

Short Communication

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Greater than the sum of its parts: focusing SRP research through a systems approach lens

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Abstract: The National Institute of Environmental Health Sciences Superfund Research Program (SRP) funds diverse transdisciplinary research to understand how hazardous substances contribute to disease. SRP research focuses on how to prevent these exposures by promoting problem-based, solution-oriented research. SRP's mandate areas encompasses broad biomedical and environmental science and engineering research efforts and, when combined with research translation, community engagement, training, and data science, offers broad expertise and unique perspectives directed at a specific big picture question. The purpose of this commentary is to adapt a systems approach concept to SRP research to accommodate the complexity of a scientific problem. The SRP believes a systems approach offers a framework to understand how scientists can work together to integrate diverse fields of research to prevent or understand environmentally-influenced human disease by addressing specific questions that are part of a larger perspective. Specifically, within the context of the SRP, a systems approach can elucidate the complex interactions between factors that contribute to or protect against environmental insults. Leveraging a systems approach can continue to advance SRP science while building the foundation for researchers to address difficult emerging environmental health problems.

Introduction

The National Institute of Environmental Health Sciences (NIEHS) Superfund Research Program (SRP) funds university-based, transdisciplinary basic research on human health and the environment to provide scientific and practical solutions to issues related to hazardous substances. The central goal of the SRP is to link exposure to disease and reduce those exposures using a variety of tools and technologies. Basic SRP research can be translated to the public and end users to help improve human health.

For over 30 years, the SRP has defined priorities for environmental health research. Many of the priorities identified early on in the program, such as working across scientific disciplines or identifying biomarkers to better characterize exposures and predict disease, are still relevant to scientific innovation today (e.g., Ref. [1–8]).

Using a variety of funding mechanisms, the SRP supports research at colleges and universities across the United States. SRP-funded multi-project center grants are the cornerstone of the program, where scientists and engineers working in transdisciplinary teams contribute their diverse expertise to address the center's research focus.

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Leading the way in transdisciplinary research

A traditional approach to problem-solving is based on reducing multi-faceted problems into their simpler components; however, to understand complex factors affecting human health and the environment, it is necessary to include different perspectives from a variety of disciplines and sectors to realize the broader picture. SRP recognized early on the value of bringing diverse points of view together to provide a more comprehensive understanding

of how people are exposed to a harmful contaminant, how those exposures result in disease, and integrating that knowledge to prevent or mitigate those exposures.

This transdisciplinary approach has uncovered new ways of thinking about complex problems. For example, SRP-funded researchers have been at the forefront of research on the exposome, which aims to characterize the totality of exposures across the lifespan (e.g., Ref. [9, 10]). Research to better characterize the exposome using innovative omics approaches has evolved because of new knowledge and tools developed within the SRP.

The SRP's emphasis on research translation, community engagement, and data sharing also helps to bring in diverse perspectives to ensure that SRP research addresses a specific problem with the goal of finding a solution to prevent or reduce exposures [11, 12]. For example, centers are required to proactively communicate their scientific accomplishments to end users and to facilitate the use of research findings through community engagement and research translation [11]. The ultimate intent is to bring together investigators, communities, decision makers, and other end users, collectively referred to as stakeholders, to enhance collaboration and utilization of SRP research.

The transdisciplinary approach to training also teaches the next generation of scientific leaders how to think collaboratively [13]. Unique training opportunities (e.g., externships) within and outside of the center expand trainees' capacity by providing additional training and experience to augment their skill set to better answer research questions and bring these skills back to their own lab. By broadening training experiences to include research translation and community engagement activities, SRP-supported trainees gain many diverse skills they will need to be successful and to bring new perspectives and ideas to their field of research [13].

Sharing information across projects and disciplines does not often happen naturally. The multi-project center approach creates opportunities for catalyzing new research and ideas by connecting researchers that are normally separated by varying disciplines. By bridging basic biomedical research, public health, environmental science, and engineering, SRP grantees are creating a coordinated effort to address pressing environmental health issues.

Maximizing the impact of SRP research

The SRP's unique transdisciplinary approach has created new perspectives, empowering researchers to understand

some of the toughest environmental health problems, and has led to diverse accomplishments for a single grant funding program (e.g., Ref. [14–16]). SRP-funded research has led to the development of remediation and site monitoring tools involved in the cleanup of potentially hazardous substances. For example, this was seen in five case studies of SRP-funded technologies that estimated that these technologies saved more than \$100 million in cleanup costs compared to traditional approaches [17]. These technologies also added environmental, economic, and societal benefits by promoting sustainable practices [18]. SRP-funded basic biomedical research has enhanced understanding of how harmful chemicals may result in disease. This research has also informed the development of policies and interventions to reduce exposure to environmental contaminants to improve public health [19]. Importantly, achieving these wide-ranging benefits required transdisciplinary research that cut across sectors.

Proactive and evolving

SRP has been proactive in identifying new opportunities to leverage funded research for maximum impact. One example is through sharing and integrating data, which can reveal how research findings connect across disciplines and help answer complex questions. SRP has fostered opportunities for centers to share data, expanding data initiatives and equipping centers with critical infrastructure to combine and integrate diverse datasets. By incorporating data streams from biomedical, engineering, and environmental fields, SRP researchers will be better positioned to uncover more answers to complex research questions and understand the interplay between exposures and health [12]. SRP joined in other exposure science initiatives within the National Institutes of Health (NIH), such as the Human Health Exposure Analysis Resource [20, 21], which promotes data sharing and re-use to enable researchers to integrate more information and perspectives on human exposure and disease.

Through these and other initiatives over the last 30 years, SRP has constantly worked to improve the science funded by the program and its utility for solving problems. While SRP's unique transdisciplinary approach has long served as a model for integrating diverse disciplines and holistic thinking [2, 4, 8, 22–24], the program is now mature enough to focus SRP research through a more refined systems approach lens.

Systems approach to complex problems

Systems approach

A system is a set of elements whose interconnections and interdependencies determine their behavior and the behavior of the entire system [25]. System theory focuses on understanding the complete system as a whole and the underlying interactions of all the forces that make up that system [26]. It focuses on understanding the big picture goals of a program and identifying patterns within complex processes. By discovering the common principles that govern the behavior of systems, researchers can begin to understand the complexity and interconnectedness of the system.

Systems thinking has been used in diverse disciplines, from biology, anthropology, physics, psychology, and mathematics, to management, industry, and computer science [25]. As a result, the terminology, tools, and frameworks are equally diverse.

For example, scientists use systems biology approaches to understand the big picture of how molecules, pathways, cells, tissues, and organs interact in an organism. In immunology, scientists use sophisticated computational models and simulations to understand the complex biochemical networks that regulate the interactions among the immune system's cells and between these cells and infectious organisms [27]. In toxicology, systems approaches can be used to integrate *in vitro* and *in vivo* data to better understand the underlying modes of action of harmful exposures, leading to broader characterization of adverse outcome pathways [28].

Systems approaches also integrate disciplines to address complex problems. For example, in the field of environmental management, the Social Ecological Systems (SES) approach explores the theoretical foundation for transdisciplinary science and resilience through conceptual and empirically based models and frameworks. SES frames relationships between human, social, and ecological components as part of a complex system with multi-scale feedback loops and interdependencies [29]. Similarly, the U.S. Environmental Protection Agency uses conceptual site models (CSM) to summarize information about environmental contamination at a site and the relationships among factors that are important for decision-making. CSMs help decision makers evaluate the data gaps and uncertainty associated with geology, hydrology, contaminant sources, and exposure pathways, among others [30]. Systems approaches can shed light on the

different interactions between cities, the health of its people, and the state of the planet to inform adaptation strategies that promote health in the face of climate change [31].

Strengths of systems thinking

Systems approaches define and capture the complex and multidisciplinary elements and factors involved in an interconnected network. Even small-scale systems may combine genetics, proteomics, cell signaling, hormone disruption, statistics, analytical chemistry, and biochemistry. With broader systems come broader disciplines, from human behavior and psychology to ecology, meteorology, geology, and soil science. Systems thinking provides a structured framework for these disciplines to interact and share ideas to better understand the system as a whole. It also offers a wide range of tools for gaining deeper insight into complex problems [32].

Integrating information from diverse disciplines is critical to addressing the fundamental challenges associated with implementing systems thinking in environmental health [33]. Systems thinking can elucidate how elements operate independently and how they depend on one another, including non-linear relationships and complex interactions between multiple environmental stressors that might have greater positive or negative impact than the sum of their parts [34].

Systems approaches can also provide guidance for future data collection and raise new research questions. It provides new opportunities to understand, test, and revise our understanding of the system as a whole, including how to intervene to improve people's health [25]. It can shed light on the interconnections and feedback loops within the system and help identify leverage points where drivers of health can be manipulated upstream [34].

In a system, a leverage point is the location where a relatively small local change can be implemented to produce major effects throughout the system [31, 35, 36]. These small, usually positive, changes can be anything that disrupts the status quo [36]. Often referred to as disruptors, these changes may include adoption of preventative behaviors, implementation of a new policy to prevent hazardous releases at the source, or breakthrough technologies that reduce exposure. Systems thinking allows researchers to solve problems without creating secondary problems or unintended consequences [37] as research iteratively identifies leverage points and disruptors while considering downstream effects on the rest of the system.

Another strength to a systems framework is its scalability, providing a framework upon which to connect basic mechanistic research within the context of the environmental factors that contribute to the burden of disease [33, 37]. This scalability, from molecular to individual to environment, is critical for environmental health research programs because environmentally influenced disease and dysfunction are not solely defined by what is happening at the molecular level, but also by exposure pathways defined by the individuals' environment. By pairing current research trends in bottom-up approaches (e.g., genes or molecules to cells, tissues, organs and organism) with parallel development of top-down approaches (e.g., social, ecosystem, physical environment), researchers are better able to consider the exposome and complex human-environment interactions to inform decision making that protects health.

SRP is uniquely situated to leverage systems thinking to address complex environmental health problems. Much of how SRP grantees think about and approach research is already rooted in this perspective. By focusing SRP research through a systems approach lens, center teams can embrace the complexity of biomedical, environmental, and engineering science while maintaining a clear problem-solving focus.

Focusing SRP research and training through a systems approach lens

Since its inception, a key focus of the SRP has been basic research. SRP basic research aims to achieve a fundamental understanding of biological, environmental, and engineering processes and apply this knowledge to address hazardous waste-related issues. SRP's mandate areas encompass broad transdisciplinary research, broadened further by integrating research translation, community engagement, training, and data science (Figure 1). This complexity can make it challenging to maintain a focus, with research questions becoming too diffuse or disconnected to effectively solve problems. A systems approach can address this challenge by encompassing the complexity of the full system while still being focused and problem solving.

Answering difficult questions

SRP researchers strive to answer complex questions about environmental health. SRP researchers investigate co-exposures to multiple contaminants, dietary factors, and other stressors and protective factors that encompass the

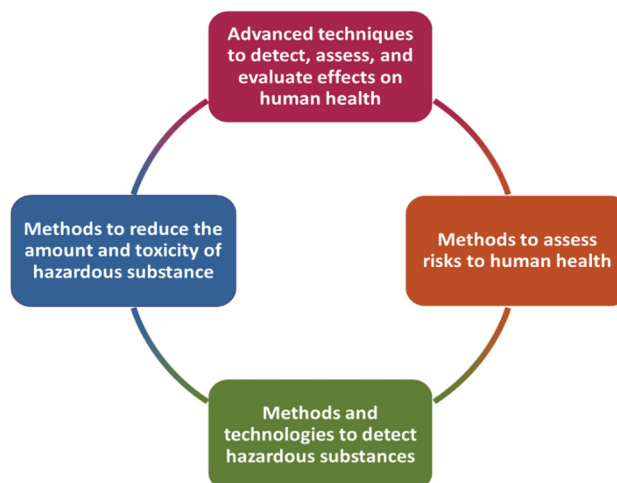


Figure 1: SRP mandates include the development of: 1. Advanced techniques for the detection, assessment, and evaluation of the effects on human health of hazardous substances. 2. Methods to assess the risks to human health presented by hazardous substances. 3. Methods and technologies to detect hazardous substances in the environment. 4. Basic biological, chemical, and physical methods to reduce the amount and toxicity of hazardous substances.

exposome, including how nutrition can modulate the toxicity of environmental pollutants [38]. They explore gene-environment interactions that make some individuals more or less susceptible to environmental insults; and critical windows of exposure or periods where people are more vulnerable to environmental insults. Teams seek to understand the role of underlying health conditions and comorbidities that influence the relationship between the environment and health, and long latencies between exposure and disease. They explore approaches to intervene to prevent exposures or improve disease outcomes, including promoting health-protective lifestyle changes. They also study geological or meteorological factors that control exposures, and the use of cutting-edge devices and tools to measure and remove hazardous substances. While SRP researchers have been leaders in these fields over the last 30 years, disentangling the complex interrelationships that contribute to the total accumulated stress on the body, or allostatic load, remains a challenge. Systems thinking offers a useful multidirectional framework to link diverse perspectives and continually gain new insight.

Defining the system

One of the keys to defining system boundaries is to clearly define the research scope. SRP-funded research aligns with

the four mandates, which also gives researchers an intuitive opportunity to begin defining the scope of their research and the boundaries of their system of interest. As an institution of the NIH and part of NIEHS, disease and dysfunction and the role of hazardous substances in the environment are essential components that also help to define the system.

Integrated and interconnected

All components of an SRP center interconnect to inform the overall system (Figure 2). By looking through a more holistic systems lens, a center's research projects and cores complement each other to answer questions that a single project or core could not answer alone. This may mean looking to institutions beyond the center's university to assemble the right team, expertise, and technical capabilities to address the multidimensional components that connect exposure to disease (e.g., environmental factors, combined exposures, latency, and comorbidity). Multi-disciplinary teams incorporate research around a common system to study one or more chemical exposures, associated health impacts, and related detection and remediation technologies that are critical for understanding and reducing exposures. This approach to thinking helps researchers identify the feedbacks, interdependencies, and dynamics driving the research and its translation to identify new opportunities to intervene.

Community members and stakeholders are also an important part of the system. Research translation and community engagement help define the system in the real world. This systems approach may expand the breadth of SRP stakeholders by identifying new key stakeholders or areas of expertise needed to solve these complex problems. As diverse research becomes more interconnected, leveraging community engagement and research translation provides broader stakeholder input and perspectives to move research forward so that it is available for communities, decision makers, and others.

Data science efforts also present opportunities to combine and integrate diverse datasets from engineering, biomedical research, and environmental fields to better understand the interplay between exposures and health. Data sharing and integration can more clearly define how data from one project can inform the overall center system and how integrating external data provides additional insight for problem solving. Training efforts ensure that transdisciplinary approaches, systems thinking, and data science are unified in the next generation of researchers who continue to move the science forward.

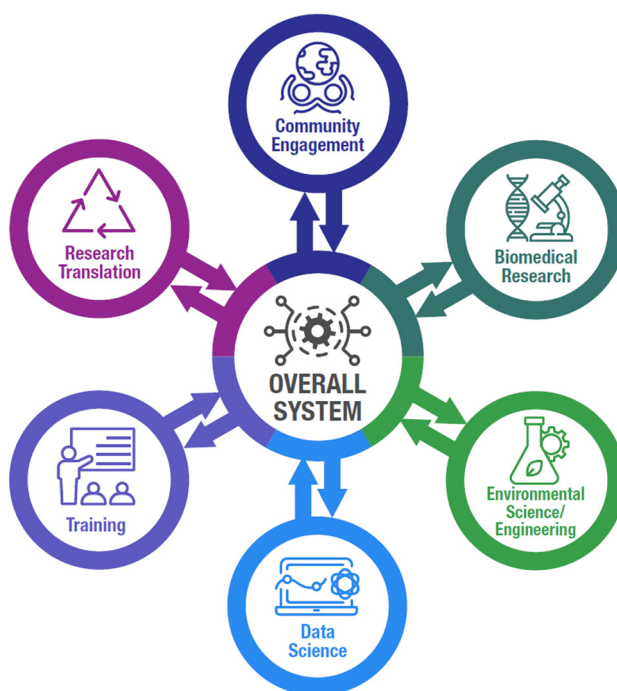


Figure 2: SRP-funded centers combine biomedical research, environmental science and engineering, research translation, community engagement, training, and data science to understand and address a specific problem. A systems approach offers a framework to understand how center teams can integrate diverse fields to answer questions that a single project or core could not answer alone and to identify leverage points and disruptors to reduce exposures and improve health.

Identifying leverage points and disruptors

Through systems approaches, center teams may be better equipped to consider what kind of disruptors could be introduced to implement change and where those disruptors would be most effective within the system. SRP's focus on problem-based, solution-oriented research can help identify leverage points to implement disruptors and improve health. In fact, the SRP mandates are all aimed at basic research to identify disruptors and leverage points.

In the case of SRP, disruptors are the strategies to reduce exposure to harmful contaminants and improve health. Prevention or intervention approaches are disruptors because they can reduce exposure to contaminants or the harmful effects of those exposures. These may include positive lifestyle changes such as healthful nutrition or increased physical activity, education to improve environmental health literacy, or encouraging individuals to test their water and invest in filtration devices. Another example could be through fundamental molecular research, such as developing therapeutic interventions for

molecular targets. Disruptors can also be new technologies and approaches that serve to change the system. For example, a new remediation tool can be a disruptor if it improves how contaminants are cleaned up. Development of these disruptors starts with basic research which is then informed by other research projects and implemented at specific leverage points through community engagement and stakeholder input.

For example, detection technologies can serve as leverage points by helping identify hot spots of exposure or populations with higher exposure levels so that researchers know where best to apply an intervention or remediation strategy. Similarly, basic research into markers of susceptibility may reveal individuals or groups who are most vulnerable. Research into molecular targets can also identify new leverage points, such as in other cells, organ systems, or even ecological or environmental systems. Community partnerships reveal new insight into how the system works and where prevention, intervention, or remediation approaches may be most successfully implemented. Data science also plays an important role by identifying leverage points within the overall center system, predicting the magnitude of a disruptor on the overall system, as well as how that disruptor may impact other parts of the system.

Looking at the system as a whole, center teams can better identify these leverage points and implement disruptors to advance the science, reduce exposures, and improve public health. Using a systems approach allows centers to integrate research projects and cores seamlessly so that, indeed, the whole is greater than the sum of its parts.

Conclusion

Basic, fundamental science is a critical foundation on which transdisciplinary SRP centers are built. Center teams partner with communities and other stakeholders to combine broad expertise and unique perspectives directed at specific research questions. This unique approach has empowered researchers to shed light on important environmental health problems.

SRP grantees have undertaken groundbreaking research on diverse topics, including exposure routes, underlying biological mechanisms that affect health, and biogeochemical interactions. They have also identified techniques to reduce contaminants in the environment, made discoveries that help characterize the exposome, and developed tools to more precisely explore genes and metabolites in the body. By integrating these different types of research and sharing data within and across centers,

researchers are better positioned to generate new discoveries and answer complex questions that could not be answered previously.

Focusing SRP research through a systems approach lens may help researchers see how they are breaking down barriers between disciplines, integrating diverse perspectives gained from stakeholder partnerships, and combining broad expertise to view the larger picture. SRP researchers are well positioned to use systems approaches to answer difficult and complex environmental health questions, such as disentangling exposure to mixtures, better characterizing the exposome, and understanding diseases with long latency periods to link exposures to disease earlier in the disease's progression, and allostatic load. It can also help them to predict outcomes and prioritize intervention and remediation approaches to disrupt problems within the system.

This approach enables SRP researchers to take advantage of diverse transdisciplinary research and cutting-edge advances to identify where different domains integrate. Additionally, this approach helps SRP researchers take on challenges posed by evolving and future environmental health problems. With a systems approach infrastructure in place, SRP-funded researchers can address emerging topics as they arise and translate science into improved public health.

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