

Applying Research to Public Health Questions: Timing and the Environmentally Relevant Dose

doi:10.1289/ehp.0901417

The mission of National Institute of Environmental Health Sciences (NIEHS) is to improve the health of the American people by understanding the role of environmental exposures in disease and dysfunction. We accomplish this mission by conducting and funding research—including *in vitro*, animal, and human studies—on the health effects of environmental agents. Our goal is to prevent disease by identifying and reducing exposures to environmental agents that compromise health. It is clear that every complex disease has both an environmental and a genetic component. Thus, NIEHS-sponsored research must play an important role in understanding disease etiology. In the last few years there have been workshops (Melnick et al. 2002; vom Saal et al. 2007), manuscripts (Myers et al. 2009a, 2009b), and even society-position papers (The Endocrine Society 2009) indicating that increased use of environmental health science data by policy makers should lead to reductions in the human burden of disease.

There are several recent examples of how research supported by the NIEHS is leading to paradigm shifts in understanding how environmental toxicants—even at very low-level exposures—can have significant consequences, including dysfunction and disease. These paradigm shifts are being informed by new approaches for dose measurement. NIEHS researchers are turning their attention to the “environmentally relevant dose,” which is the dose in the range of typical human exposure as measured in tissue, blood, and urine of study subjects. Simply put, the environmentally relevant dose is based on the internal concentration of the toxicant rather than the administered dose.

In 2007, the NIEHS invited a panel of experts to Chapel Hill, North Carolina, for a scientific review of all literature published on bisphenol A (BPA). The expert panel then issued a consensus statement (vom Saal et al. 2007), which concluded that low environmentally relevant doses of BPA could cause numerous diseases in animal models, and that there was evidence for both low-dose effects and for nonmonotonic dose–response relationships. Overall, similar conclusions were reached by the National Toxicology Program’s Center for the Evaluation of Risks to Human Reproduction (NTP 2008), which focused on the developmental and reproductive effects of BPA.

An article in this issue of *Environmental Health Perspectives* (Myers et al. 2009b) highlights this discussion of low-dose effects and notes that nonmonotonic, or biphasic, dose–response curves are commonly observed in endocrinology. This suggests that high doses may not be appropriate to predict the safety of low doses when hormonally active or modulating compounds are studied. Their conclusions are supported by the position statement published by the Endocrine Society (2009). This debate—whether chemicals with endocrine-disrupting activity can cause toxicity at environmentally relevant doses—has been under way for more than a decade (Melnick et al. 2002). There are now low-dose data not only on BPA but also on phthalates, polychlorinated biphenyls (PCBs), dioxins, heavy metals such as lead and mercury, perchlorate, and some diverse pesticides such as hexachlorobenzene and atrazine. Indeed, the doses used in many animal toxicology studies result in internal concentrations that are in the range of human exposures.

Many of these low-dose studies demonstrate that the timing of exposure is critical to the outcome and that exposures during early life stages (fetal, infant, and pubertal) are particularly important. This recognition of critical windows of vulnerability not only demonstrates



Linda S. Birnbaum

the developmental basis of disease but also that the timing, as well as the dose, makes the poison.

Understanding the connection between our health and our environment, with its mixture of chemicals, diet, and lifestyle stressors, is no less complex than understanding the intricacies of the human genome; just as we have moved beyond “one gene, one disease,” we must move beyond “one chemical, one dose (range), one health outcome.” Reliability and validity are established in science by replication of findings in multiple independent studies. A weight-of-evidence approach is essential in understanding the public health impacts of environmental exposures.

Linda S. Birnbaum

Director, NIEHS and NTP
National Institutes of Health
Department of Health and Human Services
Research Triangle Park, North Carolina
E-mail: birnbaumLS@niehs.nih.gov

Linda S. Birnbaum is director of the NIEHS and the NTP. She oversees a budget that funds multidisciplinary biomedical research programs, and prevention and intervention efforts that encompass training, education, technology transfer, and community outreach. Birnbaum has received numerous awards, including the Women in Toxicology Elsevier Mentoring Award, the Society of Toxicology Public Communications Award, the U.S. Environmental Protection Agency’s (EPA) Health Science Achievement Award and Diversity Leadership Award, and 12 Science and Technology Achievement Awards. She is the author of more than 700 peer-reviewed publications, book chapters, abstracts, and reports. Birnbaum received her M.S. and Ph.D. in microbiology from the University of Illinois, Urbana. A board certified toxicologist, she has served as a federal scientist for nearly 29 years: 19 years with the U.S. EPA Office of Research and Development, preceded by 10 years at the NIEHS as a senior staff fellow, a principal investigator, a research microbiologist, and finally as a group leader for the institute’s Chemical Disposition Group.

REFERENCES

- Melnick R, Lucier G, Wolfe M, Hall R, Stancel G, Prins G, et al. 2002. Summary of the National Toxicology Program’s report on the endocrine disruptors low-dose per review. *Environ Health Perspect* 110:427–431.
- Myers JP, vom Saal FS, Akingbemi BT, Arizono K, Belcher S, Colborn T, et al. 2009a. Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case for bisphenol A. *Environ Health Perspect* 117:309–315.
- Myers JP, Zoeller RT, Vom Saal F. 2009b. A clash of old and new concepts in toxicity, with important implications for public health. *Environ Health Perspect* 117:1652–1655.
- NTP. 2008. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Bisphenol A. NIH Publication No. 08-5994. Research Triangle Park, NC:National Toxicology Program. Available: <http://cerhr.niehs.nih.gov/chemicals/bisphenol/bisphenol.pdf> [accessed 9 February 2009].
- The Endocrine Society. 2009. Position Statement: Endocrine-Disrupting Chemicals. Available: <http://www.endo-society.org/advocacy/policy/upload/Endocrine-disrupting-chemicals-position-statement.pdf> [accessed 7 October 2009].
- vom Saal FS, Akingbemi BT, Belcher SM, Birnbaum LS, Crain DA, Eriksen M, et al. 2007. Chapel Hill bisphenol A expert panel consensus statement: integration of mechanism, effects in animals and potential to impact human health at current levels of exposure. *Reprod Toxicol* 24(2):131–138.

Steve McCaw, Image Associates