

## Pulling Back the Curtain: Improving Reviews in Environmental Health

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The environment is increasingly being recognized as an important driver of human health and the weight of the evidence is sufficiently high, thus warranting timely preventative action (Diamanti-Kandarakis et al. 2009; President's Cancer Panel 2010; Woodruff et al. 2008). However, it is a challenge to keep abreast of the deluge of scientific literature linking the environment to health. The volume and highly variable quality of data, as well as the barrage of bits and pieces of information, can leave the public and policy makers (and scientists) confused and overwhelmed as they try to grapple with the meaning behind the information. A perusal through PubMed on any of the hot topics in environmental health [e.g., bisphenol A, phthalates, PBDEs (polybrominated diphenyl ethers)] finds numerous studies on each topic. Each of us tries to sort through the accumulating evidence to understand its meaning, whether at the most personal level (e.g., should I give my baby water using a sippy cup made from polycarbonate plastic) to a more global level (e.g., should a pesticide be banned from use). Too much noise can diffuse rather than coalesce our common perception of the signal and undermine our capacity to act wisely.

Thus, reviews of scientific evidence are a critical step toward speeding the incorporation of the science into action to prevent harm. Reviews assemble and synthesize the evidence across studies to inform an overall conclusion about state-of-the-science knowledge. Simple in concept, but challenging in application, lessons can be learned from the clinical field, which has grappled with a parallel need to incorporate the meaning of the science in a systematic and timely manner into beneficial patient treatment decisions and prevention methods.

Historically, the clinical field relied largely on a system of expert reviews on which to base treatment decisions (Rennie and Chalmers 2009). However, starting in the 1970s, the role of expert reviews began to be questioned for a number of reasons (e.g., potential bias of experts, timeliness of information); this led to the development of systematic approaches that would use rigorous, transparent, and explicit methodology to evaluate a clearly formulated question. Landmark papers published in the clinical literature, such as Antman et al. (1992), showed that reviews based solely on expert opinion "did not work" and demonstrated the superiority of systematic reviews for patient outcomes (Rennie and Chalmers 2009).

The need for a comparable approach to reviews is equally compelling in the field of environmental health science because of the large number of studies and because they are as subject to bias as those in the clinical sciences. Notably, the influence of financially conflicted sources of funding is well recognized in the clinical world (Rennie 2010), and widely used examples of systems that utilize best practices for weighing and communicating the strength of the scientific evidence (West et al. 2002) prohibit sponsorship by any commercial source or sources [i.e., Cochrane Reviews (Higgins and Green 2006)] or recommend that the quality of potentially conflicted evidence be downgraded when evaluated [i.e., Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (Guyatt et al. 2008)]. Similar concerns have been raised in the environmental health literature (President's Cancer Panel 2010) and warrant similar attention.

However, although the clinical sciences point the way, these systems are not fully transferable to environmental health science because of differences in the types of evidence generally available and how decisions to expose populations and individuals are made. For example, in the clinical setting, *in vivo*, *in vitro*, and human experimental evidence



Tracey J. Woodruff



Patrice Sutton

combined with an analysis of risks and benefits have informed human exposure decisions prior to the the

entry of the substances into the marketplace. Systematic reviews in the clinical sciences proceed from this evidence and context.

In stark contrast, population exposure to exogenous substances in the environment typically occurs before regulatory scrutiny of a compound and in the absence of risk-benefit analysis, because of the current regulatory structure for governing manufactured chemicals. Ethical considerations virtually preclude experimental human data from the environmental health evidence stream, so we must rely on *in vitro* and *in vivo* studies for early warnings of adverse effects and on human observational studies to assess the nature and extent of the damage.

To rapidly move the best science into improved health outcomes, we need to apply the pertinent lessons and embrace the continued challenges of the clinical sciences. To that end, we are collaborating with 22 scientists and clinicians from the United States and Europe to craft the Navigation Guide, a systematic and transparent methodology that proceeds from GRADE but reflects the differences in evidence and decision contexts. Professional societies, health care organizations, government agencies, and other potential guideline developers working with toxicologists can use the Navigation Guide to craft consistent and timely recommendations to improve patient and population health outcomes.

Finally, the science of systematic reviews in the clinical sciences has evolved to be a relatively well-resourced and respected academic field in its own right. Currently, the science of environmental health science review and synthesis is largely relegated to regulatory and other government agencies, and few resources are allocated to the science of interpretation. The rising prominence of the environment as a key determinant of health requires that we devote concordant effort to primary scientific discovery and to the building upon and synthesis of the research through the systematic and transparent reviews. The reviews in this issue of *Environmental Health Perspectives* are a welcome step in the right direction.

**Tracey J. Woodruff  
Patrice Sutton**

Program on Reproductive Health and the Environment  
Department of Obstetrics, Gynecology, and Reproductive Sciences  
University of California, San Francisco  
Oakland, California  
E-mail: woodrufft@obgyn.ucsf.edu

*Tracey J. Woodruff is an associate professor in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the University of California, San Francisco (UCSF), and the Director of the Program on Reproductive Health and the Environment (PRHE). Her expertise is in environmental health research and public policy, with a particular emphasis on early-life development.*

*Patrice Sutton is a research scientist in the PRHE, UCSF, with over 20 years of experience in occupational and environmental health research, industrial hygiene, public health practice, policy development,*

and community-based advocacy. She is spearheading the development and uptake of PRHE's Navigation Guide, a systematic and transparent methodology to translate environmental health sciences into preventative action in clinical and policy arenas.

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## Evolution in Environmental Health: Incorporating the Infectious Disease Paradigm

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In this issue of *Environmental Health Perspectives*, Feingold et al. (2010) propose a unique step forward for toxicology: incorporating infectious disease agents and theory into the toxicological paradigm.

The fields of infectious disease and toxicology intersect on many different levels. First, they can act concurrently, as when global bands of various tropical diseases widen due to increased atmospheric temperatures. For example, in *A Human Health Perspective on Climate Change*, the Interagency Working Group on Climate Change and Health (2010) identified health effects from climate change, as well as the health benefits from mitigating climate change. These various health effects range from respiratory and cardiovascular disease, to developmental and neurological disorders, to food- and waterborne illness, and vectorborne and zoonotic disease. It is increasingly clear that climate change—a marquee issue in the field of environmental health—and infectious disease are linked.

Second, the two fields can also act antagonistically: For example, the newly renewed appeals for global use of DDT (dichlorodiphenyltrichloroethane) to combat malaria will pit the well-known hazardous effects of DDT against the scourge of malaria. In many countries DDT has been banned for agricultural use; it is considered a Class II or “moderately hazardous” pesticide by the World Health Organization (International Programme on Chemical Safety 2005), and its use is strictly limited by the 2001 Stockholm Convention. However, use of DDT is still permitted for vector control. This balance of risks and benefits is a conundrum for scientists and policy makers, but it reveals the serious issues raised when infectious disease and environmental health interests clash.

Third, these two disciplines can act synergistically, as in the interactions between hepatitis B and aflatoxin in hepatic cancer. Both hepatitis B and aflatoxin are independent factors in liver cancer. However, when combined, they act powerfully to raise the risk of



Linda S. Birnbaum



Paul Jung

hepatic cancer up to 60 times that of unexposed individuals (Groopman et al. 2005). This National Institute

of Environmental Health Sciences (NIEHS)-funded research is a primary example of the interaction between environmental health and infectious disease and can serve as a model for future research efforts.

Suppression of the immune response by polychlorinated biphenyls (PCBs) was first shown in mice and nonhuman primates. Recently, in another example of concurrent interaction, NIEHS-funded studies led by Philippe Grandjean have shown that perinatal and developmental exposure to PCBs adversely impact immune responses to childhood vaccinations (Heilmann et al. 2006, 2010).

We have an opportunity at the NIEHS to embrace this new paradigm. As we have shown with our investment in research into the aflatoxin–hepatitis B and PCB–vaccine interactions, the NIEHS has a track record that could promote a wider interest in this field of inquiry.

Ideas like these are supported not only at the institute level but also throughout the National Institutes of Health (NIH). Recently, NIH director Francis Collins (2010b) wrote, “NIH can play a major role in ramping up the discovery of novel targets in both pathogen and host and work to facilitate advances in prevention . . .” Collins (2010a) also wrote, “the best outcomes are generally when you don’t have walls between parts of the organization that prevent people from learning from each other.”

A recent presentation at the NIEHS outlined a vision for the institute that included the infectious disease and environmental health intersection within the context of the rapid evolution in the field of environmental health, specifically in epigenetics. As we