74. Key Characteristics. Identifying the key characteristics of hazardous chemicals and other exposures: a collaborative approach, 2021, https://keycharacteristics.org/
75. Li A, Lu X, Natoli T, Bittker J, Sipes NS, Subramanian A, Auerbach S, Sherr DH, Monti S. The Carcinogenome project: in vitro gene expression profiling of chemical perturbations to predict long-term carcinogenicity. *Environ Health Perspect* 2019;**127**:47002
76. Reif DM, Truong L, Mandrell D, Marvel S, Zhang G, Tanguay RL. High-throughput characterization of chemical-associated embryonic behavioral changes predicts teratogenic outcomes. *Arch Toxicol* 2016;**90**:1459–70
77. Knecht AL, Truong L, Simonich MT, Tanguay RL. Developmental benzo[a]pyrene (B[a]P) exposure impacts larval behavior and impairs adult learning in zebrafish. *Neurotoxicol Teratol* 2017;**59**:27–34
78. Slotkin TA, Skavicus S, Card J, Giulio RT, Seidler FJ. In vitro models reveal differences in the developmental neurotoxicity of an environmental polycylic aromatic hydrocarbon mixture compared to benzo[a]pyrene: neuronotypic PC12 Cells and embryonic neural stem cells. *Toxicology* 2017;**377**:49–56
79. Lassiter TL, Ryde IT, Levin ED, Seidler FJ, Slotkin TA. Neonatal exposure to parathion alters lipid metabolism in adulthood: interactions with dietary fat intake and implications for neurodevelopmental deficits. *Brain Res Bull* 2010;**81**:85–91
80. Lassiter TL, Ryde IT, Mackillop EA, Brown KK, Levin ED, Seidler FJ, Slotkin TA. Exposure of neonatal rats to parathion elicits sex-selective reprogramming of metabolism and alters the response to a high-fat diet in adulthood. *Environ Health Perspect* 2008;**116**:1456–62
81. Slotkin TA, Brown KK, Seidler FJ. Developmental exposure of rats to chlorpyrifos elicits sex-selective hyperlipidemia and hyperinsulinemia in adulthood. *Environ Health Perspect* 2005;**113**:1291–4
82. Heacock ML, Amolegbe SM, Skalla LA, Trottier BA, Carlin DJ, Henry HF, Lopez AR, Duncan CG, Lawler CP, Balshaw DM, Suk WA. Sharing SRP data to reduce environmentally associated disease and promote transdisciplinary research. *Rev Environ Health* 2020;**35**:111–22
83. NIEHS Superfund Research Program. Highlights in data integration, 2021, https://www.niehs.nih.gov/research/supported/centers/srp/science_digest/2021/6/features/index.cfm
84. Ahadi S, Zhou W, Schüssler-Fiorenza Rose SM, Sailani MR, Contrepois K, Avina M, Ashland M, Brunet A, Snyder M. Personal aging markers and ageotypes revealed by deep longitudinal profiling. *Nat Med* 2020;**26**:83–90
85. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell* 2013;**153**:1194–217
86. Wortzel JD, Wiebe DJ, Elahi S, Agawu A, Barg FK, Emmett EA. Ascertainment bias in a historic cohort study of residents in an asbestos manufacturing community. *Int J Environ Res Public Health* 2021;**18**:2211
87. Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev* 2005;**14**:1847–50
88. Guillien A, Cadiou S, Slama R, Siroux V. The exposome approach to decipher the role of multiple environmental and lifestyle determinants in asthma. *Int J Environ Res Public Health* 2021;**18**:1138
89. Yano Y, Schiffman C, Grigoryan H, Hayes J, Edmands W, Petrick L, Whitehead T, Metayer C, Dudoit S, Rappaport S. Untargeted adductomics of newborn dried blood spots identifies modifications to human serum albumin associated with childhood leukemia. *Leuk Res* 2020;**88**:106268
90. Andra SS, Austin C, Wright RO, Arora M. Reconstructing pre-natal and early childhood exposure to multi-class organic chemicals using teeth: towards a retrospective temporal exposome. *Environ Int* 2015;**83**:137–45
91. Curtin P, Austin C, Curtin A, Gennings C, Arora M, Tammimies K, Willfors C, Berggren S, Siper P, Rai D, Meyering K, Kolevzon A, Mollon J, David AS, Lewis G, Zammit S, Heilbrun L, Palmer RF, Wright RO, Bölte S, Reichenberg A. Dynamical features in fetal and postnatal zinc-copper metabolic cycles predict the emergence of autism spectrum disorder. *Sci Adv* 2018;**4**:eaat1293
92. Figueroa-Romero C, Mikhail KA, Gennings C, Curtin P, Bello GA, Botero TM, Goutman SA, Feldman EL, Arora M, Austin C. Early life metal dysregulation in amyotrophic lateral sclerosis. *Ann Clin Transl Neurol* 2020;**7**:872–82
93. Yu M, Tu P, Dolios G, Dassanayake PS, Volk H, Newschaffer C, Fallin MD, Croen L, Lyall K, Schmidt R, Hertz-Piccioto I, Austin C, Arora M, Petrick LM. Tooth biomarkers to characterize the temporal dynamics of the fetal and early-life exposome. *Environ Int* 2021;**157**:106849
94. Human Health Exposure Analysis Resource (HHEAR), 2021, https://hhearprogram.org/
95. HHEAR. Are you eligible for HHEAR services? 2021, https://hhearprogram.org/are-you-eligible-hhear-services
96. NIEHS Superfund Research Program. SRP contributes to human health exposure analysis resource, grantees eligible to use resource, 2021, https://www.niehs.nih.gov/research/supported/centers/srp/news/2020news/hhear/index.cfm
97. Grandjean P, Barouki R, Bellinger DC, Casteleyn L, Chadwick LH, Cordier S, Etzel RA, Gray KA, Ha EH, Junien C, Karagas M, Kawamoto T, Paige Lawrence B, Perera FP, Prins GS, Puga A, Rosenfeld CS, Sherr DH, Sly PD, Suk W, Sun Q, Toppari J, van den Hazel P, Walker CL, Heindel JJ. Life-long implications of developmental exposure to environmental stressors: new perspectives. *Endocrinology* 2015;**156**:3408–15