Review

William A. Suk*, Michelle L. Heacock, Brittany A. Trottier, Sara M. Amolegbe, Maureen D. Avakian, Danielle J. Carlin, Heather F. Henry, Adeline R. Lopez and Lesley A. Skalla

Benefits of basic research from the Superfund Research Program

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Abstract: The National Institutes of Health (NIH), National Institute of Environmental Health Sciences (NIEHS) Hazardous Substances Basic Research and Training Program [Superfund Research Program (SRP)] funds transdisciplinary research projects spanning the biomedical and environmental sciences to address issues related to potentially hazardous substances. We used a case study approach to identify how SRP-funded basic biomedical research has had an impact on society. We examined how transdisciplinary research projects from the SRP have advanced knowledge and led to additional clinical, public health, policy, and economic benefits. SRP basic biomedical research findings have contributed to the body of knowledge and influenced a broad range of scientific disciplines. It has informed the development of policies and interventions to reduce exposure to environmental contaminants to improve public health. Research investments by the SRP have had a significant impact on science, health, and society. Documenting the benefits of these investments provides insight into how basic research is translated to real-world applications.

Keywords: exposure and disease; Superfund Research Program; transdisciplinary research.

***Corresponding author: 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, USA, E-mail: suk@niehs.nih.gov
Michelle L. Heacock, Brittany A. Trottier, Danielle J. Carlin and Heather F. Henry: 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, USA
Sara M. Amolegbe, Maureen D. Avakian, Adeline R. Lopez and Lesley A. Skalla: MDB, Inc., Durham, NC, USA

Background

The National Institute of Environmental Health Sciences (NIEHS) Superfund Basic Research and Training Program (SRP) uses a transdisciplinary approach for research and training. Since its inception in 1987, the SRP has brought together researchers from the biomedical and environmental science and engineering fields to better understand how exposures to hazardous substances in the environment affect health and disease (1).

The SRP was established by the U.S. Congress to provide support for a broad university-based research program to address scientific uncertainties facing the national Superfund program via the Superfund Amendments and Reauthorization Act (SARA) of 1986 (2). SRP-funded researchers work together to study the health effects of potentially hazardous substances and to determine sustainable ways to remediate these substances (3, 4). 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 people may be more susceptible than others. In this paper, basic research is defined as fundamental research that generates new ideas, principles, and theories, which may not be immediately applied, but advance fundamental knowledge, in different fields.

The foundation of the SRP is its university-based, multi-project center grant program. SRP centers consist of scientists and engineers from different disciplines who build collaborative research teams to address the complex issues related to potentially hazardous substances. The SRP places a high importance on communicating and disseminating research and emphasizes the importance of sharing research findings and data to reveal new scientific connections that can be used to understand the link between exposures and health. The SRP also encourages data sharing and its reuse among a wide range of SRP projects to leverage previous findings and accelerate the pace of research (5). SRP program staff and grantees actively engage with colleagues at federal and state agencies to improve the Program's ability to address societal needs, share the most recent research results, and identify potential future research needs (2).

The translation of research findings into application for public health benefits is often non-linear. For this reason, it is necessary to capture a variety of societal benefits at different points along the translational research continuum (6). To capture some of these benefits, we previously used a case study approach to identify economic and societal benefits of SRP-funded research that led to the development of remediation and site monitoring tools involved in the cleanup of potentially hazardous substances. We identified five technologies supported by the SRP with the most complete information on cost savings and estimated that more than $100 million was saved when compared to traditional approaches. We also found that the use of a customized case study approach was valuable in uncovering a diverse range of SRP research outcomes and identifying technologies that provide faster and/or cheaper remediation of potentially hazardous substances (7).

Although the SRP has supported a significant amount of basic environmental science and engineering research that has been previously reported, our focus for this paper will be to examine the impact of SRP-funded biomedical research on improving public health and reducing disease. As the impacts of basic, or fundamental, biomedical research are difficult to quantify, we broadened our assessment to identify qualitative benefits on science, health, and society, using a case study-based approach.

Objectives: identifying benefits

The challenge of assessing the impacts of basic biomedical science is well established (8–10). There is often considerable latency between research initiation and downstream impacts, and it can be difficult to correctly assign contribution of specific projects to long-term impacts (11, 12). Multiple research studies across the translational spectrum are often required to build the scientific evidence needed to meaningfully impact public health. Despite these challenges, there is significant interest by universities, funding agencies, and the public to understand the wider value of basic biomedical research and how it impacts science, health, and society. This is evident by the growing literature describing approaches to measure research impact beginning over 20 years ago with the Payback Framework, which today is the most common structure used to examine the 'impact' or 'payback' of health research. The Payback Framework consists of five categories to classify impacts: knowledge, benefits to future research, benefits to policy/decision-making, benefits to health, and broader economic benefits. Numerous other frameworks have been proposed since the Payback Framework including the Research Impact Framework, Canadian Academy of Health Sciences Framework, and the Becker Medical Library Model for the Assessment of Research Impact, with evaluators customizing frameworks by modifying or adding additional impact categories and expanding and/or modifying the associated indicators used to document evidence of impact (13–16).

To understand how SRP-funded basic research discoveries have impacted science, health, and society, we examined SRP research outputs through the lens of five domains described in the Becker Medical Library Model for the Assessment of Research Impact, the most relevant and transferable to SRP-funded research, with slight modifications to better capture outputs in environmental health science (17). These customized domains include the following:

1. Advancement of knowledge: research outputs and/or activities such as publications and patents that contribute to the scholarly record.
2. Clinical benefits: application or adoption of research outputs in clinical or health applications and includes tools and products (e.g. biological factors, biomedical technology, drugs) as well as procedures and guidelines (e.g. diagnostic or therapeutic methods/techniques).
3. Public health benefits: increases in the well-being of the community as a result of research outputs and/or activities and includes health activities and products, and health promotion.
4. Policy benefits: research outputs and/or activities used to create laws, guidelines, standards, or policies and includes advisory activities.
5. Economic benefits: economic outcomes as a result of research outputs and/or activities and includes commercial products, financial savings, and benefits.

We applied these five domains of research impact to research funded by the SRP to identify research projects that fall within these categories. Because the research from the program is in different stages of maturation, the domains were applied with the understanding that not all five domains would be represented in every case study.

Basic bibliometric analysis

To understand how the SRP has contributed to the advancement of knowledge within the field of environmental health and beyond, we used basic bibliometric analysis techniques to measure and visualize the impact of SRP publications. Because Web of Science (WOS) only began systematically collecting and indexing funding acknowledgment data in 2008, we took advantage of our in-house SRP publications database, which contains grantee-authored publications since 1995, to analyze publications over a period of 20 years (1995–2015) (18). This approach also had the added benefit of compensating for inconsistent reporting of grant numbers in the acknowledgments section by including publications that SRP grantees reported directly to the Program (19). Bibliographic records for publications in the SRP database to be used for citation analysis were retrieved in PubMed (20) and Clarivate Analytics' WOS (21) by searching for unique identifiers including PubMed ID (PMID) and Digital Object Identifier (DOI). We assessed a variety of publication metrics including productivity and citation impact from WOS and InCites (provided by the National Institutes of Health Library services), as well as Dimensions, a new bibliographic tool launched by Digital Science that includes a citation database and offers a free version (22, 23). We also utilized National Institutes of Health (NIH)'s new tool, iCite, to access a dashboard of bibliometrics for SRP-funded publications including the Relative Citation Ratio (RCR), a field-normalized metric that shows the citation impact of articles relative to the average NIH-funded paper (24). iCite also includes a translation module that allows the user to create heat maps showing where publications fall within the Triangle of Biomedicine, a trilinear map of science used to identify translational science (25), to visualize the movement of research from molecular/cellular and animal systems to humans (available on the iCite webpage: https://icite.od.nih.gov).

Identification of case studies

In addition to analyzing citation impact-based metrics, we also sought to identify how the research has influenced diverse scientific fields of study. We utilized publication citation networks to visualize the diversity of SRP-funded research. Publication citation networks, or bibliographic mapping, is an increasingly utilized method to both analyze and illustrate the relationships among publications (26–28). The free bibliometric network analysis tool, VOSviewer (Visualization of Similarities viewer; Version 1.6.9) was used to create bibliographic coupling and co-citation network maps (29, 30), revealing the publication collaborations among the disciplines.

Because of the long latency from initial research and the complex iterative nature of translating research to results, it is difficult to systematically track and evaluate all potential outcomes. To identify projects that have resulted in research impact within the five domains described earlier, we searched our database of research findings. To gain a more complete understanding of the application of the research, we also asked SRP Centers to provide examples of how their research projects have moved from a fundamental or basic biomedical research question to having an impact on science, health, and society. Centers provided lists of their projects that had moved from a fundamental or basic biomedical research question to having an impact on science, health, and society. Through this process, we received 58 potential projects and narrowed the list based on the strongest evidence of clinical, public health, policy, or economic benefits. Although we did not expect each of the case studies to cover all impact categories, we selected case studies that represent different strengths and aspects of the program with the most robust evidence of benefits. Finally, we contacted those SRP-funded researchers directly associated with the respective case study research projects to collect additional information not typically captured in publications, including how findings have been used to support public health efforts such as legislation.

Discussion

Basic bibliometric analysis

Dissemination of research findings through peer-reviewed publications is the cornerstone of knowledge advancement and is one aspect of evaluating research impact. Analyzing publication trends provide valuable information about the dissemination of research results and analyzing citation trends gives insight into the spread and influence of that research. Our goal was to first assess citation impact for SRP-funded research and then to conduct targeted analyses focusing on the specific case studies. Looking at publications from 1995 to 2015 (n = 7529), we were able to identify publication trends. For the bibliometric analyses, we then narrowed the set down to include only those publications associated with a PMID, DOI, or WOS accession ID (n = 7518). Citation impact was assessed using both Clarivate Analytics' InCites and NIH's iCite analysis tools.

We used these publication IDs to query and retrieve bibliometric data from WOS and InCites and retrieved 6992 and 6967 records, respectively. Table 1 summarizes

Table 1: Citation Impact Scores from Clarivate Analytics' InCite for SRP publications from 1995 to 2015.

	Number of publications	Total citation count	Percentage of publications cited (%)	Category normalized citation impact score (CNCI)	Percentage of publications in the top 10% (%)
Overall publications	6967	359154	99.3	1.74	22.88
Publications by WOS subject category					
Toxicology	1943	84156	99.5	1.65	20.8
Environmental sciences	1913	80066	99.3	1.45	16.5
Public, environmental, and occupational health	981	48148	99.1	1.94	29.4
Biochemistry and molecular biology	825	59661	99.8	1.70	18.2
Environmental engineering	633	30463	99.7	1.53	15.6
Pharmacology and pharmacy	629	27495	99.4	1.66	19.7
Oncology	401	20453	99.0	1.78	17.2
Biotechnology and applied microbiology	372	22831	100.0	1.78	24.2
Analytical chemistry	334	11134	99.1	1.33	12.9
Genetics and heredity	295	20505	99.7	2.26	17.6
Cell biology	273	25818	100.0	1.79	20.1
Microbiology	245	17253	99.6	1.89	23.7
Neurosciences	234	10672	99.6	1.17	12.4
Endocrinology and Metabolism	221	10798	99.5	1.32	19.5
Biochemical research methods	219	9550	98.2	1.33	15.5
Water resources	213	7475	99.1	1.46	18.3
Chemistry, multidisciplinary	212	11869	100.0	1.52	14.6
Medicinal chemistry	145	8097	100.0	2.05	29.0
Marine and freshwater biology	133	3625	100.0	1.16	9.0
Physical chemistry	105	5322	97.1	1.54	22.9

SRP, Superfund Research Program; WOS, Web of Science.

citation impact data provided by InCites for the overall publication set and broken down by WOS subject categories (determined at the journal level). The table includes the total number of publications, the total number of times publications were cited (Total Citations), the percentage of publications that were cited, the overall Category Normalized Citation Impact (CNCI) score, and the percentage of documents in the Top 10%, by WOS subject category. Overall, the publication data show that research supported by SRP are prolific and extremely multi-disciplinary in scientific areas such as public, environmental, and occupational health and environmental sciences, with toxicology being the most prevalent WOS subject category.

Because there are large differences in the number of citations received by a paper across subject fields (e.g. biology vs. mathematics) and over time, citation rates need to be normalized by discipline, age of publication, and document type to fairly compare different types of papers across different fields and different years. Normalized bibliometric indicators such as the CNCI compare the citation impact of a paper of interest with a citation impact baseline defined by articles published in the same subject and publication year, in order to correct for the effects of these variables (31). The CNCI is calculated by dividing the number of citing items by the expected citation rate for articles with the same document type, year of publication, and subject area. A CNCI score of 1.0 indicates the average number of citations for a paper in its field, whereas a score of 2.0 indicates that research is cited 2.0 times the average expected. The overall mean CNCI score across all SRP-funded publications was 1.74, meaning that SRP research is performing above the average rate of citation for similar articles (Table 1, shaded area). Publications within the topics of genetics and heredity and medicinal chemistry had CNCI scores of 2.26 and 2.05, respectively, indicating that these articles were cited more than twice as often as comparable articles (Table 1, shaded areas). Another indicator of influence is to compare the proportion of articles that are in the top 10% of cited articles. An average publication set would have 10% of articles in the top 10% so values greater than 10, as observed for almost all of these publication categories, are considered above average in performance. Of note, almost 30% of medicinal chemistry, and public, environmental and occupational health articles were in the top 10% of similar research (Table 1, shaded areas).

Table 2: Results from NIH iCites for SRP publications from 1995 to 2015.

Total pubs	Pubs/year	Cites/year				Relative citation ratio (RCR)				Weighted RCR
		Max	Mean	Sem	Med	Max	Mean	Sem	Med	
5977	284.62	275.17	3.42	0.10	1.88	82.25	1.71	0.04	1.08	10100.81

SRP, Superfund Research Program. Results show publication information, citation data, and RCR values (maximum, mean, standard error of the mean, and median).

We also assessed comparative citation impact using the RCR metric (24). Because the RCR value is calculated for individual publications in PubMed, only SRP articles with a PMID (n = 6649) could be uploaded into iCite, retrieving a total of 6638 publications. We then excluded non-research articles (e.g. reviews and commentaries) resulting in a total of 5977 articles with a mean of 3.42 cites/year and a mean RCR of 1.71 (see Table 2). The RCR value is citations/year received by an article, normalized by field. An RCR score equal to 1.0 means the paper has received the same number of citations per year as the average NIH-funded paper and a paper with an RCR of 2.0 has received twice as many citations per year as the average. Therefore, the 1995–2015 SRP publication RCR average indicates that SRP publications received close to twice the number of expected citations per year as the average NIH-funded paper in the same field. Fifty-three percent (3162/5977) of SRP publications were above the NIH 50th percentile, indicating that slightly more than half of SRP publications had higher citation impact than the average NIH-funded article from the same field and same year. In addition, the weighted RCR is the sum of the RCRs for articles in the group. According to the iCite website, a publication set is highly influential if the weighted RCR is higher than the number of total publications, indicating that the SRP publication set is highly influential.

Both the CNCI and RCR are comparative citation impact metrics that demonstrate an article's research influence by comparing similar articles (i.e. peer articles in the same field). While several studies have shown that both indicators yield similar results (32, 33), the RCR does have several advantages. First, the RCR field normalizes dynamically based on the co-citation network of the article instead of assigning a field based on journal categories which might be advantageous for an interdisciplinary field of research such as SRP (24). Second, RCR scores are benchmarked to NIH R01-funded articles and therefore are particularly relevant for analyses of NIH-funded programs such as the SRP. A final benefit of using RCR scores from NIH's iCite is that it is not proprietary and is therefore freely available for public use.

To further visualize the multidisciplinary nature of SRP research, we generated a journal landscape map using the free bibliometric network analysis tool, VOSviewer (Version 1.6.9). Out of a total of 7518 SRP publications from 1995 to 2015 with available PMIDs, DOIs, and WOS accession numbers, 6992 were retrieved from WOS. These records were imported into VOSviewer and used to derive a journal bibliographic coupling network as shown in Figure 1. Circles (or nodes) represent journals, and the connections (or edges) between circles represent shared references between documents. Circle size is determined by the number of articles in each journal. The more references shared, the more related the journals, and the closer together the circles. Groups of related journals form clusters, differentiated in VOSviewer by color. As shown in Figure 1, SRP-funded publications are published in a

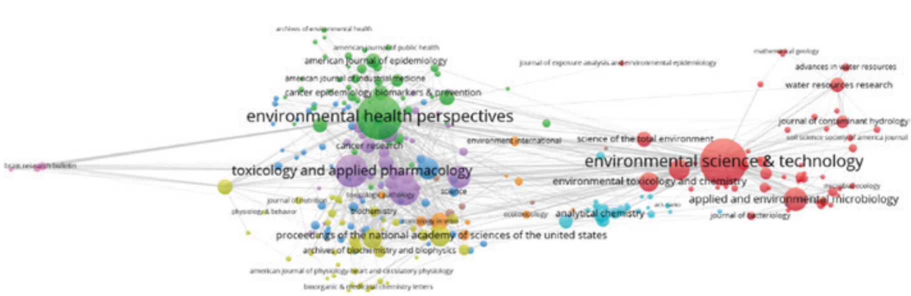

Figure 1: Journal bibliographic coupling network for SRP publications set (n = 6992 publications), 1995–2015 (VOSviewer).
Circles represent journals and the connections between circles represent shared references between documents. Circle size is determined by the number of articles in each journal and the position of the circles is determined by the relatedness of the journals, differentiated in VOSviewer by color.

variety of journals representing a wide range of scientific disciplines, falling into two major categories: biomedical-related research clustered on the left (i.e. environmental health perspectives) and environmental science and engineering fields clustered on the right (i.e. environmental science and technology). Interestingly, these two distinct fields of research have strong connections to each other, as revealed by the many edges between the two clusters of journals and illustrating the strong transdisciplinary nature of SRP research.

Case studies: benefits of basic research

We also sought to understand the impacts of this highly cited research and how it has informed policies or interventions that improved public health. Here we present five case studies of long-standing SRP-funded projects that highlight these impacts. These case studies, which include aspects of the Becker Library model of impact, include findings that improved our knowledge of potentially hazardous contaminants and diseases, and in turn, informed the formation of policies or interventions that improved public health. These case studies illustrate how research is built upon and expanded to uncover new insights that have far-reaching benefits.

The first case study illustrates long-standing efforts by SRP Center grantees that have used different approaches to understand and mitigate the health effects of arsenic. The resulting advances have led to a range of public health, clinical, and policy benefits. Following the arsenic case study, we describe distinct and targeted scientific approaches from SRP Centers that have led to public health, policy, and economic benefits. The selected case studies illustrate the breadth of biomedical research funded by the SRP.

Case study 1: improving health protections for arsenic

Arsenic contamination of water and food is associated with major environmental public health issues in the United States and around the world. Arsenic has been found in at least 1149 of the 1750 current and former National Priority List (NPL) sites identified by the Environmental Protection Agency (EPA) (34, 35). In addition, millions of U.S. residents are exposed due to naturally occurring arsenic in their household well water (36).

Transdisciplinary teams of researchers from SRP Centers across the country have made important contributions to arsenic research. Each center represents a collaboration of highly interactive research projects focused on improving understanding of health effects, geochemistry, hydrology, and remediation of arsenic. Many teams also aim to lower the risks associated with exposure to arsenic by guiding the focus of interventions in high-risk areas.

Advancing knowledge

Using keyword searches for arsenic, and its common forms, arsenate and arsenite, in the title of SRP publications in our database, and for SRP-funded publications in PubMed, we identified over 673 research articles published by SRP-funded researchers between 1995 and 2015.

These studies have identified important disease associations, defined metabolic and toxic pathways, validated biomarkers of exposure and disease, and described genetic differences in vulnerable populations [(37), see Table 3].

Many of these basic research projects have generated data and provided knowledge that has formed the basis for subsequent research. Landmark discoveries about the human health impacts of arsenic exposure have also been translated to human impacts (See Figure 2 and Table 4). The comparative citation impact of these publications was found to have a mean RCR of 2.0, indicating that these publications received more than twice the number of expected citations per year as the average NIH-funded paper in the same field. In addition, 64.2% of these publications were greater than the 50th percentile rank amongst NIH-funded publications.

Public health benefits

Importantly, SRP-funded Centers have worked closely with affected communities to address their concerns and provide them with important information regarding potential exposure to arsenic and its health implications.

For example, the Dartmouth SRP Center has been evaluating private well testing behavior, including barriers to well testing. They also worked to encourage private well testing and empower well water users with the tools they need to keep their drinking water safe, including a website, community toolkit, and online application (97–99).

Building on their basic research elucidating the pathways that facilitate the excretion of arsenic from the

Table 3: A selection of important arsenic-related discoveries funded by the SRP.

SRP center	Discovery	Reference
Columbia University	Established a large cohort, the Health Effects of Arsenic Longitudinal Study (HEALS) cohort, in a region of Bangladesh with arsenic-contaminated groundwater. HEALS has identified numerous health effects resulting from exposure to arsenic (see Figure 2 and Table 4)	(4, 38)
	First to report arsenic, like lead, has adverse effects on cognitive function in Bangladeshi children; exposure to arsenic impacts intelligence and alters motor function in children	(39–42)
	Evidence of peripheral neuropathy among Bangladeshi children even at low to moderate levels of arsenic exposure	(43)
	Reported fetal blood levels of arsenic were higher than maternal levels of arsenic in HEALS participants, indicating a potential increased toxic effect for in utero exposure	(44)
	Arsenic in well water may diminish intelligence in Maine and New Hampshire children; levels of arsenic in drinking water greater than 5 parts per billion, but below the EPA standard of 10 parts per billion, were associated with reductions of approximately 5–6 points in both Full Scale Intelligence Quotient (IQ) and index scores related to perceptual reasoning, working memory, and verbal comprehension	(45)
Dartmouth University	Developed technique to accurately measure very low arsenic concentrations, improving exposure estimates	(46)
	Verified toenails can be used as a reliable biomarker of exposure to arsenic	(47)
	Reported arsenic is a potent endocrine disrupter	(48)
	Characterized arsenic exposure via diet	(49)
	Elevated levels of arsenic in rice, brown rice syrup, and related products	(50)
	Conducted the first long-term study showing arsenic exposure may increase blood pressure in pregnancy	(51)
	Reported an association between low arsenic exposure and birth outcomes, including decreased fetal growth	(52)
	Exposure to arsenic at low levels negatively impacts the immune response in the lungs	(53, 54)
UC Berkeley	Arsenic induces genetic damage in the form of chromosome breakage in the bladder epithelium	(55)
	Association between arsenic exposure and bladder cancer in cohorts in Argentina and Chile	(56, 57)
	Increased chromosomal alterations in bladder cancer cases at higher arsenic levels	(58)
	People exposed to both arsenic and other known or suspected carcinogens have very high risks of lung or bladder cancer	(59, 60)
	Skin lesions associated with low levels of arsenic exposure; potential role of malnutrition in susceptibility	(61)
	Population cancer mortality rates remain increased even 25 years after a major decrease in arsenic exposure	(62)
	Association between early-life arsenic exposure and adult mortality from lung, bladder, and kidney cancer	(63–67)
	Association between early-life arsenic exposure and type 2 diabetes and hypertension in adults	(68, 69)
University of Arizona	Pioneering research on arsenic metabolism and the speciation of arsenic	(70–73)
	Monomethylarsonous acid [MMA(III)] is more toxic than inorganic arsenite in vitro and in vivo	(74, 75).
	Characterized organic arsenic metabolites in human urine	(76)
	Arsenic metabolite MMA(III) plays an important role in carcinogenesis	(77)
	Described underlying mechanisms of arsenic-induced non-cancerous respiratory impacts	(78)
	Early-life exposure to arsenic alters airway structure and function	(79)
University of North Carolina, Chapel Hill	Identified metabolites in umbilical cord blood associated with arsenic exposure in utero; provided evidence that changes in the neonatal metabolome may be linked to prenatal arsenic exposure, which may have implications for later-life health effects	(80)

SRP, Superfund Research Program. These discoveries have generated data and provided knowledge, forming the basis for subsequent research.

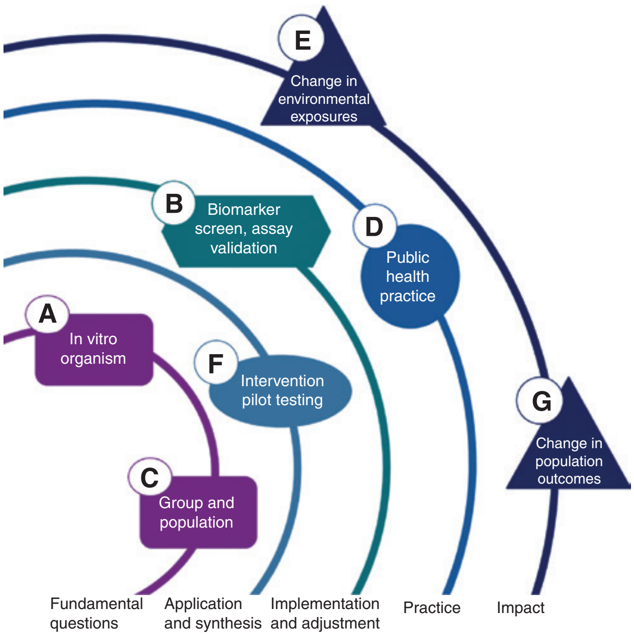

Figure 2: Translational research framework activities at the Columbia University SRP Center (See Table 4 for supporting details).
The Columbia University SRP Center's research offers an opportunity to illustrate the complex translational nature of basic research as it moved from fundamental research questions to impact. The translational research framework developed by NIEHS (6) was used to provide a visual representation of the findings outlined in Table 4. The graphic demonstrates the iterative process of how fundamental research questions are translated into human impacts. While the Columbia University SRP Center's research covers most of the nodes represented in the translational research framework, here we focus on a few key contributions that represent impactful changes. Categories of translational research accomplished by the Columbia SRP Center include: (A) In vitro studies describing the underlying mechanisms of arsenic genotoxicity; (B) Methodological advances to measure arsenic and arsenic metabolites in blood; (C) Identified numerous health impacts of arsenic exposure in the HEALS cohort; (D) Provided valuable public health infrastructure and facilities to the HEALS community; (E) Installed hundreds of deep wells to reduce arsenic exposure in the HEALS community; (F) Conducted pilot interventions with folate supplementation to reduce blood arsenic and improve health outcomes; (G) Documented reduced lung and bladder disease and improved working memory with reduced arsenic exposure. See Table 4 for specific details for each of these nodes and associated references.

human body, the Columbia team has been exploring intervention approaches using folic acid to lower the health risks associated with arsenic exposure. They uncovered the role of folic acid supplementation in increasing arsenic metabolism and decreasing arsenic toxicity in adults (96, 100–105). Subsequent work revealed that reductions in blood arsenic levels were sustained for at least 12 weeks (106). Similarly, the Columbia team identified folate deficiency in Bangladeshi children with arsenic toxicity and found that folate facilitates arsenic methylation in children (107). Based on their findings in adults, folate supplementation may prove promising for interventions with children.

Additionally, the Columbia team partnered with state and local government agencies in New Jersey to promote private well testing and arsenic treatment. They are conducting a pilot project with health care providers to encourage private well testing and treatment. They have also provided education and risk communication to arsenic-exposed populations in Maine, New Jersey, and Bangladesh and investigated the impact of health education on behavior change to reduce exposures (108–111).

Researchers at the University of Arizona SRP Center have characterized arsenic uptake into the edible portion of homegrown vegetables in mining-impacted soils (112) to help communities understand their potential exposure and health risks. As part of a community-engaged research project, called Gardenroots, they found that the main sources of arsenic exposure were drinking water and incidental soil ingestion (113, 114). They also learned that although ingestion of home garden vegetables may contribute more arsenic than that of store-bought vegetables, the exposure was generally relatively low compared to exposure from water ingestion (113).

Policy and economic benefits

Many important SRP findings have been used to inform decision-making about arsenic and further protect human health at the local and federal level. This includes contributions that informed the arsenic maximum contamination level, the Integrated Risk Information System (IRIS) assessment on arsenic, and the U.S. Food and Drug Administration (FDA) limit of arsenic in infant food.

Changes to the arsenic maximum contaminant level

Several of the SRP's arsenic researchers have informed EPA policy on regulations of arsenic in drinking water. In 1999, the EPA reevaluated their enforceable maximum contaminant level (MCL) in drinking water of 50 parts per billion (ppb) arsenic based on more recent studies (115). The MCL is the maximum level allowed of a contaminant in water which is delivered to any user of a public water system. This enforceable standard is set by the EPA and is used to limit the levels of contaminants in water and to protect human health.

Part of this reevaluation included a new analysis of the data on which the MCL was based. This was done

Table 4: Research activities and discoveries from the Columbia University SRP Center team illustrated in the translational research framework (Figure 2).

Translational research framework area	Research activities and discoveries	Reference
In vitro organism (see Figure 2A)	Described the role of reactive oxygen species in arsenic mutagenicity in mammalian cells	(81)
	Found that arsenite is a potent gene and chromosomal mutagen, debunking the previous school of thought that it was a nongenotoxic carcinogen	(82)
	Discovered that mitochondria are an important target for arsenic-induced genotoxicity and that the genotoxicity of arsenic is mediated by a combination of reactive oxygen species and reactive nitrogen species	(83)
Biomarker screen, assay validation (see Figure 2B)	Increased the capability to measure total arsenic and arsenic metabolites in blood, where concentrations are an order of magnitude lower than those in urine. Blood arsenic is a sensitive biomarker of arsenic exposure and is directly associated with the risk for arsenic-induced skin lesions	(84)
Group and population (see Figure 2C)	Identified numerous health impacts of arsenic exposure through the HEALS cohort, including skin lesions, increased mortality rate, lung cancer, heart disease, impaired lung function, and pediatric pneumonias. Reported health effects such as skin lesions, neurological impairments, and signs of respiratory and cardiovascular diseases even at low exposure levels	(43, 85–92)
Public health practice (see Figure 2D)	Provided valuable public health infrastructure and facilities to the surrounding HEALS cohort community, including health evaluations and education that participants did not otherwise have access to. For example, the study area now has a pharmacy, primary care facilities, and dentistry services	(38, 93)
Change in environmental exposures (see Figure 2E)	Reduced arsenic exposure in the community by helping families in Bangladesh gain access to drinking water with lower levels of arsenic by installing hundreds of deep wells	(94)
Intervention pilot testing (see Figure 2F)	Conducted pilot studies to determine the effectiveness of folate supplementation to reduce blood arsenic and improve health outcomes	(95)
Change in population outcomes (see Figure 2G)	Evaluated the impact of reduced water arsenic concentration on health outcomes in the population. For example, in a follow-up study 2 years after installing deep wells, the team found that reduced arsenic exposure was associated with improved working memory	(94)
	Analyzed NHANES data and found after the EPA lowered the limit for arsenic in drinking water, exposure to arsenic dropped significantly among people using public water systems in the U.S. They reported a 17% decrease in urinary arsenic levels, equivalent to an estimated reduction of at least 200 cases of lung and bladder disease every year, and as many as 900 per year	(96)

EPA, Environmental Protection Agency; HEALS, Health Effects of Arsenic Longitudinal Study; NHANES, National Health and Nutrition Examination Survey.

by University of California (UC) Berkeley SRP Center researchers, who performed a risk assessment analysis and derived cancer estimates of 1 in 100 for people drinking water containing 50 ppb of arsenic, a much higher incidence than previously thought (116).

The EPA analysis also considered UC Berkeley SRP Center research that focused on communities in Chile exposed to high levels of arsenic for a defined period (117). The Chilean cohort data suggested substantial cancer risks from exposure to arsenic in drinking water at lower concentrations than previously recognized (57). These SRP contributions were key components of the evaluation process for the EPA that led to the lowering of the MCL to 10 ppb in 2001 (117).

Several SRP-funded publications were cited in the MCL rule (56, 57, 76, 118). SRP researchers also served on the National Research Council (NRC) subcommittee on arsenic in drinking water, which informed the EPA evaluation. The NRC Report referenced 42 SRP-funded publications (119).

The economic analysis for the EPA's MCL rule notes that reducing the standard to 10 ppb would result in an estimated \$139–200 million in annual health benefits related to decreases in bladder cancer and lung cancer combined (120). Specifically, it is noted that at the 10 ppb

MCL level, approximately 37–56 bladder and lung cancer cases would be avoided annually.

Columbia SRP Center researchers analyzed National Health and Nutrition Examination Survey (NHANES) data and found that after the EPA lowered the limit for arsenic in drinking water, exposure to arsenic dropped significantly among people using public water systems in the U.S. They reported a 17% decrease in urinary arsenic levels, equivalent to an estimated reduction of at least 200 cases of lung and bladder disease every year, and as many as 900 per year (96). Their results indicate that the EPA cost-benefit analysis underestimated the reduction of cancer cases, and therefore the cost savings associated with those reductions.

SRP researchers also informed a reduction of the arsenic MCL in New Hampshire. The rule, signed into law on July 12, 2019, cuts the state standard in half from the federal level of 10 ppb to 5 ppb. In proposing the rule, the New Hampshire Department of Environmental Services (NHDES) consulted with Dartmouth SRP Center researchers to identify health effects to consider in a review of the limit (121). They cited work from the Dartmouth and Columbia SRP Centers linking arsenic levels common in New Hampshire to adverse birth outcomes and infections in infants and gestational diabetes in mothers (41, 45, 52, 122). Partnering with epidemiologists at Dartmouth, the NHDES reported that the new limit could prevent several arsenic-related deaths and illnesses over the next 70 years, including up to eight cancer-related deaths, up to 19 cases of bladder- and lung-related cancer cases, and four cases of skin cancer (121).

The Integrated Risk Information System assessment on arsenic

The EPA IRIS Program identifies and characterizes the health hazards of chemicals found in the environment. IRIS assessments are the preferred source of toxicity information used by the EPA and are also an important source of toxicity information used by state and local health agencies, other federal agencies, and international health organizations (123).

The EPA began reevaluating the IRIS assessment for arsenic shortly after the MCL was lowered to include more recent scientific data. A draft assessment was presented to Congress in 2010, and the NRC was asked to review the draft assessment to ensure thoroughness in evaluating currently available science. Again, research led by SRP-funded Centers played a key role in determining potentially unsafe levels of arsenic. Overall, the IRIS 2010 report cites 80 SRP-funded publications, and the NRC report cites 42 SRP-funded publications.

Findings from the Health Effects of Arsenic Longitudinal Study (HEALS) cohort are cited in the ongoing arsenic risk assessment being conducted by the EPA (124). In addition, HEALS cohort data also contributed to a physiologically based pharmacokinetic (PBPK) model for inorganic arsenic developed by the EPA with major implications for arsenic risk assessment in populations exposed to low or moderate arsenic levels (125).

Several SRP researchers were part of the NRC Committee on Inorganic Arsenic, which was tasked with reviewing the 2010 draft IRIS assessment in 2013. Five of the 15 committee members and the NRC Committee Chair were SRP grantees (126). Their selection for this important review reflects the standing of SRP researchers as leaders in arsenic-related biomedical research.

FDA limit of arsenic in infant food

Based on their findings of arsenic in brown rice syrup, the Dartmouth SRP Center initiated the Collaborative on Food with Arsenic and Associated Risk and Regulation (C-FARR) to address important issues surrounding arsenic in food. C-FARR convened a team of scientists and stakeholders to work together over a 2-year period to gather and analyze data and publish a series of papers related to sources of arsenic and human exposure via food consumption (127–131).

This work also informed the FDA's recommendation to limit the amount of arsenic in infant food containing rice syrup. The FDA's recommendation primarily references a 2013 NRC report that cites 80 SRP-funded publications (126).

Case study 2: PCE-contaminated drinking water and its health effects

In 1997, Boston University (BU) SRP Center researchers initiated a study in the Cape Cod region of Massachusetts to determine whether exposure to tetrachloroethylene (PCE) is linked to negative health effects. PCE is a manufactured chemical used for dry cleaning and metal degreasing and has been found in at least 945 NPL sites identified by the EPA (132).

BU SRP Center researchers started to explore potential health effects resulting from exposure to PCE to improve what we know about its health effects, particularly in groups who may be more vulnerable to PCE exposure, such as pregnant women and their children. Before they initiated the study, animal experiments had suggested an adverse effect of prenatal exposure to PCE on offspring weight and growth, but epidemiological studies had inconsistent results (133).

The BU SRP Center focused on residents in Cape Cod who were inadvertently exposed to PCE during a specific window of time, providing a natural experiment to explore how early-life exposures to PCE may lead to health effects later in life. Beginning in 1968, a vinyl liner containing PCE was applied to pipes in the Cape Cod drinking water distribution system. The vinyl liner was improperly cured, leaching PCE into the water supply. Due to the irregular pattern of the affected pipes, the drinking water in the region had a range of PCE concentrations. The PCE contamination was discovered in 1980 and the PCE levels in water have since been brought down. Using records of the water pipes to estimate exposure, BU SRP Center researchers began studying women and their children in the area (134).

Advancing knowledge

The research team found small increases in breast cancer risk among women exposed to PCE from public drinking water (135). A larger study confirmed this finding (136), suggesting that women with the highest PCE exposure levels have a small to moderate increased risk of breast cancer.

The study also linked prenatal and early-life exposure to PCE with increased risk of epilepsy and cancer (134), visual dysfunction (137), and mental illness (138) later in life. They discovered that risky behaviors, particularly drug use, are more frequent among adults with high PCE exposure levels during gestation and early childhood (139), and that prenatal exposure to both alcohol and PCE may combine to increase the risk of using multiple illicit drugs as a teenager (140).

The team also found that pregnant women who drank water contaminated with PCE were up to twice as likely to have a stillbirth due to placental dysfunction. The researchers observed that the odds of stillbirth increased as a woman's level of exposure to PCE increased (141). They also observed that mothers with higher PCE exposure levels during the first trimester had increased odds of having a child with spina bifida, cleft lip with or without cleft palate, and hypospadias (142).

Public health and policy benefits

This work spanning over two decades by the BU SRP Center has helped bring attention to potential links between PCE and health effects in the Cape Cod region and beyond. PCE remains a major contaminant of groundwater, with U.S. surveys of drinking water contaminants detecting it in 11% of tested wells and 38% of surface water supplies (143).

The studies also contributed to guidance on health care and disability for veterans and their families exposed to drinking water contaminated with trichloroethylene and PCE from 1957 to 1987 at the Marine Corps base at Camp Lejeune, North Carolina (144). In accordance with the Honoring America's Veterans and Caring for Camp Lejeune Families Act of 2012, the Veterans' Administration (VA) provides cost-free health care for certain conditions to veterans who served at least 30 days of active duty at Camp Lejeune from 1957 to 1987, and their families (145). The list of health conditions, which includes breast cancer, was informed by a report by the NRC Committee on Contaminated Drinking Water at Camp Lejeune (146), which cited the BU SRP Center breast cancer research (135, 136) as findings that contributed substantially to identifying priorities.

Additionally, these studies contributed to subsequent recommendations by the Institute of Medicine committee to expand the range of conditions covered by the VA for disability compensation to veterans and their families exposed to contaminated drinking water at Camp Lejeune (147). Drawing from the BU SRP Center Cape Cod studies (137–139, 148–151), the committee recommended that the VA consider adding several neurobehavioral effects to the list of conditions that qualify for disability benefits, including those due to neural tube birth defects, as well as adolescent and adult illicit drug use, bipolar disorder, and problems with contrast sensitivity and color discrimination.

As of 2017, the VA concluded that there was insufficient evidence to establish presumptions of service connection for neurobehavioral effects. However, disability claims would be reviewed on a case-by-case basis (152). Through the Institute of Medicine report and recommendations, the BU SRP Center research has brought additional potential health effects to the attention of the VA.

In a more recent example, in Duxbury, Massachusetts, which is adjacent to Cape Cod, 15 miles of vinyl-lined pipes were installed in the 1970s. The town government agreed to replace all vinyl-lined pipes in 1997, but several miles of lined pipes remain today. In January 2019, Duxbury Safe Water Group, a citizen's action committee, invited the lead researcher on the project to speak at a public meeting to describe her findings linking PCE and health effects. The group was concerned because certain areas still had detectable PCE levels in drinking water and cancer rates were elevated in some neighborhoods. After hearing about the research findings, the town voted to replace the remaining vinyl-lined pipes in an effort to prevent PCE exposures (153).

Publication metrics: evidence of transdisciplinary reach

Given these public health impacts, we sought to determine how this work complemented the scientific literature and influenced other scientific work. We looked at the citation impact of 21 studies published by BU SRP Center researchers related to the health effects of PCE-contaminated drinking water from 1998 to 2018. This was accomplished using Dimensions, a new research platform that includes a citation database (23). Citation count, the number of times an article has been cited by subsequent publications, is a commonly used indicator of the influence of published work within the scientific community. PMIDs were used to query Dimensions, resulting in 21 publications that were cited a total 358 times.

Analyzing the fields of research of the citing publications can demonstrate the diffusion of knowledge from the original cited publications and show how the research is being used. Dimensions assigns research topics (Fields of Research) at the article level using existing classification systems and a machine-learning approach (154). The original 21 research articles comprised four health-related research topics, with some articles tagged with more than one research category. The categories included public health/health services (n = 20), pediatrics/reproductive medicine (n = 4), psychology (n = 2), and oncology/carcinogenesis (n = 1). Figure 3 shows the expansion to 19 fields of research (top 12 fields shown) for the publications citing these articles (n = 358). The figure illustrates how health research generated from this cohort, and primarily published in the field of public health and health services, has been cited by fields as diverse as statistics (n = 14), environmental engineering (n = 6), and applied economics (n = 3), providing evidence that this research has moved beyond discipline-specific approaches and is being used to inform problems in a variety of different disciplines. The dominant field of research remains public health/health services (n = 225); however, it decreased from being the field of research for 75% of the original publications to 67% of the second-generation publications. Knowledge generated by these original studies on the health effects of PCE-contaminated drinking water is being utilized, expanding the reach of the research findings and broadly diffusing knowledge to reach additional disciplines.

Case study 3: immunoassay technologies to detect hazardous chemicals

One of the mandates of the SRP is to develop methods and technologies to detect, assess, and evaluate the effects of

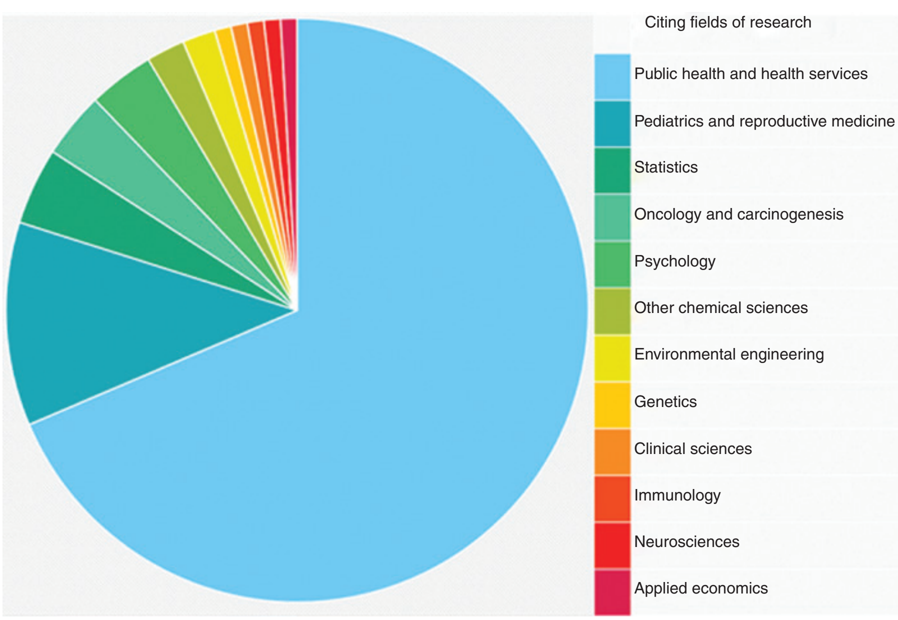

Figure 3: Research types citing Aschengrau's SRP-funded research.
Field of research categories (top 12) for all articles in Dimensions (n = 358) that cite the original 21 articles published on the health effects of PCE-contaminated drinking water from 1998 to 2018.

toxic substances on human health. To address high analysis costs for assessing toxic substances in the environment as well as the need for more sensitive indicators of exposure to humans, the University of California, Davis SRP Center researchers pioneered the use of immunoassay technologies to detect hazardous chemicals. Immunoassays use antibodies to bind to a chemical of interest, and labels on the antibodies detect this binding to measure the presence and concentration of the chemical.

Advancing knowledge

As part of an SRP-funded project, UC Davis SRP Center researchers and colleagues began developing biochemical tools to monitor contaminants in the environment as well as in biofluids (e.g. metabolites in urine) to estimate human exposure (155, 156). This led to the development of immunoassays. They allow simple and sensitive measurements and can be used on multiple samples for quick results, often achieved onsite. The same immunochemical reagents can be formatted for sensitive laboratory assays or formatted as qualitative or semi-quantitative rapid field tests. They are attractive for analyzing pesticides and other environmental contaminants when large numbers of samples must be examined for a small number of compounds, when tests need to be run in the field or in remote laboratories, when automated fluidic devices must be used, or when particularly complex structures must be analyzed (155).

Building off of the SRP-funded work, more than 40 immunoassays for pesticides, pesticide metabolites, and other environmental contaminants have been developed (157). These immunoassays, which were originally developed with SRP funding, have since been developed with a variety of funding sources to detect a large number of chemicals including immunoassays to detect polybrominated diphenyl ether BDE-47 (158), the insecticide fipronil (159), and the antimicrobials triclocarban (160) and triclosan (161).

This early work has led to an entirely new immunoassay approach. As part of the SRP project, researchers are pioneering recombinant nanobodies from animals in the camel family to make more cost-effective and sensitive immunoassays (162).

Public health, clinical, and policy benefits

In general, using this immunoassay technology is more than 10 times cheaper than traditional liquid chromatography-mass spectrometry detection methods and is easy to scale up for screening large numbers of samples (Hammock, Personal Communication). Because immunoassays do not require expensive equipment or extensive training, UC Davis SRP Center researchers work with partners to facilitate their use in the field. They are initiating a project with the Yurok Tribe in northern California, training them to use immunoassays to identify and monitor exposure to pesticides and other contaminants (163). Their immunoassays are also used to test pesticide exposures in agricultural workers to identify the need to limit exposure or promote the use of additional protective equipment (155, 164).

The UC Davis team have distributed their immunoassays worldwide free of charge for academic and commercial development (Hammock, Personal communication). Following a recall across Europe in which millions of eggs contained the insecticide Fipronil, UC Davis SRP researchers were contacted by three private companies and several research institutions for immunoassay reagents and their fipronil standard. As part of these requests, they provided the fipronil immunoassay reagents to Biorex Food Diagnostics, who used the technology to develop the first fipronil screening test for liquid egg (Vasylieva, Personal communication). This screening test can be used by egg producers to ensure the safety of their eggs and reduce the risk of a similar contamination from occurring again (165).

They also employed the immunoassay technology to test for emerging contaminants of concern. By combining the immunoassay with a battery of mechanism-based approaches, they found that triclosan and triclocarban, contaminants in wastewater and at hazardous waste sites, altered hormonal activity (166). The UC Davis SRP Center explored this relationship further, displaying significant absorption of triclocarban from soap during showering (167), and showing that triclosan weakens heart and skeletal muscle activity in animal models (168). Further research in collaboration with SRP researchers at UC San Diego found that exposure to triclosan may alter normal hormone function and promotes growth of liver tumors in laboratory mice (169, 170).

In 2013, the FDA issued a proposed rule banning the sale of any over-the-counter consumer soaps and body washes containing triclosan and triclocarban, unless the product undergoes approval as a drug. This proposed rule cited research from the UC Davis SRP Center (167, 168) as well as SRP grantees from Arizona State University (171). The final FDA rule banning the sale of over-the-counter soaps containing triclosan and triclocarban took effect September 6, 2017.

Figure 4: Journal categories representing UC Davis SRP-funded publications.
Web of Science research categories Treemap created in Clarivate Analytics' Web of Science. 130 publications from the SRP publication set focusing on the UC Davis immunoassay research project (1995–2015) including the UC Davis Center Director as an author (Bruce Hammock) were retrieved from Web of Science and are shown in this figure. The top 15 categories are shown.

Publication metrics

UC Davis SRP Center research on immunoassays has resulted in the publication of 146 papers from 1995 to 2015 related to the development or use of immunoassay technologies. Of these, 130 are available in WOS and InCites. Figure 4 shows a journal Treemap generated in WOS of the top 15 WOS research categories and illustrates the analytical nature of the publications. The majority of journals are classified as analytical chemistry, food science technology, and applied chemistry. The application of the immunoassays to measure pesticides is reflected in the large number of publications in the *Journal of Agriculture and Food Chemistry*. CNCI values from InCites show that 44% of these publications (57/130) had a CNCI of greater than 1.1 (1.0 having average impact in field), indicating that close to half of the publications had a greater than expected citation impact. Eighteen percent (23/130 publications) had a CNCI >2 indicating that these articles were cited more than twice as often as comparable articles. The RCR for this publication set was slightly less than the CNCI (mean RCR 1.07; 38% of publications above the 50th percentile); however, only 118 publications were retrieved from iCite, so the difference could be attributed to a smaller publication set.

Table 5 shows the percentage of documents in the top 10% for the most common subject categories in this publication set including analytical chemistry, food science and technology, applied chemistry, and multidisciplinary agriculture. An average publication set would have 10% of articles in the top 10% so values greater than 10, as observed for these publications, are considered above average performance.

Table 5: Percent publications in the top 10% from Clarivate Analytics' InCites for UC Davis SRP Center's 130 immunoassay-related publications in WOS from 1995 to 2015.

WOS subject category	WOS documents	% Documents in top 10%
Chemistry, analytical	54	16.6
Food science and technology	32	12.5
Chemistry, applied	30	13.3
Agriculture, multidisciplinary	28	17.9
Environmental sciences	20	15.0
Toxicology	18	11.1
Biochemical research methods	16	12.5

SRP, Superfund Research Program; WOS, Web of Science.

Case study 4: using nutrition to mitigate harmful exposures

Due to their relative chemical stability and pervasiveness in the environment, chlorinated organic contaminants such as polychlorinated biphenyls (PCBs) pose significant health risks and enduring remediation challenges. PCBs have been found in at least 500 of the EPA NPL sites (172). In addition, obesity and diabetes are at epidemic levels, affecting nearly 40% of adults and nearly 20% of children in the U.S. (173, 174). These diseases are also associated with heart disease, which is the leading cause of death in the U.S., estimated to cost approximately $200 billion annually (175).

Advancing knowledge

The University of Kentucky (UK) SRP Center findings clarified the mechanism of PCB toxicity that leads to cardiovascular disease by disrupting vascular endothelial cells (176). Importantly, the research team also gathered in vitro and in vivo evidence that coplanar PCBs disrupt endothelial function by increasing oxidative stress (177, 178) and inducing expression of inflammatory genes (179).

A UK SRP Center study was the first to link exposure to low levels of PCBs to obesity-associated atherosclerosis using in vitro and in vivo rodent models, finding that these changes were mediated by the aryl hydrocarbon receptor (AhR) (180). The research also showed that dioxin-like PCBs increase systemic inflammation and accelerate atherosclerosis even with a low-fat diet (181).

UK SRP Center researchers further discovered that the type of fat in the diet, and not just the amount of fat, can make a difference in cell damage triggered by environmental chemicals (182). They found that omega 6 fatty acids, like linoleic acid, can increase endothelial dysfunction induced by coplanar PCBs (183, 184) and demonstrated that mice fed oils rich in omega 6 fatty acids and exposed to PCBs had higher proinflammatory cytokine levels and increased vascular inflammation compared to mice exposed to PCBs alone (182).

UK SRP Center researchers also reported that mice exposed to PCBs had increased blood levels of trimethylamine N-oxide (TMAO), a biological marker of cardiovascular disease that is produced when the body metabolizes certain foods (185). Their work suggested a novel diet-toxicant interaction that results in increased production of TMAO (185), providing evidence that exposure to PCBs may contribute to inter-individual variability in blood TMAO levels. Based on these findings, the team analyzed a human population and observed a link between exposure to dioxin-like PCBs and elevated TMAO levels (186).

Through the UK SRP Center, researchers uncovered how nutrition can reduce harmful effects of hazardous chemicals and promote health. For example, they found that antioxidant nutrients such as vitamin E and healthy omega-3 fatty acids can reduce cell damage caused by PCBs and other pollutants by interfering with oxidative stress and proinflammatory signaling pathways (187, 188).

Other studies revealed that plant-based antioxidants, called "phytonutrients" or, more specifically "flavonoids", can modulate PCB-induced oxidative stress and endothelial toxicity (189) and prevent PCB-induced endothelial cell inflammation (190). Animals that consumed a diet enriched with dietary flavonoids were better prepared to counteract a subsequent exposure to dioxin-like PCBs as evidenced by decreased oxidative stress and increased antioxidant defense proteins (189, 191, 192). Building off these findings, they also explored the use of polyphenols, a larger class of plant-based antioxidants including flavonoids, in removing PCBs from the environment. Moreover, the work stimulated discoveries in remediation. They have developed novel nanoparticle systems containing polyphenols to bind to PCBs, which offer a cost-effective alternative to current PCB remediation approaches (193).

Public health benefits

Based on basic research into the protective mechanisms of nutrition in mitigating the harmful effects of PCB exposure, and supporting human data, where the team discovered that diets rich in flavonoids from fruits and vegetables can reduce the risk for PCB-associated type 2 diabetes (194), UK SRP Center researchers are designing and implementing educational programs and interventions to increase fruit and vegetable consumption among people exposed to ubiquitous compounds like coplanar and dioxin-like PCBs. Many of these programs focus on older adults, who may be more susceptible to the harmful effects of hazardous exposures (195).

For example, the UK SRP Center developed a nine-lesson extension curriculum, "Body Balance: Protect Your Body from Pollution with a Healthy Lifestyle", and partnered with the Kentucky Family and Consumer Sciences Cooperative Extension Service to pilot the curriculum in Kentucky communities. Pre- and post-lesson questionnaires revealed increased knowledge and awareness of the effects of environmental pollution on health, and the protective role of healthy nutrition. Focus group participants self-reported positive behavior changes based on increased environmental health literacy through the curriculum (196). They also developed and implemented nutrition education for older adults and found that it can significantly increase fruit and vegetable consumption (197). They have plans to test these interventions to assess changes in nutrition to changes in PCB-related health outcomes.

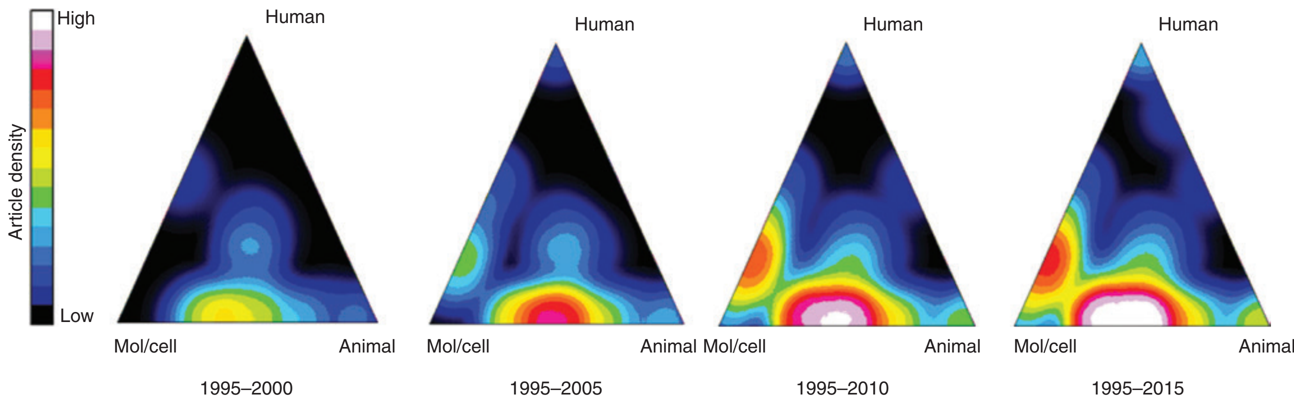

Figure 5: UK SRP Center publications study types over time.
iTrans heat maps show the translational development of UK SRP publications over time (n = 100). Colors range from dark (low article density) to bright (high article density). Publications with MeSH terms from all three groups (Human, Animal, and Molecular/Cellular Biology) fall into the center of the triangle. During the early stages of this research (1995–2000), there were no studies tagged as humans with the majority of publications in between molecular/cellular and animal categories. From 2000 to 2015, a number of human studies appeared though the focus of this body of research remains firmly on the basic side of the spectrum.

Publication metrics

As further evidence of the impact of these findings, bibliometric analyses of UK SRP Center's 100 original research articles (published 1995–2015) averaged an RCR of 1.39, well above the average citation rate for an NIH-funded publication in its field. Sixty-two percent of these publications had an RCR above the median NIH-funded publication (RCR: 1.01–4.18), illustrating their significant contributions to this field of research. Further, UK SRP Center research has expanded from basic research in cells and mice to a broader understanding in human cells and most recently, in human populations. This translation of basic research to human research can be clearly observed in the iTrans heat map shown in Figure 5. iTrans, a new NIH tool, uses MeSH terms to classify and plot publications (using PMIDs) on the Triangle of Biomedicine (25) to show how a set of publications has moved from molecular/cellular- and animal-based research to more human-based research over time.

Case study 5: linking low-level benzene exposure to cancer

UC Berkeley SRP Center researchers have developed and applied biological markers of benzene exposure, which has led to a more detailed understanding of benzene carcinogenicity. Benzene is widely used in the U.S. and ranks among the top 20 chemicals for production volume (198). Although benzene has been known to have toxic effects on blood and bone marrow at high levels, UC Berkeley researchers revealed effects at levels below the occupational standard at the time (199). They continued to explore the effects of benzene on health and have measured biomarkers in over 1000 benzene-exposed human populations and controls in numerous studies.

Advancing knowledge

A UC Berkeley SRP Center study demonstrated that exposure to benzene levels in air below the U.S. occupational standard of 1 part per million (ppm) can lead to a decrease in circulating blood cells, and that benzene is toxic to progenitor cells, the unspecialized cells from which all other blood cells develop (199). According to UC Berkeley SRP findings, benzene affects the blood-forming system at low levels with no evidence of a threshold, and there is probably no safe level of exposure to benzene (200).

The UC Berkeley research team discovered protein adducts formed after exposure to benzene in humans that serve as measurable indicators, or biomarkers, of benzene metabolism (201–203). They found that enzyme pathways involved in rapidly metabolizing and excreting low levels of benzene begin to saturate at exposure levels as low as 1 ppm, which can lead to accumulation of benzene in tissue (201). Building on this work, they studied a group of non-smoking women and identified an unknown pathway responsible for benzene metabolism at low levels (204). Although benzene exposure was previously associated with higher risk of leukemia (205), the UC Berkeley SRP

Center results provided evidence that the metabolism of benzene was greater in the population than previously thought, and that the leukemia risks could be substantially greater (204).

The UC Berkeley SRP Center continues to systematically explore benzene exposure and biomarker relationships over a wide range of occupational and environmental exposures. In a large-scale evaluation of genes, SRP researchers identified associations between benzene toxicity and five genes related to DNA repair and genomic maintenance. They also provided evidence that these genes play an important role in benzene-induced damage to blood cells (206).

UC Berkeley SRP Center studies also demonstrated that low-level benzene exposure altered the expression of immune and inflammatory response genes and pathways in peripheral blood mononuclear cells and that the altered expression of gene pairs could predict benzene exposure (207–209). SRP research reported the dose-dependent induction of leukemia-related aneuploidies monosomy 7 and 8 in the blood progenitor cells (210) and identified increased levels of diverse human serum albumin modifications in the benzene-exposed workers, suggesting that benzene can increase leukemia risks via multiple pathways involving reactive molecules (211).

Public health, policy, and economic benefits

UC Berkeley SRP Center research on benzene carcinogenicity was cited by the EPA in its rule to lower the benzene content of gasoline to an average of 0.62% by volume from its previous level of 1% by volume (212). The rule points to their findings on greater-than-proportional production of benzene-related protein adducts at air concentrations of less than 1 ppm (201–203).

The rule, informed by UC Berkeley SRP Center research, estimated that extraction of benzene from gasoline would require a very low-cost technology. According to the rule, once the new standards are fully implemented by 2030, they are expected to reduce benzene emissions by 6000 tons/year. They estimated that by 2030, the highway vehicle contribution to benzene cancer risk will be reduced on average by 43% across the U.S. (212).

Although they did not quantify the economic benefits of the benzene reductions specifically, the EPA estimated that implementation of the rule would result in an estimated cost of $400 million/year while producing $6 billion/year of health benefits from particulate matter reductions by 2030 (212).

Publication metrics

UC Berkeley produced 83 publications related to their benzene research between 1995 and 2015, including 69 original research articles in iCite, with an average RCR of 1.63 and a weighted RCR of 112.5, indicating an influential body of research whose citation activity is well above the average NIH-funded article. Forty-six out of 69 publications, or 66.7% of these articles, received more citations per year than the median NIH-funded publication.

When examining the citation impact for Lan et al. (199), a key UC Berkeley Center publication demonstrating benzene toxicity, the citation impact is 8.7 times more influential than similar NIH-funded articles from the same field (RCR = 8.7) and is in the 97.7 percentile of NIH papers. In addition to showing strength of influence, we can

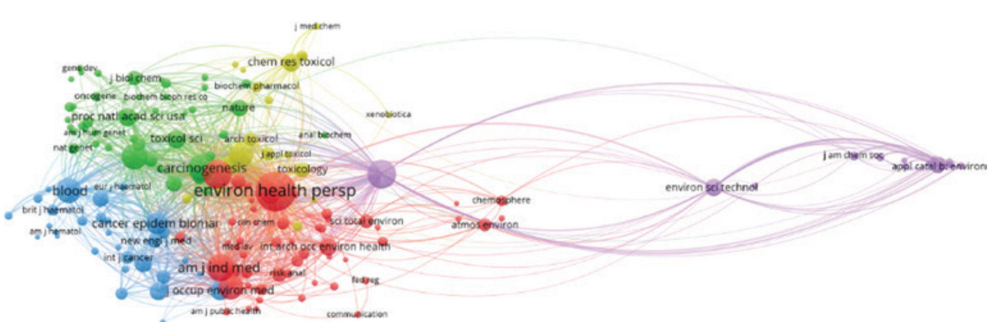

Figure 6: Journal co-citation network for Lan et al.
Journal co-citation network map for the 340 citing articles of Lan et al. (199) (Science node). This co-citation journal map shows the frequency with which journals are cited together, illustrating the different clusters of research. The size of the node reflects the number of citations, lines correspond to a citation, and distance between nodes indicate relatedness (i.e. journals that are located closer together are likely more closely related than journals far apart). Each journal cluster (represented by different colors) reflects different research disciplines. The original cited article (published in *Science*) can be seen in the center of the bibliographic map with biomedical journals clustered on the left and the few more environmental journals clustered far to the right.

also visualize the reach of this research by mapping the co-citation network for the 340 citing articles identified in WOS in VOSviewer as shown in Figure 6. This journal co-citation map illustrates how this publication has been cited in a variety of journals, indicating that this work has informed new research in diverse fields. Because articles that cite the same publication are likely to be similar in topic, co-citation networks are useful for visualizing the research topics influenced by the cited publication.

Conclusion

The SRP's unique transdisciplinary approach has empowered grantees to understand some of the toughest human health problems associated with environmental exposures, leading to a wide range of accomplishments and public health benefits. We found examples of how SRP basic research projects advanced knowledge and contributed to public health and economic benefits. We also identified examples of SRP-funded research findings that have informed policies to protect public health. Our analysis of publications showed that SRP research overall received an RCR score of 1.71, indicating that SRP publications received close to twice the number of expected citations per year as the average NIH-funded paper in the same field.

Our assessment revealed the importance of making connections along the translational research trajectory from fundamental knowledge to implementation, practice, and impact. This basic mechanistic understanding can open possibilities for intervention and provide information that is broadly applicable to other diseases. The knowledge generated from this type of research is the foundation on which decisions can be made to further protect human health.

We found that economic and public health benefits attributed to research findings can be difficult to determine. Lessons learned from this approach might be applied to improve benefit analyses in the future by improving data collection during research and its application. Using a case study-based approach, we identified qualitative measures of impact by providing examples of how SRP basic research has grown and evolved in many different directions and led to several societal benefits.

The research we identified for the five case studies has been funded by the SRP for 18 years or more. It is likely that this long funding period is one reason these five emerged as strong case studies, as it often takes time for researchers to develop partnerships and for the benefits of the research to be realized (7, 11). It is our hope that these case studies illustrate the value of following the trajectory of research findings from fundamental research questions through the many steps that ultimately lead to health benefits.

Attribution of key contributors to outcomes and multiple funding sources for research projects make it difficult to associate benefits to specific research programs. For example, SRP research studies that informed the policies described in this commentary were a few among many other studies that supported the decisions.

Investments by the SRP have had significant public health benefits over the years. Documenting the benefits of these investments provides insight into how basic research is translated to the real world. Identifying these projects helps us to recognize the long-term benefits of innovation and investments in research.

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