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Author manuscript

*Curr Opin Pediatr.* Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

*Curr Opin Pediatr.* 2017 June ; 29(3): 385–389. doi:10.1097/MOP.0000000000000491.

## The Children's Health Exposure Analysis Resource (CHEAR): Enabling Research into the Environmental Influences on Children's Health Outcomes

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### Abstract

**Purpose of review**—The Children's Health Exposure Analysis Resource (CHEAR) is a new infrastructure supported by the National Institute of Environmental Health Sciences to expand the ability of children's health researchers to include analysis of environmental exposures in their research and to incorporate the emerging concept of the exposome.

**Recent findings**—There is extensive discussion of the potential of the exposome to advance understanding of the totality of environmental influences on human health. Children's health is a logical choice to demonstrate the exposome concept due to the extensive existing knowledge of individual environmental exposures affecting normal health and development and the short latency between exposures and observable phenotypes. Achieving this demonstration will require access to extensive analytical capabilities to measure a suite of exposures through traditional biomonitoring approaches and to cross-validate these with emerging exposomic approaches.

**Summary**—CHEAR is a full-service exposure assessment resource, linking up-front consultation with both laboratory and data analysis. Analyses of biological samples are intended to enhance studies by including targeted analysis of specific exposures and untargeted analysis of small molecules associated with phenotypic endpoints. Services provided by CHEAR are made available without cost but require a brief application and adherence to policies detailed on the CHEAR webpage at <https://chearprogram.org/>.

### Keywords

Children's environmental exposures; environmental impact on children's health; exposome; laboratory analysis; data science

### Introduction

Because of a variety of factors, including their rapid development, differences in metabolic function, and behaviors, children have increased susceptibility to the harmful effects of environmental exposures compared to adults (1). Environmental health researchers now

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**Conflicts of Interest:** The authors have no conflicts to disclose.

recognize that low-level exposures, especially during early developmental growth periods, such as *in utero* or the neonatal period, can have long-lasting effects. These health effects can also vary dramatically throughout distinct developmental periods, which can also be influenced by their parent's environmental exposures; therefore, it is critical to examine the effects of exposure throughout early life from preconception through pregnancy to early development to puberty and adolescence. The concept of developmental origins of health and disease or DOHaD, (2) is often represented as the trajectory from pregnancy to health effects later in life, but the reality is that differing exposures at specific developmental windows can have distinct biological consequences. In addition, environmental exposures occur in mixtures, and it is rare that an individual, regardless of age, is exposed to a single stressor at any point in time. The health effects of environmental exposures are complex—not a simple relationship between a particular type and level of exposure and disease. Thus, a more holistic approach to characterize exposures and their associated responses is needed.

The concept of the exposome, originally proposed by Dr. Christopher Wild in a 2005 commentary (3), seeks to develop a framework to analyze the effects of multiple exposures throughout the life-course. The last decade has seen an intense discussion of the importance of this concept in the environmental health sciences and the challenges of analyzing the exposome (4). Many of the early efforts to implement the exposome concept in the environmental health sciences have revolved around the use of untargeted metabolomics to analyze biomarkers of exposure and biological response (5-7). The essence, and unique power, of this untargeted approach is the ability to approach associations between multiple environmental exposures and biological response indicators. Progress to date, however, has been limited by a number of factors including the technical limitations of the untargeted analysis and the cross-validation of those discovery-driven approaches with traditional biomonitoring methods. In addition, adequate statistical power and the ability to assess associations across developmental life-stages may be impractical to achieve within a single, focused, study. What is needed is a systematic evaluation of multiple environmental exposures and their associations with health-related endpoints across developmental windows. This is beyond the scope of any one potential study and will require integration and the validation of accumulated evidence from several independently conducted studies.

## The Children's Health Exposure Analysis Resource (CHEAR)

To address these issues, the National Institutes of Health and the National Institute for Environmental Health Sciences is supporting a consortium of grantees to provide the children's health research community access to an infrastructure for laboratory and data analyses that add or expand the inclusion of environmental exposures in children's health research. CHEAR will support exposure analysis through traditional targeted biomonitoring methods and will also support the untargeted analysis of the exposome on NIH funded research studies. In the near term, CHEAR seeks to expand the number of studies that include environmental exposure analysis. As more of the research community takes advantage of the resource, CHEAR will support the analysis of the exposome through the harmonization of studies enabled by a CHEAR-developed ontology for children's health, exposure and associated data, and metadata standards. These foundational efforts will culminate in the creation of a public database of children's exposures and their health

consequences. The services provided by CHEAR are free of charge to the investigators; however, they require sharing of data through the repository of children's health and exposure data.

Access to CHEAR resources is through a web portal at <https://chearprogram.org/>. The CHEAR consortium has a straightforward list of eligibility criteria which include:

- Having an ongoing or completed epidemiological or clinical study of children's health which has been supported, at least in part, by a grant from the NIH.
- Proposing to add environmental exposure data to your study which does not already address exposures or conduct more extensive analysis beyond those already included in the research.
- Being eligible to apply for an NIH grant at your home institution.
- Having existing biological samples collected from children and/or their parents.
- Agreeing to work collaboratively with CHEAR including sharing information on experimental design and supporting data needed to facilitate the analysis.

CHEAR has created an online, user-friendly application process that provides early, expert, consultative services, which may particularly benefit those who have not previously considered environmental exposures in their research. These consultations are also available to guide sample collection and selection of appropriate hypotheses and analyses for studies that are in the initial phases of their plans but are considering using CHEAR services at a later date.

The core of the services offered by CHEAR is traditional biomonitoring analysis. These analyses are directed by specific hypotheses about potential associations between exposures, such as pesticides, metals, or tobacco, with a health-related endpoint. Although CHEAR has extensive analytical capabilities, an exhaustive list of analyses available by CHEAR is impractical. However, the CHEAR web page has a list of common, core analytes that we expect will be frequently requested for which CHEAR has extensive analytical capacity across the six funded laboratories (<https://chearprogram.org/access/lab-analysis-services/targeted>). One critical aspect of these analyses is the quality control and harmonization of the CHEAR services. CHEAR is implementing rigorous internal quality control procedures and is also participating in international proficiency testing efforts such as the New York State Department of Health Proficiency Testing scheme (<http://www.wadsworth.org/programs/ehs/pt>) and the German External Quality Assessment Scheme for analysis of biological materials (<http://www.g-equas.de/>). These efforts provide assurances that any analyses offered adhere to strict performance metrics and are comparable not only within CHEAR but with services provided by other expert laboratories around the world. In addition, the resource includes a component to support the development of methods either to measure emerging environmental exposures or to utilize new biological matrices that do not currently have existing, well-validated biomonitoring methods in place.

The targeted biomonitoring analyses provided by CHEAR are complemented by a parallel, hypothesis- free, untargeted assessment that builds on existing metabolomics methods (8).

These approaches seek to provide a characterization of the exposome to generate hypotheses for future, hypothesis-driven analyses. One of the attractive features of untargeted exposure assessment by metabolomics is the direct linkage of indicators of environmental exposure with alterations in endogenous molecules, which can be mapped onto biological pathways to provide a simultaneous assessment of both exposure and response. Similar to the traditional targeted biomonitoring approaches offered by CHEAR, the untargeted approaches undergo rigorous quality control measures and take advantage of a common quality control material that will be analyzed across all CHEAR laboratories and for each study being analyzed in order to facilitate the harmonization of results from each study. The CHEAR untargeted analyses are also being benchmarked against other metabolomics programs, such as the NIH Common Fund metabolomics program, to ensure that the highest quality services are being provided.

The third set of laboratory analytical services offered by CHEAR are a suite of well-validated measures of biological response (9). These assays represent a very broad range of methods from high-throughput genomic and epigenomic analyses to assays for molecular markers of common biological pathways such as DNA damage sensing and repair, inflammatory signaling, and oxidative stress markers. These analyses will serve as additional intermediate phenotypes to provide greater understanding of the molecular mechanisms underlying the linkages between exposures and health-related phenotypes provided by the parent epidemiological study. These should complement, not duplicate, existing response measures from the study.

In addition to the comprehensive laboratory analyses provided by CHEAR, the resource contains a full-service Data Center. The CHEAR Data Center provides a secure venue to access the data generated by the CHEAR laboratories, as well as linked data provided by the study investigators, which can include additional exposure data as well as data on health-related phenotypes. The CHEAR data sharing plan (<https://cheарprogram.org/content/data-sharing-plan-cheар-data-repository-dsp>) incorporates the same principles as the NIH Genomic Data Sharing Policy. The data contained within the repository are all being mapped to an overarching ontology developed by the CHEAR Data Center which links several existing open source ontologies focused on environmental exposure and children's health and serves as an organizing framework to support meta- and pooled-analyses of the data across CHEAR-supported studies. The Data Center also includes a statistical services resource that provides access to statistical methods and informatics tools for the analysis both of individual CHEAR studies as well as for meta and pooled analysis across all studies supported by CHEAR or added by individual investigators. It is intended that these analyses will eventually include linkages across developmental windows and multiple environmental factors; it will also include the direct linkage and cross-validation of targeted, untargeted, and biological response data.

## International coordination on implementation of the child's health exposome

Children's health is very a very powerful initial target for demonstrating the power of the exposome given the disproportionate burden of exposure, the increased susceptibility to exposures during critical developmental windows, and the shorter latency of associations between chronic exposures and health-related outcomes. Consequently, many of the initial large, government-driven efforts to implement the exposome focused on children's health studies. The first major, governmentally driven study to explicitly link the exposome concept with children's health was the European Union's (EU) Framework 7 Programme (FP7). Through this effort the EU funded three separate projects to implement the exposome, each of which included children's health as a focus (10, 11) and <http://www.heals-eu.eu/>. These three programs all seek to establish links between large numbers of existing cohorts across Europe and to harmonize information on exposure and outcome to generate sufficient power to support an exposome analysis. By contrast, the Japanese Environment and Children's Study, JECS (<http://www.env.go.jp/en/chemi/hs/jecs/>) was launched in 2011 with a goal of prospectively recruiting 100,00 parent-child pairs to assess the impact of multiple environmental exposures with children's health and development (12). Recruitment of these families was completed in 2014 and the children will be followed until they are 13 years old. In the United States, several independent exposome efforts have been supported in addition to centralized infrastructure support such as the CHEAR program to enable the exposome. The largest, and newest, effort however is the recently funded Environmental influences on Children's Health Outcomes (ECHO, <https://www.nih.gov/echo>) program which, similar to the European Union FP7 programme, seeks to form a synthetic cohort harmonizing several existing studies, linking broadly measured common environmental factors with children's health outcomes in five domains: neurodevelopment and behavior; upper and lower airway; obesity; pre-, peri-, and post-natal outcomes, and normal health and development.

## Conclusion

While each of these international programs, including CHEAR, is distinct and independent, they provide a major opportunity for international coordination, cross-study harmonization, data integration, and the demonstration of the power of the exposome. This international coordination may, in turn, enable a greater understanding of the emerging concept of biological resilience and the idea that the critical aspect of environmental exposures is the accumulated burden of damage resulting from multiple environmental exposures which decreases the ability of the individual to appropriately compensate for the next exposure, almost regardless of the nature of that exposure (9, 13). With their success and a concerted effort for international cooperation and coordination the next decade promises to yield a significant advancement in our understanding of normal children's development and the interaction between environmental exposures in altering the normal trajectory.

## Acknowledgments

The authors would like to thank the members of the CHEAR executive committee (Barbara O'Brien, Westat; Susan Teitelbaum and Robert Wright, Icahn School of Medicine at Mount Sinai; Gary Miller, Emory University; John

Meeker, University of Michigan; Lisa Peterson and Stephen Hecht, University of Minnesota; Kenneth Aldous, New York Department of Health Wadsworth Center; and Timothy Fennel, Research Triangle Institute) and all participants of the funded CHEAR projects for their contributions to the development of the CHEAR infrastructure and this review. The authors also would like to thank Drs. Bonnie Joubert and Daniel Shaughnessy for their thoughtful critique and comments.

**Financial Support and Sponsorship:** DMB, GWC, KAG, and CLT are employees of the United States government and this work is supported by the NIH, National Institute of Environmental Health Sciences as part of their official duties.

## References

- 1\*\*. Vrijheid M, Casas M, Gascon M, Valvi D, Nieuwenhuijsen M. Environmental pollutants and child health-A review of recent concerns. *Int J Hyg Environ Health*. 2016; 219(4-5):331–42.  
\*\*This is a rigorous review of recent epidemiological literature of a range of environmental exposures on children's health outcomes. [PubMed: 27216159]
2. Winett L, Wallack L, Richardson D, Boone-Heinonen J, Messer L. A Framework to Address Challenges in Communicating the Developmental Origins of Health and Disease. *Current environmental health reports*. 2016; 3(3):169–77. [PubMed: 27449924]
3. Wild CP. Complementing the genome with an “exposome”: The outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev*. 2005; 14(8):1847–50. [PubMed: 16103423]
4. Cui Y, Balshaw DM, Kwok RK, Thompson CL, Collman GW, Birnbaum LS. The Exposome: Embracing the Complexity for Discovery in Environmental Health. *Environ Health Perspect*. 2016; 124(8):A137–40. [PubMed: 27479988]
5. Rappaport SM. Biomarkers intersect with the exposome. *Biomarkers*. 2012; 17(6):483–9. [PubMed: 22672124]
6. Uppal K, Walker DI, Liu K, Li S, Go YM, Jones DP. Computational Metabolomics: A Framework for the Million Metabolome. *Chemical research in toxicology*. 2016
7. Athersuch T. Metabolome analyses in exposome studies: Profiling methods for a vast chemical space. *Arch Biochem Biophys*. 2016; 589:177–86. [PubMed: 26494045]
- 8\*. Dennis KK, Marder E, Balshaw DM, Cui Y, Lynes MA, Patti GJ, et al. Biomonitoring in the Era of the Exposome. *Environ Health Perspect*. 2016 \*This review highlights a series of recommendations developed in an NIEHS sponsored workshop for evolving the field of biomonitoring in light of the emergence of the exposome concept.
9. Dennis KK, Auerbach SS, Balshaw DM, Cui Y, Fallin MD, Smith MT, et al. The Importance of the Biological Impact of Exposure to the Concept of the Exposome. *Environ Health Perspect*. 2016 \*This review highlights a series of recommendations developed in an NIEHS sponsored workshop for enhancing the integration of biological response with the discovery based analysis of exposures within the concept of the exposome.
10. Vineis P, Chadeau-Hyam M, Gmuender H, Gulliver J, Herceg Z, Kleinjans J, et al. The exposome in practice: Design of the EXPOSOMICS project. *Int J Hyg Environ Health*. 2016
11. Vrijheid M, Slama R, Robinson O, Chatzi L, Coen M, van den Hazel P, et al. The human early-life exposome (HELIX): project rationale and design. *Environ Health Perspect*. 2014; 122(6):535–44. [PubMed: 24610234]
12. Kawamoto T, Nitta H, Murata K, Toda E, Tsukamoto N, Hasegawa M, et al. Rationale and study design of the Japan environment and children's study (JECS). *Bmc Public Health*. 2014; 14:25. [PubMed: 24410977]
13. Miller GW, Jones DP. The Nature of Nurture: Refining the Definition of the Exposome. *Toxicol Sci*. 2014; 137(1):1. + [PubMed: 24213143]

### Key Points

- Children are uniquely susceptible to environmental exposures during distinct developmental windows
- Children's increased burden of exposure and the shorter time-period between exposure and outcome make children's health a particularly powerful focus for early exposome efforts.
- The Children's Health Exposure Analysis Resource (CHEAR, [www.chearprogram.org](http://www.chearprogram.org)) seeks to provide access to expert laboratory and data analysis to implement the exposome on existing studies of children's health
- International coordination between major children's health exposome efforts in the next decade will revolutionize our understanding of normal children's health and development as well as the influence of multiple environmental factors on that normal trajectory.