profiles in a national sample of U.S. adults. *Soc Sci Med.* 2008;66(1):72–87.

40. U.S. Environmental Protection Agency. *Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document.* Washington, DC: National Center for Environmental Assessment; 2007.

41. Barzyk TM, Conlon KC, Chanine T, et al. Tools available to communities for conducting cumulative exposure and risk assessments. *J Expo Sci Environ Epidemiol.* 2010;20:371–385.

42. Zartarian VG, Schultz BD. The EPA's human exposure research program for assessing cumulative risk in communities. *J Expo Sci Environ Epidemiol.* 2010;20(4):351–358.

43. Payne-Sturges D, Gee GC. National environmental health measures for minority and low-income populations: tracking social disparities in environmental health. *Environ Res.* 2006;102:154–171.

44. Payne-Sturges D, Gee GC, Crowder K, et al. Workshop summary: connecting social and environmental factors to measure and track environmental health disparities. *Environ Res.* 2006;102:146–153.

45. Morello-Frosch R, Lopez R. The riskscape and the color line: examining the role of segregation in environmental health disparities. *Environ Res.* 2006; 102:181–196.

46. Su JG, Morello-Frosch R, Jesdale BM, et al. An index for assessing demographic inequalities in cumulative environmental hazards with application to Los Angeles, California. *Environ Sci Technol.* 2009; 43(20):7626–7634.

47. World Health Organization. *Urban HEART: Urban Health Equity Assessment and Response Tool. WHO Center for Health Development.* Kobe, Japan: WHO Publications; 2010.

48. National Environmental Justice Advisory Council. *Nationally Consistent Environmental Justice Screening Approaches.* Report submitted to the Office of Environmental Justice, U.S. Environmental Protection Agency. Washington, DC: NEJAC; May 2010.

49. National Environmental Justice Advisory Council. *Ensuring Risk Reduction in Communities with Multiple Stressors: Environmental Justice and Cumulative Risks/Impacts.* Report submitted to the Office of Environmental Justice, U.S. Environmental Protection Agency. Washington, DC: NEJAC; 2004.

50. Sexton K, Linder SH. The role of cumulative risk assessment in decisions about environmental justice. *Int J Environ Res Public Health.* 2010;7(11):4037–4049.

Expanding the Scope of Environmental Risk Assessment to Better Include Differential Vulnerability and Susceptibility

Joel Schwartz, PhD, David Bellinger, PhD, and Thomas Glass, PhD

The central paradigm of the Environmental Protection Agency is risk assessment. We examined how differential responses across population groups could be better integrated into the environmental risk assessment process, providing tools to achieve greater equity in health status in addition to risk reduction.

Such integration was difficult with paradigms like reference dose and was easier with consideration of dose–response curves, which incorporated nontrivial effects observed at low doses for common exposures.

We identified 6 assumptions implicit in standard chemical risk assessments that should changed: (1) risk independence, (2) risk averaging, (3) risk nontransferability, (4) risk synchrony, (5) risk accumulation and chaining, and (6) quantification of numbers of persons above certain thresholds or limit values sufficient to characterize risk. (*Am J Public Health.* 2011;101:S88–S93. doi:10.2105/AJPH.2011.300268)

THE CENTRAL PARADIGM FOR the US Environmental Protection Agency (EPA) standard setting is risk assessment. Based on scientific data, the EPA prepares quantitative estimates of changes in health status that will result in different potential levels of a standard, and uses that quantification as input into decision-making for situations in which risk management depends on other data as well. Specific regulatory actions are targeted to particular environmental agents, whose marginal impacts, sources, and control strategies often differ. A cruder approach is often taken. An acceptable dose of a chemical is defined (e.g., reference dose [RfD]), and risk assessment merely quantifies the number of people above versus below this dose or number for different regulatory choices. Implicit in the latter approach is that this quantity is meaningful and that risk is zero below the RfD and the same above the RfD, irrespective of the extent to which actual exposure exceeds the RfD. These simplifying assumptions can lead to both inaccuracy in risk estimation and inattention to distributional aspects.

A recent US National Academy of Sciences report declared that "..risk assessment is at a crossroads."[1(p.ix)] Its key recommendation was to abandon the RfD approach whenever possible and move to a quantitative estimate of changes in health. We support the National Academy of Science's conclusions, arguing that only with actual quantification of risk can differential patterns of susceptibility be examined, and point out that this makes understanding the shape of the dose–response relation central to risk assessment. In this article, the conceptual issues are addressed, and in 2 related articles,[2,3] examples are provided of where these concepts are important. Methodology is also discussed.

SUSCEPTIBILITY AND VULNERABILITY IN THE CONTEXT OF HEALTH

The standard definition of a person who is susceptible is one who is more responsive to exposure. Recently, the word vulnerability was used either to describe situations where the susceptibility arises from psychosocial, cultural, or economic differences, or as encompassing these plus biological vulnerability, but with the understanding that these components of overall vulnerability were different.[4] This distinction is not a good one, because recent research into how socioeconomic factors and stress exert influence on health identified clear biological pathways. Stress is associated with differential baseline levels and the differential response of the hypothalamic–pituitary–adrenal system. That is, these social factors describe people with different biological states. They are merely the "causes of the causes."[5(p1153)] Further, there are complex feedback loops between outside conditions and biological stress that make separating these phenomena even more difficult. A more useful distinction is one versus many. Just as in physics, collections of particles are capable of behavior quite

different than what one would expect when examining them singly or via simple 2 way interaction. Humans' health and response to external stimuli depends in part on the fact that humans live in groups. Hence, differences between people in which groups they live in will influence their responses to stressors. To assess this, scientific studies need to include group level effects, and risk assessments need to incorporate those results.

ASSUMPTIONS UNDERLYING RISK ASSESSMENT

Typical risk assessments for chemical contaminants often make implicit assumptions that simplify the risk assessment, but these sometimes fail. Six of the more common assumptions that sometimes fail are discussed.

Risk Independence

Risk assessment traditionally assumes that exposures and their health impacts are independent of one other and, therefore, can be evaluated singly. Evaluating different agents separately inherently presumes that the impacts are independent and additive at the exposure ranges of interest. Hence, one can compute the incremental effect of substance A and make decisions on that basis, independent of exposure to substance B. When there are interactions between A and B, this approach can produce spurious results. For example, risk assessments of National Ambient Air Quality Standards have always treated other pollutants as independent.

Risk Averaging

The standard risk assessment paradigm reduces the multidimensional aspects of risk (the risk of each individual in the population, given their particular attributes) to a single estimate: the overall risk in the population (the mean risk). Much work in risk assessment recently focused on understanding the uncertainty in this scalar estimate.[6,7] However, recent work in epidemiology, toxicology, and exposure science suggested that a more multidimensional approach is also needed. Two main problems arise from this. First, if risks are substantially elevated primarily in a subpopulation that is small, overall risk estimates may be low, masking the substantial burden of risk to the subpopulation. This is not an issue of inaccuracy in the estimate of the overall burden, but rather failure to provide the risk manager with an estimate of the distribution of the burden. Second, exposure with opposite effects in different subpopulations may appear to have no effect. Both issues point to the potential importance of the distribution of risk.

The mean or population attributable risk is a good single metric when the typical risk of exposure to individuals is low, reducing concerns about the details of the distribution. This situation does not imply a trivial public health impact, because for environmental agents, the population exposed is often large, resulting in an important population attributable risk. As an analogy, the relative risk of mortality associated with a 7 millimeters of mercury change in blood pressure (typical of the reduction produced by antihypertensive drugs) is modest, but the population impact of a 7 millimeters of mercury shift in the distribution of the population is huge. As an environmental example, EPA's risk assessment for controlling off-road diesel engine emissions estimated it would save more than 12 000 lives per year by 2030, although individual risk reduction was estimated to be small.[8] Implicit in this focus on attributable risk was that although individual risks might vary from the mean, the risks in a definable subpopulation were assumed not to reach a level of concern (defined by decision makers such as the EPA Administrator) that would require additional efforts.

The focus of this article identified situations when, despite low population average risks, there was insufficient attention to 2 important factors that are the subject of much of this and the other 2 articles on vulnerability and susceptibility in this issue[4,5]: (1) the distribution of risks was not random or uniform, and (2) the vulnerability of individuals and populations might vary as a function of factors related to persons or places.

Risk Nontransferability

Another common assumption in risk assessment is that the risks apply to each person exposed without reference to the exposure status of others. Secondhand tobacco smoke is an example of the failure of this assumption, and new studies of environmental exposures suggested that some risk might be transgenerational and even hereditable. Epigenetics is the science of changes to the chromosome that do not involve changes in the nucleotides, but do affect transcription. The new field of environmental epigenomics has begun to show, for the first time. that heritable environmentally induced epigenetic modifications underlie reversible transgenerational alterations in phenotype.[9,10] Some of these changes can occur in children whose mothers are exposed during pregnancy, and although these changes might be nongenetic, some may be hereditary. For example, exposure of rats to endocrine disrupting compounds during pregnancy resulted in reduced spermatogenesis in their male offspring, a pattern that was transmitted for at least 3 subsequent generations of unexposed animals.[11] This was the result of hereditable changes in DNA methylation patterns in the offspring. Further research indicated the same exposure produced transgenerational changes in gene expression in the hippocampal area in the brain, as well as transgenerational changes in anxiety behavior.[12] There is growing evidence that exposure to other environmental agents, such as bisphenol A,[13] lead,[14] traffic pollution,[15] and metal-rich particles,[16] results in epigenetic changes in humans.

Psychosocial factors may also mediate transgenerational effects. Yehuda and Bierer[17] recently showed that offspring of parents exposed to holocaust trauma had altered neuroendocrine responses suggestive of epigenetic programming across generations. Collins et al.[18] showed that parents exposed to poverty appeared to transmit increased risk to their offspring through low birth weight and other deleterious effects. This research showed the myriad ways in which social environment altered fetal programming across generations, suggesting that the exposed person might not be the only person experiencing the consequence of the exposure and that individuals might start life with varying degrees of vulnerability to subsequent environmental risk factors.

Obviously, where such evidence is lacking, current approaches are sufficient. However, the EPA needs to develop protocols to guide risk assessment in growing situations where such evidence does exist.

Risk Synchrony

Risk assessment sometimes relies on snapshots of exposure based on one point in time or lifetime exposure, without sufficient attention to the issues of critical windows, dose rate, or the ways in which underlying vulnerability changes as risk accumulates across the entire life course. When available, methods for looking at critical windows and dose rates are considered in risk assessment, but less attention has been paid to the timing of vulnerability. Several models have been proposed to move from a synchronous (or snapshot) view of risk to a diachronic (or movie) approach. These include the study of allostatic load,[19–21] the weathering hypothesis,[22–24] as well as life course epidemiology.[25,26] Obviously, the information necessary for such approaches may not be available, but attention to the issue is necessary. Cumulative exposure to individual environmental agents, or to all environmental agents acting along similar pathways may, in some cases, represent a better metric for risk assessment. For example, tibia lead levels are a cumulative index of exposure to lead, and show stronger associations with some health outcomes.[14,27–29] Also finding the best indicator for environmental exposures' cumulative impact on health is acquiring greater importance. There are some candidate markers that should be considered in risk assessments.

Risk Accumulation

Lastly, a single scalar estimate of risk will also fail to capture important aspects of the public health problem, even in the absence of differences in susceptibility and exposure to a particular environmental agent. If there are skewed distributions of other underlying risk factors, these result in substantially different cumulative burdens in one subpopulation than in another. That is, one input into policymaking may be how a given option changes the distribution of cumulative risk because of all the risk factors in the population, and not merely how it changes the distribution of risk because of the targeted exposure. Again, because the distributions of multiple sources of risk are not independent, this can produce cascading inequities even in the absence of interactions.

MOVING TOWARD DIFFERENTIAL VULNERABILITY

What if this set of assumptions is not met? What if the distribution of risk in the population is skewed or markedly higher in one group and lower in another? What if risk factors accumulate in synergistic ways to create population groups that are differentially susceptible? This can happen in several ways. The first brings us back to interactions. Differential responses can result from differences in genetic susceptibility or because of exacerbations or ameliorations of the effect of exposure by underlying disease status, psychosocial factors (e.g., stress), or sociomaterial factors (e.g., poverty). Differential response can also flow from more complex social or physical factors or more than one interaction. Several examples include persons with diabetes who have twice the risk of cardiovascular mortality after exposure to particulate air pollution compared with persons without the disease,[30] stress modifying the effects of lead on blood pressure and cognition,[31] race and educational level strongly modifying mortality risk on very hot days,[32] and genes related to oxidative stress defenses modifying the risk of air pollution.[33–35]

These risk modifiers are rarely independently distributed, nor do they occur randomly throughout the population. Assuming independence often produces underestimates. For instance, risk assessments underestimated the risk of the Chernobyl disaster because the assessments assumed independent distributions of individual actions, rather than the systemic behaviors that actually occurred.[36] In the case of environmental exposures, many modifiers are not independently distributed. Both diabetes and stress are more prevalent among Black Americans. For some pollutants, exposure is greater among this group as well. A risk assessment that seeks to capture the distributional aspects of risk should include the covariance of the risk modifiers, which could greatly increase the actual skewness of risk in the population.

DOSE–RESPONSE CONSIDERATIONS

Dose–response can be an important part of the improvement of risk assessment. For some substances, such as lead or air pollution, the EPA used quantitative risk assessment based on epidemiological dose–response or exposure–response curves. In other cases, they computed RfDs or some similar estimate of a dose that conveyed "de minimus" risk. The National Research Council recently recommended that the EPA take an integrated approach, including moving to more quantitative risk assessment in lieu of RfD. This fits well with the emphasis on cumulative risk, distribution of risk, and the interactions discussed in this article, because it is difficult to incorporate these factors into "magic numbers" such as RfDs. It is important to consider that de minimus exposure to large populations may not have de minimus aggregate risks. For example, most of the lung cancer cases attributable to radon exposure occurred in homes below the EPA guideline because there were so many of them. Similarly one must consider the possibility that some populations may be substantially more affected and that multiple exposures that accumulate may yield risks that are no longer de minimus.

One special topic discusses the shape of the exposure–response or dose–response relationship. Many studies failed to consider adequately whether there was a threshold in the association between exposure and response. Thresholds had traditionally been assumed in toxicology for most outcomes, except for cancer. However, as epidemiology studies considered more exposure–response relations in relevant exposure ranges, a striking finding was the lack of evidence for departure from linearity in many associations for noncarcinogens, down to the lowest observable exposures in the general population. For example, the concentration–response between fine particulate matter (≤ 2.5 μm and mortality is linear, and the dose–response between blood lead levels and IQ is supralinear; that is, the slope is substantially higher at lower doses.

In an article in 2000 reporting on a method (meta-smoothing) for combining data across studies to examine the shape of the exposure–response, Schwartz and Zanobetti[37] developed a theoretical basis for such findings.

Suppose each individual has a threshold for a serious health response (e.g., mortality). These thresholds differ across individuals based on differences in existence and intensities of current illnesses, differences in intensities of chronic illnesses, and in general, differences in all the genetic, social, and psychosocial modifiers discussed in the section, Moving Toward Differential Vulnerability: Interactions and Beyond. At any given exposure in a population, the number of individuals having the event will be the sum of all individuals whose threshold is at or below the given exposure. That is, the exposure–response curve in the population will be the cumulative distribution curve of individual thresholds. Because the distribution of thresholds in the general population is the sum of the distribution because of multiple acute illnesses, multiple chronic conditions, multiple social factors, multiple stressors, multiple genetic factors, etc., that distribution will tend, by the central limit theorem, to approach the normal distribution. Therefore, the cumulative distribution of the thresholds (which is the exposure–response curve in the total population) will tend to approach the logit or probit curve. Because we generally deal with exposures at levels where the probability of an event in any individual is small, we are at the low dose end of those exposure–response curves. The low dose ends of the logistic and probit curves are linear. Hence, as a population exposure–response to an exposure with multiple sources of susceptibility, a linear association is not unexpected, even in the presence of individual thresholds. Another implication is that when populations exposed to higher doses are examined, the expectation is to be on a different part of the curve, with different slopes, including the part of the logistic curve where slopes are declining. This is important both for extrapolating high-dose epidemiologic results for risk assessment at lower doses and for doing the risk assessment on populations with a wide distribution of exposure.

Because of that article,[37] many additional studies reported no-threshold relationships among ambient levels of daily particles and daily deaths,[38–40] daily nitrous oxide and daily deaths,[41] long-term exposure to particulate air pollution and survival,[42] the effect of lead on IQ,[43] and the effect of arsenic on cancer risk.[44] The implications of significant public health risks at low exposure concentrations are large, as recent EPA regulatory impact assessments demonstrated. Hence, identifying whether the association is linear, or what shape it has, has become a central issue, and is critical in assessing the relative effects in different populations. Among the other techniques introduced to determine the shape of the exposure–response are regression splines,[45] penalized splines,[46] and Bayesian model averaging.[47] The existence of these no-threshold, and often linear, associations is now widely accepted.

For example, the National Research Council, in 2002 stated

> For pollutants such as PM10 and PM2.5, there is no evidence for any departure of linearity in the observed range of exposure, nor any indication of a threshold.[48(p109)]

DIFFERENTIAL RISK: EXPOSURE

A single scalar estimate of risk may also fail to fully characterize the public health problem of substantial differences in the distribution of exposure, again resulting in a skewed distribution of risk. For example, the distribution of lead exposure is highly skewed, with greater exposure among minorities and persons in poverty.[49–51] Over the last 30 years, multiple national surveys documented increasing skewness of blood lead distribution, as general sources of lead exposure (e.g., gasoline lead) have been reduced, although less universal sources of exposure have decreased more slowly. That is, the decrease in exposure in all parts of the population has not been proportional. Hence, inequity in the distribution of risk has increased.

The main point is that much of the risk assessment literature ignores such distributional issues. The landscape of exposure to chemicals reflects inequities in the distribution of resources more generally and should not be treated as exogenous. Although the impact of particular exposures on overall population risk is well known, far less is known about the socioenvironmental processes that deliver those risks differently to different groups. As Link and Phelan[52] argued, there is an obligation to consider as fundamental causes of disease those factors that place individuals at risk for risk. However, epidemiologic and toxocologic studies struggle to classify and incorporate "upstream" factors that account for differential distribution of risks. Such factors as racial discrimination, social disintegration and marginalization, and social inequality are hard to incorporate into a causal modeling framework. It is often difficult to envision meaningful counterfactuals or to conduct experiments in which one factor (such as discrimination) is altered, and all other factors remain the same. Glass and McAtee[53] suggested the concept of a risk regulator, which features the built and social environments that impact the distribution of risks across places or populations. Increasingly, systems analysis is also being used to generate new models and approaches for understanding the social patterning of risk.[54–56]

CONCLUSIONS

These arguments about distributional aspects of risk were derived ultimately from a moral judgment. Suppose an emission source increases the risk of dying by 1 in 100 000 in a large community around the source, resulting in an expectation of 1 additional death per year. Contrast this with an alternative: it increases the risk of dying by 1 in 10 in a small neighborhood around the plant, resulting in the same number of excess deaths per year. The attributable risk (i.e., the total number of cases attributable to the exposure) is the same, but many people would be less comfortable with the second scenario, because all the risk is concentrated in a small group, and because the level of the focused risk seems unconscionably high. That is, equity matters. How to deal with equity in public policy decisions is a societal judgment. However, unless risk assessors provide the relevant information, those judgments will be made in ignorance. This example is for clarity; it is not suggested that the EPA does not take into account differential exposure in their risk assessments (e.g., air toxics). However, they rarely take into account different slopes, which can matter just as much for equity. Failure to identify subgroups based on

differential vulnerability can lead to masking of pockets of inequity.

The call to pay greater attention to the clustering of risk and differential vulnerability is more than a concern about technical or methodological issues. In part, the emphasis of individual-level biological and genetic factors arises from the fact that these are the sort of data that are easier to collect and for which there are more mature tools of investigation. We cannot, however, escape that fact that the clustering of high and low risk regimes in particular environments also represents social, political, and economic processes at work.[57] Although less familiar and harder to study, these "upstream" factors are important drivers of disparities in health outcomes.[58] Disparities in health arise from inequities in the distributions of resources and risks. Those inequities are sensitive to policies that are often not considered part of the health policy domain, but which can be powerful levers of intervention. The example of the ozone hole and the banning of chlorofluorocarbons is an important historical example. However, beyond the caliber of the science, there is a moral imperative to augment risk assessment approaches in the pursuit of greater social justice.[59,60] In part, this involves the need to link, to a greater extent, exposure and health data to social and demographic data using geographic information systems.[61] However, it also means treating inequities in the delivery of environmental risk as a fundamental problem that requires explanation and action. ■

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References

1. Committee on Improving Risk Analysis Approaches. *Science and Decisions: Advancing Risk Assessment.* Washington, DC: National Research Council; 2008.

2. Schwartz J, Glass T, Bellinger D. Exploring potential sources of differential vulnerability and susceptibility in risk from environmental hazards to expand the scope of risk assessment. *Am J Public Health.* 2011;101(suppl 1): S94–S101.

3. Schwartz J, Bellinger D, Glass T. Expanding the scope of risk assessment: methods and illustrative examples for the study of differential vulnerability and susceptibility. *Am J Public Health.* 2011;101(suppl 1):S102–S109.

4. Forum RA. *Framework for Cumulative Risk Assessment.* Vol EPA/630/P-02/001F. Washington, DC: US EPA; 2003.

5. Marmot M. Achieving health equity: from root causes to fair outcomes. *Lancet.* 2007;370(9593):1153–1163.

6. Levy JI, Baxter LK, Schwartz J. Uncertainty and variability in health-related damages from coal-fired power plants in the United States. *Risk Anal.* 2009;29(7): 1000–1014.

7. Barendregt JJ. The effect size in uncertainty analysis. *Value Health.* 2010; 13(4):388–391.

8. *Final Regulatory Analysis: Control of Emissions from Nonroad Diesel Engines.* Washington, DC: US Environmental Protection Agency; 2004.

9. Dolinoy DC, Jirtle RL. Environmental epigenomics in human health and disease. *Environ Mol Mutagen.* 2008; 49(1):4–8.

10. Jirtle RL, Skinner MK. Environmental epigenomics and disease susceptibility. *Nat Rev Genet.* 2007;8(4):253–262.

11. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science.* 2005;308(5727): 1466–1469.

12. Skinner MK, Anway MD, Savenkova MI, et al. Transgenerational epigenetic programming of the brain transcriptome and anxiety behavior. *PLoS ONE.* 2008; 3(11):e3745.

13. Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. *Proc Natl Acad Sci USA.* 2007;104(32): 13056–13061.

14. Pilsner JR, Hu H, Ettinger A, et al. Influence of prenatal lead exposure on genomic methylation of cord blood DNA. *Environ Health Perspect.* 2009;117(9): 1466–1471.

15. Baccarelli A, Wright RO, Bollati V, et al. Rapid DNA methylation changes after exposure to traffic particles. *Am J Respir Crit Care Med.* 2009;179(7):572–578.

16. Tarantini L, Bonzini M, Apostoli P, et al. Effects of particulate matter on genomic DNA methylation content and iNOS promoter methylation. *Environ Health Perspect.* 2009;117(2):217–222.

17. Yehuda R, Bierer LM. Transgenerational transmission of cortisol and PTSD risk. *Prog Brain Res.* 2008;167:121–135.

18. Collins JW Jr, David RJ, Rankin KM, Desireddi JR. Transgenerational effect of neighborhood poverty on low birth weight among African Americans in Cook County, Illinois. *Am J Epidemiol.* 2009; 169(6):712–717.

19. McEwen BS. Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology.* 2000;22(2):108–124.

20. McEwen BS, Stellar E. Stress and the individual. Mechanisms leading to disease. *Arch Intern Med.* 1993;153(18): 2093–2101.

21. Seeman TE, Singer BH, Rowe JW, et al. Price of adaptation–allostatic load and its health consequences. MacArthur studies of successful aging. *Arch Intern Med.* 1997;157(19):2259–2268.

22. Geronimus AT. Understanding and eliminating racial inequalities in women's health in the United States: the role of the weathering conceptual framework. *J Am Med Womens Assoc.* 2001;56(4):133–136, 149–150.

23. Geronimus AT. The weathering hypothesis and the health of African-American women and infants: evidence and speculations. *Ethn Dis.* 1992;2(3): 207–221.

24. Geronimus AT, Hicken M, Keene D, Bound J. "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. *Am J Public Health.* 2006;96(5):826–833.

25. Davey Smith G, ed. *Health Inequalities: Lifecourse Approaches.* Bristol, UK: The Policy Press; 2003.

26. Kuh D, Ben-Shlomo Y, Lynch J, et al. Life course epidemiology. *J Epidemiol Community Health.* 2003;57(10):778–783.

27. Weisskopf MG, Weuve J, Nie H, et al. Association of cumulative lead exposure with Parkinson's disease. *Environ Health Perspect.* 2010;118:1609–1613.

28. Weisskopf MG, Jain N, Nie H, et al. A prospective study of bone lead concentration and death from all causes, cardiovascular diseases, and cancer in the Department of Veterans Affairs Normative Aging Study. *Circulation.* 2009;120(12): 1056–1064.

29. Weisskopf MG, Proctor SP, Wright RO, et al. Cumulative lead exposure and cognitive performance among elderly men. *Epidemiology.* 2007;18(1):59–66.

30. Bateson TF, Schwartz J. Who is sensitive to the effects of particulate air pollution on mortality? A case-crossover analysis of effect modifiers. *Epidemiology.* 2004;15(2):143–149.

31. Peters JL, Kubzansky L, McNeely E, et al. Stress as a potential modifier of the impact of lead levels on blood pressure: the Normative Aging Study. *Environ Health Perspect.* 2007;115(8):1154–1159.

32. O'Neill MS, Zanobetti A, Schwartz J. Modifiers of the temperature and mortality association in seven US cities. *Am J Epidemiol.* 2003;157(12):1074–1082.

33. Madrigano J, Baccarelli A, Wright R, et al. Air pollution, obesity, genes, and cellular adhesion molecules. *Occup Environ Med.* 2010;67:312–317.

34. Curjuric I, Imboden M, Schindler C, et al. HMOX1 and GST variants modify attenuation of FEF25-75% decline due to PM10 reduction. *Eur Respir J.* 2010;35: 505–514.

35. Chahine T, Baccarelli A, Litonjua A, et al. Particulate air pollution, oxidative

stress genes, and heart rate variability in an elderly cohort. *Environ Health Perspect.* 2007;115(11):1617–1622.

36. Reason J. Human error: models and management. *BMJ.* 2000;320: 768–770.

37. Schwartz J, Zanobetti A. Using meta-smoothing to estimate dose-response trends across multiple studies, with application to air pollution and daily death. *Epidemiology.* 2000;11(6): 666–672.

38. Daniels MJ, Dominici F, Zeger SL, Samet JM. The National Morbidity, Mortality, and Air Pollution Study. Part III: PM10 concentration-response curves and thresholds for the 20 largest US cities. *Res Rep Health Eff Inst.* 2004;(94 Pt 3):1–21, discussion 23–30.

39. Samoli E, Analitis A, Touloumi G, et al. Estimating the exposure-response relationships between particulate matter and mortality within the APHEA multicity project. *Environ Health Perspect.* 2005; 113(1):88–95.

40. Schwartz J, Laden F, Zanobetti A. The concentration-response relation between PM(2.5) and daily deaths. *Environ Health Perspect.* 2002;110(10):1025–1029.

41. Samoli E, Touloumi G, Zanobetti A, et al. Investigating the dose-response relation between air pollution and total mortality in the APHEA-2 multicity project. *Occup Environ Med.* 2003;60(12): 977–982.

42. Schwartz J, Coull B, Laden F, Ryan L. The effect of dose and timing of dose on the association between airborne particles and survival. *Environ Health Perspect.* 2008;116:64–69.

43. Lanphear BP, Hornung R, Khoury J, et al. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. *Environ Health Perspect.* 2005;113(7): 894–899.

44. Morales KH, Ryan L, Kuo TL, et al. Risk of internal cancers from arsenic in drinking water. *Environ Health Perspect.* 2000;108(7):655–661.

45. Eilers PHC, Marx BD. Flexible smoothing with *B*-splines and penalties (with discussion). *Stat Sci.* 1996;11:89–121.

46. Wood S. Modeling and smoothing parameter estimation with multiple quadratic penalties. *J Roy Stat Soc B.* 2000; 62:413–428.

47. Hoeting JA, Madgan D, Rafferty AE, Volinsky CT. Bayesian model averaging: a tutorial. *Stat Sci.* 1999;14:382–417.

48. National Research Council. *Estimating the Public Health Benefit of Proposed Air Pollution Regulations.* Washington, DC: National Academy Press; 2002.

49. Baghurst PA, Tong S, Sawyer MG, et al. Sociodemographic and behavioural determinants of blood lead concentrations in children aged 11-13 years. The Port Pirie Cohort Study. *Med J Aust.* 1999;170(2):63–67.

50. Bellinger D, Leviton A, Waternaux C, et al. Low-level lead exposure, social class, and infant development. *Neurotoxicol Teratol.* 1988;10(6):497–503.

51. Elreedy S, Krieger N, Ryan PB, et al. Relations between individual and neighborhood-based measures of socioeconomic position and bone lead concentrations among community-exposed men: the Normative Aging Study. *Am J Epidemiol.* 1999;150(2):129–141.

52. Link BG, Phelan J. Social conditions as fundamental causes of disease. *J Health Soc Behav.* 1995;Spec No:80–94.

53. Glass TA, McAtee MJ. Behavioral science at the crossroads in public health: extending horizons, envisioning the future. *Soc Sci Med.* 2006;62(7):1650–1671.

54. Diez Roux AV. Integrating social and biologic factors in health research: a systems view. *Ann Epidemiol.* 2007;17(7): 569–574.

55. Galea S, Riddle M, Kaplan GA. Causal thinking and complex system approaches in epidemiology. *Int J Epidemiol.* 2010;39:97–106.

56. Gibbons MC, Brock M, Alberg AJ, et al. The Sociobiologic Integrative Model (SBIM): Enhancing the integration of sociobehavioral, environmental, and biomolecular knowledge in urban health and disparities research. *J Urban Health.* 2007;84(2):198–211.

57. Rhodes T. Risk environments and drug harms: a social science for harm reduction approach. *Int J Drug Policy.* 2009;20(3):193–201.

58. Diez-Roux AV. Multilevel analysis in public health research. *Annu Rev Public Health.* 2000;21:171–192.

59. Morello-Frosch R, Shenassa ED. The environmental "riskscape" and social inequality: implications for explaining maternal and child health disparities. *Environ Health Perspect.* 2006;114(8):1150–1153.

60. Morello-Frosch RA. Discrimination and the political economy of environmental inequality. *Environ Plann C Gov Policy.* 2002;20:477–496.

61. Waller LA, Louis TA, Carlin BP. Environmental justice and statistical summaries of differences in exposure distributions. *J Expo Anal Environ Epidemiol.* 1999;9(1):56–65.