Guest Commentary

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Environmental Chemicals in People: Challenges in Interpreting Biomonitoring Information

Abstract

Biomonitoring, the measurement of chemicals in blood, urine, and other tissues or fluids, is becoming an increasingly common tool in the study of human exposure to environmental chemicals and the potential health effects of those chemicals. The National Health and Nutrition Examination Survey (NHANES) now includes biomonitoring data for hundreds of chemicals as well as information on other health and demographic endpoints for thousands of individuals in the United States. The NHANES databases provide valuable information for deriving reference ranges and trend information and can be used for hypothesis-generating analyses, but they cannot be used to establish causal relationships between environmental chemicals and health effects. This commentary examines issues unique to the use of such databases and the interpretation of biomonitoring-based epidemiological studies.

Introduction

The risk assessment paradigm, which serves as the basis for public health evaluations and actions with respect to environmental chemicals, requires not only an assessment of the potential toxicity of a chemical but also an estimate of human exposure. Biomonitoring, the direct measurement of chemicals or their metabolites in blood, urine, or other bodily fluids or tissues, is becoming an increasingly common exposure assessment tool. As noted in the recent National Research Council review of the use of biomonitoring data in health risk assessment, "The ultimate objective of the biomonitoring research is to link biomarkers of exposure to biomarkers of effect and susceptibility to understand the public health implications of exposure to environmental chemicals" (National Research Council [NRC], 2006, page 23).

Advances in analytical methods, an increase in the number of available data sets including biomonitoring and health data, and improved computational capability have resulted in a greater number of studies examining associations between biomonitoring data and health endpoints. Reported associations between measured levels of chemicals in human blood or urine and health outcomes may be interpreted readily by the press and public as demonstrating cause and effect. In turn, health care providers or public health officials may be queried on relationships between biomonitored chemicals and illness as reported in the press. Most health care providers, however, do not have extensive experience or training in this area (NRC, 2006). Thus, we seek here to highlight key issues affecting the interpretation of studies on associations between biomonitoring data and human health.

In the United States, the most comprehensive biomonitoring effort has been conducted by the Centers for Disease Control and Prevention (CDC) as part of the National Health and Nutrition Examination Survey (NHANES). The main focus of the NHANES program has been to provide data on health and nutrition in the United States by compiling detailed health questionnaire and physical-examination data (including clinical-chemistry endpoints) on a statistically representative sample of the U.S. population. Measurement of a limited number of environmental chemicals (e.g., lead) has been part of NHANES since the 1970s. These data have yielded information on levels and trends in general U.S. population exposure to environmental chemicals (including some exposure information specific to race, gender, and ethnicity) and information on the success of regulatory efforts to limit exposures to specific environmental chemicals (Thomas, Socolow, Fanelli, & Spiro, 1999).

Recently, the number of chemicals measured in blood or urine as part of NHANES has increased dramatically (in 2001, data on 27 chemicals were released; approximately 300 chemicals are being measured in blood and urine samples collected as part of the 2003–2004 NHANES effort), and these data are publicly available in CDC's National Exposure Reports (CDC, 2005) and on the Internet (http://www.cdc.gov/nchs/nhanes.htm). The collection of large data sets on both environmental chemical exposure and health-related parameters has made it possible to evaluate these databases for statistical associations between levels of a chemical in blood or urine and aspects of participants' health. Several recent publications have used the NHANES data to explore such possible associations (Elliott, Longnecker, Kissling, & London, 2006; Lee et al., 2006; Lee, Lee, Steffes, & Jacobs, 2007; Saraiva et al., 2007).

Criteria for assessing whether reported associations may represent causal relationships between exposures and health effects are a fundamental bedrock of epidemiology and public health (Kundi, 2006). Interpretation of associations between measured levels of chemicals and health endpoints drawn from studies such as NHANES, however, poses specific challenges that have not been fully explored.

Assessing Cause and Effect in Biomonitoring-Based Studies

The Hill criteria, while they are not required "checklist" elements, provide a useful framework for evaluating the pattern of evidence and assessing whether an observed association is causal (the criteria include strength and consistency of observed associations, biological plausibility and coherence, temporality of cause and effect, dose-response, and specificity) (Kundi, 2006; Phillips & Goodman, 2004). Several characteristics of biomonitoring and health outcome studies such as NHANES present unique challenges for interpreting the relationship between cause and effect and are discussed here in the context of a few of the Hill criteria.

Strength of Association

The stronger the relationship between the independent variable and the dependent variable, the less likely it is that the relationship is due to chance or confounding by an extraneous variable. When the strength of association is being assessed, the statistical methods employed should include appropriate adjustment for multiple comparisons. In analyses relying on databases such as NHANES, which contains measured data on hundreds of chemicals and thousands of health endpoints, it is relatively easy to assess dozens, if not hundreds of potential combinations of exposure and outcome. Some associations are likely to be observed solely because of chance. Appropriate use of a priori hypotheses and statistical corrections for multiple comparisons are minimum steps required in studies such as these, but even when appropriate adjustments are used, the findings are better characterized as hypothesis-generating than as demonstration of a causal relationship.

Temporality

Cause of a health effect (i.e., exposure to an environmental chemical) must occur before the effect itself. The NHANES studies are cross-sectional in nature, however, with no individual longitudinal component, and it is not possible to determine by means of this data set if exposure precedes disease or symptom occurrence. A related issue more specific to biomonitoring data is the transient nature of blood or urine levels of many chemicals of interest, including volatile organic compounds, several pesticides, and certain drinking-water disinfection by-products. Because of the very short half-lives of these chemicals in the body, levels measured in blood drawn at one time point during the day may not reflect internal levels at another time during that day, much less across longer time periods. Thus, correlations observed between measured levels of such chemicals and a biochemical marker or other health endpoint may be highly unstable, with no consistent relationship between the internal level of the compound and the health endpoint over time. These considerations also affect assessment of the dose-response relationship. Information relating longitudinal measurements of such compounds in individuals with health endpoints is needed to explore whether an observed association may be causal.

Specificity

Ideally, under the Hill framework, a highly specific relationship between one exposure and one outcome provides strong evidence of a causal relationship. In the study of potential effects of low-level, widespread environmental exposures, however, the etiology of many health outcomes of interest is likely to be multifactorial, with environmental, lifestyle, and genetic factors involved that it is difficult or inappropriate to separate. For example, diabetes risk is related to body fat levels and fat distribution (which can be related to levels of certain environmental chemicals in the body), age, family history, and ethnicity; in addition, several other potential risk factors, including genetics, are being studied.

Recent investigations have examined a potential link between biomonitored levels of various persistent organochlorine compounds and diabetes risk (Everett et al., 2007; Fierens et al., 2003; Lee et al., 2006; Vasiliu, Cameron, Gardiner, Deguire, & Karmaus, 2006). While it may be possible to adjust statistically for some of the known risk factors through use of collected demographic data, the potential for persistent bioaccumulative compounds to contribute to risk of diabetes is much more difficult to disentangle with the NHANES database. For these compounds, current measured levels reflect historical exposure patterns, and for many persistent compounds, there are strong and in many cases highly nonlinear correlations of blood concentrations with age (Patterson et al., 2004). In addition, substantial data indicate that the elimination rates of these compounds are influenced by body fat levels (Flesch-Janys et al., 1996; Longnecker, 2006), which also affect the risk of diabetes. Standard methods of adjusting for these risk factors may not adequately address the nonlinearities in these inter-relationships.

Another issue that complicates interpretation of NHANES data relates to discrepancies between NHANES laboratory and questionnaire data. Discrepancies of this type are not unique to NHANES, and issues related to reliability of questionnaire data, including recall bias and familiarity with family history, have been described elsewhere (Chang, Smedby, Hjalgrim, Glimelius, & Adami, 2006; Mitchell et al., 2004). The lessons learned with respect to diagnostic criteria from asthma studies conducted by the National Institute of Environmental Health Sciences/U.S. Environmental Protection Agency Centers for Children's Environmental Health and Disease Prevention can inform studies of other diseases as well (Eggleston et al., 2005). These lessons include the following:

- Disease identification may require a combination of questionnaire and physiological measures. In addition to information based on recall, objective measures should be obtained.

- If medication confounds the assessment of symptoms and classification of disease severity, use of pharmaceutical compounds should be determined. In questionnaire histories, it may be appropriate to equate the use of medications with the illness.
- Longitudinal data collection is important as it provides essential data on the sequence of exposure to environmental agents and incidence of disease.

An additional complication is the issue of chemical measures that fall below the detection limit or are unreported in the database. Decisions about treatment of undetectable concentrations, such as assigning a value of zero, the limit of detection, or some other value, can affect the results of the analysis. For missing data, one approach is to exclude the participant from the analysis. For some chemical classes in which concentrations of several compounds are summed to obtain an overall estimate of toxicity, however, participants may have a partial chemical database. In this case, decisions must be made about whether to assign missing data a concentration of zero, to exclude the participant, or to select another approach. Regardless of the method used, the approach should be carefully and clearly described, and the potential affect on the statistical association should be clarified.

Finally, the interpretation of chemical data in the NHANES database in terms of public health is limited by the current lack of understanding about the relationship between the magnitude of measured levels in biological samples and the levels of chemicals in the external environment, which have traditionally been the focus of health risk assessment (Hays, Becker, Leung, Aylward, & Pyatt, 2007). If measured biomarker concentrations are far below the levels associated with external exposures (doses) that have generally been considered to be tolerable, statistical associations between biomarker levels and health endpoints should be examined carefully.

Conclusions

As CDC has noted, the presence of an environmental chemical in blood or urine does not mean that the chemical causes disease (CDC, 2005). Findings of associations between measured concentrations of chemical substances and health endpoints in cross-sectional studies and data sets such as NHANES must be subjected to critical scrutiny addressing the issues of temporality of exposure and response, multiple comparisons, likely variability in biomarker level over both short and long time frames in an individual, biological plausibility, and multiple risk factors. The NHANES databases provide valuable information for deriving reference ranges and trend information for the U.S. population. Nevertheless, with only a few exceptions for which there is consensus on chemical/clinical correlations (e.g., for lead and mercury), measurement of chemicals in blood cannot currently be used in a diagnostic fashion for individuals in a clinical or public health setting. Furthermore, the limitations and appropriate application of the NHANES and other cross-sectional data sets in the area of exposure-response evaluation must be clearly recognized:

- NHANES and other cross-sectional data sets can appropriately be used for hypothesis-generating analyses, most appropriately when combined with other information to inform the exploratory analyses.
- NHANES and other cross-sectional data sets should not be used in isolation to establish cause-and-effect relationships.

Conclusions regarding causation will continue to require detailed investigations, drawing upon multiple lines of evidence, that address the issues described above, which cannot be assessed solely in the cross-sectional NHANES data sets or other cross-sectional studies.

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radically changed. Quantum science's view of reality differs markedly from the Newtonian view.

- Our organizations, however, continue to merrily plod along as if quantum physics had never been discovered. They continue to function within a Newtonian worldview.
- As a result, organizations (to say nothing of governments, institutions, conventional wisdoms, enterprises, etc.) seem to be having more failures, more breakdowns, more intransigent problems, and more stresses, because their ways of working seem increasingly out of sync with the world in which they operate.

Wheatley's book represents an effort to take some of the new insights from modern science and apply them to how we manage and evaluate our organizations. She points out the irony that while most of our modern-day organizations have aligned themselves with how physics sees the world, that particular science has dramatically changed. Unfortunately, our organizations haven't noticed that this change has occurred. As a result, a huge gap has opened up between how science and how our organizations each see reality. This observation gives her a basis for explaining much of the chaos and dissonance in the world today.

The book makes for a stimulating, insightful, and thought-provoking read. Her reflections on the bumbling institutional responses to terrorism and Hurricane Katrina are especially riveting. Major discussion threads on self-organizing systems, the value of information, chaos theory, and the significance of "intent" push hard against conventional thinking.

By the time I had finished, I think that there were only 10 pages or so of the book's 200 pages that I hadn't written notes on!

Drawing heavily from the discoveries of quantum science, Wheatley lays out a fascinating way to look at the world, and by extension, our organizations and especially the relationships within them. She argues that the key to understanding any system lies not with a quest to define its essential parts but rather with an interest in understanding the relationships that exist between the parts. She cites the quintessential lesson from quantum physics that within the subatomic world, *nothing exists independently of a relationship.* A part without context, which is to say, a part without a relationship, has no meaning: in fact, it doesn't exist! It is through relationships that events are brought into being from what is otherwise merely a sea of probability that includes everything that could happen.

She doesn't stop there. She goes on to explain that the most powerful force in nature is self-organization. (For a much more fun take on this concept, I would highly recommend Michael Creighton's entertaining book, *Prey*.) Lacking control and command systems, nature has proven itself to be remarkably adept at building successful systems through the process of self-organization. In such a system, parts act out through their relationships with other parts. These relationships give rise to an ability to process information. As information gets processed, a meaning to it all emerges. With meaning comes intention. The system then evolves into full-fledged functionality as a "field" of intention drives the system and every part (or person) in it to honor the system's meaning.

The organizations that we all work for are systems. Wheatley's book asks us to look at our systems to see if in fact we are all working together on behalf of some larger meaning.

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