Differential vulnerability & Susceptibility: expanding the scope of risk assessment

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ABSTRACT:

Objectives: The central paradigm for EPA standard setting is risk assessment. This paradigm has served public health well for decades. However, gaps have emerged in the fabric of this framework, causing some authors to challenge certain underlying assumptions. Our overall aim is to extend the risk assessment approach by examining, both conceptually and methodologically, how differential responses across population groups can be better integrated into the risk assessment process. We illustrate these issues, focusing on two specific examples: lead and air pollution.

Relevance: Addressing inequities in health risks and health outcomes will require an extension of the risk assessment paradigm. Currently, methods and approaches are available for considering differential risk and vulnerability, but have not yet found their way into wide-spread usage. Our proposed extension is intended to increase the precision and effectiveness of risk assessment generally, and to provide additional policy tools to help target resources to achieve greater equity in the health status of populations in addition to efficient risk reduction.

Summary of Findings: Our central conclusion is that people respond differently, and this is an important enough phenomenon to require integration into risk assessment. Moreover, such integration is difficult with paradigms like reference dose, and flows more easily from a quantitative consideration of dose-response curves, which have the additional advantage of incorporating the non-trivial effects that may be observed at low dose for common exposures. We identify and discuss 6 assumptions implicit in standard risk assessment models that must change to accomplish this. For convenience, we label these 1) risk independence, 2) risk averaging, 3,) risk non-transferability, 4) risk synchrony, 5) risk accumulation and chaining, and 6) quantification of numbers of persons above certain thresholds or limit values is sufficient to characterize risk. The literature on lead and air pollution are reviewed in order to illustrate how these assumptions might be modified to take account of differential risk and vulnerability. Our main finding is that differential risk and vulnerability is a critically important but neglected area within risk assessment. However, a wide range of methodological and conceptual tools are now available for addressing these gaps.

Recommendations: If continued progress is to be made in incorporating these concepts into risk assessment, future studies of toxicant exposure-risk relationships must invest the resources necessary to measure contextual and individual-level factors that might modify these relationships. In most cases we do not know which subgroups are the most vulnerable or, if we do, subgroups are defined very broadly. We advocate defining vulnerable subgroups with greater specificity.. At the same time, information is available on differential susceptibility for

some agents, and EPA risk assessments have failed to characterize the impact of those differences on the distribution of risk. EPA should commit to making this a standard part of their risk assessments whenever the information is available to do so. To characterize more fully the bases of inter-individual differences in vulnerability, we recommend epidemiologic studies incorporate the measurements and analytical techniques to tease out effect modifiers at multiple levels. In essence, we argue for moving beyond the reliance on standard uncertainty factors and working to explicitly unpack the "black box" that represents variability in vulnerability.

A. Introduction and statement of goals

The central paradigm for EPA standard setting is risk assessment. Based on scientific data, EPA prepares quantitative estimates of the changes in health status that will result at different potential levels of a standard, and uses that quantification as input into decision-making, where risk management depends on other inputs as well. Specific regulatory actions are targeted to particular environmental agents, whose marginal impacts, sources, and control strategies often differ. Often a cruder approach is taken. A regulatorily acceptable dose is defined (e.g. the RfD or reference dose) and risk assessment merely quantifies numbers above vs below this magic number. Implicit is the latter approach is that this quantity is meaningful, which implicitly assumes that risk is zero below the RfD, and the same no matter how much above the RfD the exposure is. This paradigm has served public health for decades. However, gaps have emerged in the fabric of this framework causing some authors to begin to challenge and examine certain underlying assumptions.

A recent NAS report declared that "..risk assessment is at a crossroads"[1]. It's key recommendation to to abandon the reference dose approach whenever possible and move to a quantitative estimate of changes in health. The purpose of this paper is to review some of the assumptions inherent in those studies and to propose an expansion of the current risk assessment approach. Simply put, we suggest that risk assessment should be updated to consider, both conceptually and methodologically, the issue of differential vulnerability and susceptibility across population groups, and how this results in the inequitable distribution of risk, a key concern for environmental justice. We address the conceptual and methodological issues in turn, and build our case around lead and air pollution as running examples.

Susceptibility and Vulnerability: The standard definition of a person who is susceptible is that the person is more responsive to the exposure. More recently, the word vulnerability has been used to describe situations where the susceptibility arises from psycho-social or economic differences, rather than biologic differences among the people. We do not think this distinction is a good one, because recent research into how socio-economic factors, stress, etc exert influence on health has identified clear biological pathways. Stress is associated with differential baseline levels and differential response of the hypothalamic-pituitary-adrenal system for example. That is, these social factors really do describe people with different biological states. A more useful distinction is one vs many. Just as in physics, collections of particles are capable of behavior quite different than what one would expect examining them singly or via simple two way interactions, human's health, and response to external stimuli, depends in part on the fact

that humans live in groups. And differences across persons in the groups they live in influence their responses.

A.1. Assumptions underlying risk assessment

In this section of the paper, we examine 6 assumptions that underlie the general risk assessment framework. Some of these assumptions have been made explicitly in previous work, and others have been explored relatively little.

A.1.1. Assumption 1: Risk independence (aka risk autonomy)

Risk assessment traditionally assumes that exposures and their health impacts are independent of one other, and can hence be evaluated singly as distinct isolable factors. 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. Where there are interactions between A and B, this approach can produce spurious results.

A.1.2 Assumption 2: risk averaging

In addition, 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, or equivalently, the mean risk. Much work in risk assessment recently has focused on understanding the uncertainty in this scalar estimate. But recent work in epidemiology, toxicology, and exposure science has suggested that a more multidimensional approach may be more useful. Two main problems arise. 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. A second problem is that if a risk factor has opposing effects in populations of approximately equal magnitude, pooled estimates will “wash out” the deleterious effect in more vulnerable groups. In such a case, regulatory options should take into account that there are beneficial effects in some and deleterious effects in others, rather than assuming there is 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 mmHg change in blood pressure

(typical of the reduction produced by most anti-hypertensive drugs) is modest, but the population impact of a seven mmHg shift in the mean distribution of the population is huge. Treating hypertension in individuals produces a small change in individual risk, masking large changes in population rates of heart disease. As an environmental example, EPA's risk assessment for controlling off road Diesel engine emissions estimated it would save over 12,000 lives per year by 2030, although individual risk reduction was estimated to be small[2]. Implicit in this focus on attributable risk is that while individual risks may vary about the mean, the risks in a definable subpopulation do not reach a level of concern (defined by decision makers such as the EPA Administrator) that would require additional efforts.

Implicit in this is that while individual risks may vary about the mean, the risks in a definable subpopulation do not reach a level of concern. The risk assessment framework presumes that average risk is an appropriate and sufficient single estimate of population risk. That is, there is a focus on the distribution of outcomes within stochastic parameters, but an under-appreciation of two important factors that are the subject of much of this paper: a) the distribution of risks is not random or uniform, and b) the vulnerability of individuals and populations may vary as a function of factors related to persons or places.

A.1.3 Assumption 3: Risk non-transferability

One other standard assumption in risk assessment is that the risks may accumulate but that they apply to each person exposed without reference to the exposure status of others. But recent studies of the risks due to environmental exposures suggest that some risk may 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 [3, 4] Some of these changes can occur in children whose mothers are exposed during pregnancy; and while non-genetic, 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[5]. 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[6]. There is growing evidence that exposures to other environmental agents such as Bisphenyl A[7], lead[8], traffic pollution[9], and metal-rich particles[10] result in epigenetic changes in humans.

Psychosocial factors may play a similar role in producing transgenerational effects. For example, lead exposure is associated with increased hyperactivity and reduced executive function, which may impact parents who were exposed as children by making them less able to cope with normal stresses, which would further impact their parenting ability. Yehuda has recently shown that offspring of parents exposed to holocaust trauma have altered neuroendocrine responses suggestive of epigenetic programming across generations[11]. Collins has shown that parents exposed to poverty appear to transmit increased risk to their offspring through low birthweight and other deleterious effects[12]. This research shows the myriad ways in which the social environment alters fetal programming in ways that extend across generations, suggesting both that the exposed person may not be the only person suffering the consequence of the exposure and that individuals may start life with varying degrees of vulnerability to subsequent environmental risk factors.

A.1.4 Assumption 4: Risk synchrony

Risk assessment sometimes relies on snapshots of exposure based on one point in time or on a narrow time window, or alternatively 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[13-15], the weathering hypothesis[16-18] as well as life-course epidemiology [19, 20]. 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. Also, as attention focuses on intermediary biomarkers of health (for example blood pressure and cholesterol levels rather than cardiovascular events, are now commonly used as surrogate markers for pharmaceutical agents that represent deliberate exposure to manmade chemicals) finding the best indicator for environmental exposures' cumulative impact on health is acquiring greater importance. There are some candidate markers, which should be considered in risk assessments.

A.1.2. Assumption 5: Risk accumulation and chaining

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, if there

are skewed distributions of other underlying risk factors, resulting in substantially different cumulative burdens in one subpopulation than in another. That is, one input into policy making may be how a given option changes the distribution of cumulative risk due to all risk factors in the population, and not merely how it changes the distribution of risk due to 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.

A.2. Moving toward differential vulnerability: interactions and beyond

But what if the above set of assumptions are 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 subgroups 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 due to exacerbations of the effect of exposure by underlying disease status, by psychosocial factors (e.g., stress) or by sociomaterial factors (e.g., poverty). This is not to suggest that effect modification is always exacerbatory; diets rich in antioxidants and omega-3 fatty acids have been shown to blunt the effect of air pollution[21, 22] for example. Differential response can also flow from more complex social or physical factors or more than one interaction. Several examples are: persons with diabetes have twice the risk of cardiovascular mortality following exposure to particulate air pollution as persons without the syndrome,[23] stress modifies the effects of lead on blood pressure and cognition[24], race and educational level strongly modify the mortality risk on very hot days[25], and genes related to oxidative stress defenses modify the risk of air pollution[26].

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 they assumed independent distributions of individual actions, rather than the systemic behaviors that actually occurred[27]. In the case of environmental exposures, many modifiers are related and not independently distributed. For example, both diabetes and stress are more prevalent among black Americans. And for some pollutants, exposure is greater among this subgroup of the population as well. A risk assessment that seeks to capture the distributional aspects of risk must include the covariance of the risk modifiers, which could greatly increase the actual skewness of risk in the population.

A.3. 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, EPA has used quantitative risk assessment based on epidemiologic dose-response or exposure-response curves. In other cases they have computed reference doses, or some similar estimate of a dose that conveys *de minimis* risk. The National Research Council has recently recommended that EPA take an integrated approach, including moving to more quantitative risk assessment, in lieu of reference doses. This fits well with the emphasis here on cumulative risk, distribution of risk, and interactions, since it is difficult to incorporate those 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 occurs in homes *below* the EPA guideline, 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*.

A.3.1. Dose-response and threshold effects

One special topic is what the shape of the exposure-response or dose-response relation is. Many studies fail to consider adequately whether there is a threshold in the association between exposure and response. Thresholds have traditionally been assumed in toxicology for most outcomes, possibly excepting cancer. However, as epidemiology studies have extended to consider more exposure-response relations in relevant exposure ranges, a striking finding is the lack of evidence for departure from linearity in many associations for non-carcinogens, down to the lowest observable exposures in the general population. For example, the concentration-response between PM2.5 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 a paper in 2000 reporting on a method (meta-smoothing) for combining data across studies to examine the shape of the exposure-response, Schwartz developed a theoretical basis for such findings[28]. Suppose each subject has a threshold for a serious health response, for example mortality. These thresholds differ across subjects 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, psychosocial etc modifiers we have discussed in this paper. 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 due to 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, and hence the cumulative distribution of the thresholds (which, as noted above, is the exposure-response curve in the total population) will tend to approach the logit or probit curve. Since we are generally dealing with population exposures to environmental contaminants, 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. And 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 we look at populations exposed to higher doses, we might expect 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 epidemiologic results for risk assessment and for doing the risk assessment on population with a wide distribution of exposure.

Since that paper many additional studies have reported no-threshold relationships between ambient levels of daily particles and daily deaths[29-31], daily NO_2 and daily deaths[32], long term exposure to particulate air pollution and survival[33], the effect of Lead on IQ[34], the effect of Arsenic on cancer risk[35], etc. The implications of significant public health risks at low exposure concentrations are large, as recent EPA regulatory impact assessments have demonstrated. Hence identifying whether the association is linear, or what shape it has, has become a central issue. Among the other techniques introduced to determine the shape of the exposure-response are regression splines[36], penalized splines[37], and Bayesian model averaging[38]. 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” [39].

Nonlinearities are still possible, and still observed. For example, the dose-response curve for the cognitive effects of lead, and for the cardiovascular effects of particles, show nonlinearities, with **decreasing** effects of incremental exposures when exposures are already high. Risk assessment must clearly consider such whether steeper responses at lower levels exist in each case, particularly if we seek to understand differential effects on subpopulations whose exposures may differ. But research must also identify the reasons. Are these general

physiologic phenomena—such as saturation, or do they result from a wide distribution of susceptibility? Knowing the answer to this question could result in different choices of policy options.

A.4. Differential risk: exposure

A single scalar estimate of risk may also fail to fully characterize the public health problem where there are substantial differences in the distribution of exposure, again resulting in a skewed distribution of risk. This is distinct from the case of risk chaining (A.1.5) where the issue was the differential distribution of risk factors *other* than the exposure of interest. For example, the distribution of lead exposure is highly skewed, with greater exposure among minorities and persons in poverty[40-42]. Over the last 30 years, multiple national surveys have documented increasing skewness of the blood lead distribution, as general sources of lead exposure (e.g. gasoline lead) have been reduced, while less universal sources of exposure have fallen more slowly. That is, the decrease in exposure in all parts of the population has not been ***proportional***. Hence inequity in the sociogeography of risk has increased.

The main point is that much of the risk assessment literature regards the systematic patterning of risk in different places and in different populations as unproblematic. The landscape of exposure to chemicals reflects inequities in the distribution of resources more generally, and should not be treated as exogenous (that is, something outside of the scope of the risk assessment and risk management decisions, and taken as given). So while we know quite a bit about the impact of particular exposures on overall population risk, we know far less about the socio-environmental processes the deliver those risks differently to different groups. Insufficient attention has been paid in traditional risk assessment models to the social determinants of exposure. As Link and Phelan argue, we are obliged to consider as fundamental causes of disease, those factors that place individuals at risk for risk [43]. 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[44] have suggested the concept of a risk regulator, features of 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 [45-47]

A.5. Conclusion

These arguments about distributional aspects of risk derive ultimately from a moral judgment. Suppose an emission source increases the risk of dying by e.g. 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. But unless risk assessors provide the relevant information, those judgments will be made in ignorance. This example is for clarity, we are not suggesting that EPA does not take into account differential exposure in their risk assessments, e.g. for air toxics. But 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 a masking of pockets of inequity. This in turn provides an excuse for ignoring the ethical issues that arise.

B. Lead and Air Pollution: extended examples

This paper seeks to expand on the issues raised above, illustrate them with examples that demonstrate that the issues are not hypothetical, and suggest approaches to generalize the risk assessments to incorporate these other dimensions. To provide clarity, we will attempt to always illustrate our points with examples, and for simplicity and consistency, we will emphasize the cases of lead exposure or air pollution as our examples.

B.1. Sources of Susceptibility (Susceptibility in Response to Exposure)

B.1.1. Genetic Sources of Variable Response

B.1.1.i. General Issues

Genetic susceptibility to environmental exposures is clear from the literature, and the field is rapidly advancing. As early as the 1970's studies of subjects experimentally exposed to ozone in chambers demonstrated substantial variability in response. This variability was repeatable, and un-explained by phenotype[48]. Large scale animal studies have identified genes with human homologues that may explain this result[49]. The existence of common polymorphisms affecting Phase I and Phase II detoxification pathways indicates this is a likely source of important variations in response to multiple toxicants. If genetic susceptibility is

important for certain exposures, and several pathways contribute to that susceptibility, this could result in substantial differences in the distribution of risk.

B.1.1.ii. Lead

The evidence regarding the role of the genetic factors in health outcomes associated with increased lead exposure is mixed. Some studies suggest that carriers of the 2 allele of the amino levulinic acid dehydratase gene (i.e.,ALAD-2 carriers) are at increased risk of lead-associated neurobehavioral deficits[50, 51], while other studies, focusing on similar endpoints, suggest that this subgroup is at reduced risk[52, 53]. Some of the inconsistency in results across studies might be due to age-dependence in this association. A recent study of lead and cognitive function using NHANES data suggested modification by ALAD status in 20 to 59 year olds, but not in 12 to 16 year olds or in adults older than 60 years[54]. This also highlights our point about the importance of age at time of exposure, and not exposure alone. A similar potential age-dependence in the relationship between genotype and risk has been reported for apoliprotein E (ApoE). In adults, carriers of the APoE4 allele appear to be at increased risk of lead-associated neurobehavioral deficits[55], while this was not found in a study of children[56]. There is also evidence that the impact of APoE4 depends on (and varies according to) environmental factors including stress[57]. In males, the adverse effects of lead exposure on a test of executive functioning were greatest among those lacking the dopamine receptor D4-7[58]. In adult workers, those with the vitamin D B variant showed greater lead-associated impairment of renal function[59]. Vitamin D polymorphisms also modified the effect of lead on cognition in children in NHANES III[60].

Recent attention has been devoted to the hypothesis that lead increases the risk of neurodegenerative processes in later life by means of an epigenetic mechanism. In rodents and primates, Zawia and colleagues found that early lead exposure causes a developmental reprogramming, resulting in over-expression in adulthood of the amyloid precursor protein (APP) gene, specifically APP mRNA, APP, and beta-amyloid[61].Amyloid protein is a major factor in Alzheimer's disease. An inverse association has also been reported between prenatal lead exposure (maternal bone lead) and DNA methylation in cord blood[8], and between bone lead levels and DNA methylation in leukocytes in the elderly[62].

B.1.1.iii. Air Pollution

There is strong and growing evidence that genetic polymorphisms modify the response to air pollution. The strongest evidence to date is for polymorphisms along the oxidative defense pathway. For example, polymorphisms along this pathway have been shown to modify the effects of particles on heart rate variability[26, 63], the effects of traffic particles on homocysteine

levels[64], the effects of traffic pollutants on lengthening of the QT interval on electrocardiograms, the effects of air pollution on lung function[65, 66], the risk of ozone induced asthma[67] and wheeze[68], the risk of endothelial inflammation caused by traffic particles[69]etc. The specific genes along this pathway that matter vary amongst these studies, however, which may reflect differences in outcomes studied, stochastic variability in the results, or interactions with as yet unknown other risk modifiers. This makes it more difficult to use these results for risk assessment of specific genes, but not to acknowledge that there is a skewed distribution of risk. However, Glutathione S Transferase mu 1 (*GSTM1)* null variant is the most commonly reported modifier along this path. In addition, other genetic polymorphisms that may modify the effects of air pollution include those in the divalent metal metabolism pathway[70], the angiotensin pathway[71], the methyl metabolism pathway[72], and genes related to processing of micro RNA's, which are small non-coding RNA's that post-transcriptionally control gene expression[73].

In addition, there is growing evidence for a role of epigenetic mechanisms both as pathways for the effects of air pollution, and potential modifiers of response. Metal rich particles have been associated with reduced methylation of the promoter region of the iNOS gene[10], for example. And traffic officers have changes in methylation of cancer suppressor and promotion genes similar to those seen in leukemia[74]. Exposure to traffic particles[75] and polycyclic aromatic hydrocarbons[76] has also been shown to alter DNA methylation patterns.

B.1.2. Phenotypic (Host characteristics) Sources of Variable Response

B.1.2.i. General Issues

There are a number of theoretical arguments to suggest that physiologic and disease states of individuals may influence their response to environmental agents. In the early 1800's Scottish public health advocates, lead by William Pulteney Alison, chair of the practice of medicine at the University of Edinburgh argued that the (unkown) agents that caused infectious disease were ubiquitous, and what mattered was subject susceptibility, which was principally driven by malnutrition. They recommended prescribing food[77]. Johns Cassel similarly argued in 1976 that host factors that alter the underlying susceptibility of an individual to the deleterious effects of various exposures are of paramount importance [78]. The most obvious is that the phenotype may be characterized by disturbances among one or more physiologic pathways that are also important to the toxicity of the environmental agent. Environmental disturbances to those pathways may have greater effects if the reserve capacity for dealing with such disturbances is already impaired by the presence of disease, or allostatic load. This also has implications for cumulative risk assessment, as some pathways may be relevant to multiple

different exposures. For example, both lead and air pollution have been shown to work, in part, by increasing oxidative stress. Diabetes and obesity are phenotypes that are characterized by elevated baseline levels of oxidative stress before exposure, and co-exposure to multiple agents that produce further oxidative stress may result in nonlinear increases in risk. Indeed interactions between lead exposure and air pollution have already been reported[79]. In addition dietary antioxidants, such as vitamin C and vitamin E, or methyl related substrates such as B-vitamins or methionine, or N-3 fatty acids[21] have also been reported to modify responses to environmental agents[22, 72, 80]. The potential for highly skewed distributions in risk exist because these dietary intakes tend to be lower in more disadvantaged areas, where the prevalence of obesity and diabetes also tends to be higher, and where exposure to some environmental chemicals is also higher.

B.1.2.ii. Lead

Relatively few data are available on the issue of whether disease states modify the effects of lead. Some studies, which are somewhat controversial, suggest that lead-associated decrement in renal function is more pronounced in patients with pre-existing chronic kidney disease (e.g., hypertension, gout)[81]. In an elderly cohort, higher lead level was associated with impaired renal function, but only in diabetic subjects[82]. Among adult men, the association between increased patella lead (but not tibia lead) and autonomic dysfunction (heart-rate variability) was reported to be greatest among those with metabolic syndrome[83].

B.1.2.iii. Air Pollution

While a number of conditions have been reported to modify the effects of air pollution on health, the strongest evidence is for obesity and diabetes. The increasing prevalence of obesity and diabetes make these susceptibility factors especially important for risk assessment, since they need to take into account the changing proportion of the population that is susceptible. A 2002 study of 4 US cities found that diabetics had double the risk of a PM10-associated cardiovascular admission compared with nondiabetics[84] A study in Montreal found air pollution was associated with a much higher risk of death for diabetes than for all causes.[85] Similarly, a 2.0-fold higher mortality risk associated with PM10 exposure was found for diabetics than for controls in a 2004 case-crossover study[23]. Likewise, PM10 effects on mortality were stronger in diabetics than in non-diabetics in 9 Italian cities.[86] Other studies have reported that diabetes modified the effects of air pollution on endothelial function[87, 88], and on systemic inflammation[89, 90].

Obese individuals were found to have twice the PM2.5-induced reduction in heart rate variability than non-obese individuals, and had more PM2.5-mediated HR increases.[91] Obesity

was a significant susceptibility factor for ozone (O3) acute effects on lung function, with twice the estimated decrease in FEV1 due to O3 in obese subjects compared to non-obese subjects.[92] This is supported by animal data showing increased lung inflammation in response to ozone in obese animals[93, 94]. In addition, obesity worsened the PM2.5 effects on the HF component of HRV,[95] and there was a greater effect of traffic-related PM on inflammatory markers in obese individuals.[96,97,89] Again, in the NHANES III, metabolic syndrome modified the PM10 effect on inflammatory markers.[98]

Diet may also modify the effects of air pollution. For example, a randomized trial found that Omega-3 fatty acid supplementation reduced the effect of particles on heart rate variability.[22] A chamber study of well characterized asthmatics also found that supplementation with vitamins C and E reduced the increase in bronchial responsiveness following controlled exposure to ozone[99].

B.1.3. Psychosocial hazards and stress

B.1.3.i. General issues

Psychological stress is a physiologic response to some environmental stimuli, that can be positive and adaptive, or, under conditions including prolonged exposure, can become dysregulated, leading to a variety of negative health consequences[100]. The literature on stress is inconsistent about what it is in the environment that gives rise to a stress response. Borrowing language from an environmental science perspective, we argue that stress arises from exposure to a psychosocial hazard, defined as relatively stable, visible features of the social and built environment that gives rise to a heightened state of vigilance, alarm and fear[101, 102]. Previous studies have shown that dysregulation of the stress response system has been consistently linked to cardiovascular and other diseases.[103] The Institute of Medicine reported that potential social causes of neurodevelopmental disabilities, including social isolation and psychosocial stress, have not been well studied.[104] Recent animal studies and epidemiologic data suggest that social context modifies environmental neurotoxicants.[105] In poor communities, social and chemical hazard exposure in childhood can jointly alter development and organization of the central nervous system.[106]

B.1.3.ii. Lead

The study of how stress exacerbates the influence of lead dates back to classic studies by Selye investigating how stressors (both systemic and local) act as “conditioners”, whose effect while minor in isolation, is, when combined with lead exposure, powerful and complex[107] In studying these “pluricausal” syndromes, Selye was concerned with physiologic stressors (skin

clip), however, the implications of this work have been carried forward into the study of stress of a psychological and social origins.

A consistent finding is that stress may exacerbate the deleterious consequences of lead exposure. In a series of rodent studies of maternal stress during pregnancy (novelty, restraint, cold) and lead exposure through weaning, Cory-Slechta and colleagues showed that pups who experienced both lead-exposure and stress demonstrated more impaired learning, compared to controls, on fixed-interval schedule-controlled responding, as well as increased basal and stress-induced corticosterone responses than did pups exposed to stress alone or to lead alone[108, 109]. In addition, Schneider[110] demonstrated that animals raised in social isolation were more sensitive to the neurotoxic effects of lead than animals raised in an enriched environment. Animal studies have shown that stress can increase the hormonal mobilization of lead from bone to blood [111] and that lead exposure can alter responsiveness to environmental stress [112, 113]. Exposure to psychosocial hazards in the laboratory increases cortisol production, the primary hormonal mediator of the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol itself is associated with impaired memory and executive ability in older adults [114-116]. Further, both lead and cortisol are thought to alter common pathways in the mesocorticolimbic system including calcium and glutamate-mediated processes [113, 117, 118]. Both cortisol and lead appear to be associated with similar domains of cognitive function (especially memory and executive functioning). Glucocorticoid receptors are known to be present in relevant brain structures that govern these areas.

To date, much less human evidence bears directly on the hypothesis that stress modifies lead effects. In two studies of older men, the inverse associations between bone lead level and cognition (Mini-Mental Status Examination score) and blood pressure were more pronounced among men who self-reported greater stress[24, 119].

The potential importance of the social/physical environment in modifying lead neurotoxicity was demonstrated by a study that show that an impairment of spatial learning caused by exposing a pup to lead in utero or through lactation can be mitigated by rearing it in an enriched environment (i.e., larger cage, other rodents, toys)[120]. Moreover, the learning effects were accompanied by differences in gene expression in the hippocampus (i.e., recovery of deficits in NMDA receptor subunit 1 mRNA, induction of BDNF factor mRNA).

Another pathway by which lead effects might be expressed differentially by socioeconomic position (SEP) concerns the possibility that early life lead exposure impairs the response to a later brain insult. For example, lead-exposed rats showed reduced behavioral recovery to an induced ischemic stroke in the hind limb parietal sensory-motor cortex in

adulthood[121]. Early lead exposure also impairs the topographic organization of the columnar processing units in the barrel field somatosensory cortex in rats[122] as well as the reorganization of the barrel field that occurs following whisker follicle ablation[123].

This general finding has also been shown in human studies. A study of children by Gump[124] found that higher cord blood lead levels were associated with higher baseline systolic blood pressure (SBP), and higher early childhood lead levels were associated with greater total peripheral (vascular) resistance (TPR) responses to acute stress. Very few studies have examined the environmental backdrop that gives rise to the spatial distribution of stress dysregulation. In one such study of older adults, Glass[102] found that in those living in neighborhoods with the most psychosocial hazards, tibia bone lead concentration had a more deleterious effect on three of seven domains of cognitive function examined. Despite these findings, most studies assume risk uniformity and either do not systematically investigate how host characteristics (including stress) alter the effect of lead, or are underpowered to do so effectively[125]

B.1.3.iii. Air Pollution

Limited but growing epidemiological evidence suggests that psychological stress may also alter susceptibility to air pollution exposures. Social stress has been shown to modify traffic-related air pollution effects on asthma etiology[126] or exacerbation.[127, 128] A study of singleton births in Eastern Massachusetts examined the association between black carbon (BC) and birth weight, and investigated confounding and effect modification by individual and area-based socioeconomic measures (SEP).[129] Also, some air pollutants and psychosocial stress may independently affect common physiologic processes such as oxidative stress[130] or inflammatory cell (IgE) production.[131] Among adults, 8-hydroxy-deoxyguanosine, a marker of oxidative damage to DNA, has been linked to depressive symptoms,[132] clinical depression,[133, 134] perceived stress and perceived impossibility for alleviating stress,[132] and caregiving for advanced cancer patients (a measure of chronic stress).[135] disease.[136, 137] Given the evidence to date that both psychosocial stress and air pollutants may influence oxidative stress and cellular aging processes, further investigation of whether social-environmental interactions contribute to cardiovascular disease will be important to advancing risk assessment.

B.1.4. Socio-economic Position

B.1.4.i. General Issues

Socioeconomic position (SEP) is known to have an enduring, robust and complex association with many health states. While the mechanisms underlying the SEP gradients in health are not precisely known, different SEP groups clearly have markedly different health

status as well as vulnerability to the impact of common exposures. The relationship between SEP and poor health is not confined to poor people alone. Although it is clear that the highest risks occur among the persons with the lowest position, the dose-response is continuous[138]. At each step of the socio-economic hierarchy, individuals tend to have better health compared with those below them. Hence this potential co-risk factor and risk modifier cannot be simply dealt with by looking at the extremes.

Further, SEP can be conceptualized and measured at both the individual level and the area level (e.g., neighborhoods). Evidence suggests that each level exerts an independent influence on an individual's chances of health. That is, a wealthy person living in a poor area is exposed to the same excess of fast food, lack of nearby fresh produce, higher crime rate, greater distance to pharmacies, lack of attractive green space, etc, as their neighbors, and this tends to impact their health, and potentially their response to environmental pollutants.

B.1.4.ii. Lead

Several studies have provided evidence that the impact of lead on human health is connected in complex ways to SEP[139]. In humans, some epidemiological studies have reported that children from families of low SEP either express an exposure-associated deficit at lower biomarker levels of lead or fail to recover/compensate as quickly or completely as children with higher SEP levels[125]. A recent analysis suggested that the effect of increased blood lead levels on children's performance on an end-of-grade reading test was more pronounced at the lower than the upper tail of the distribution of reading scores[140]. In other words, the effects of increased lead exposure were greater among children who faced other risk factors for lower reading achievement. This phenomenon is not restricted to lead. Rauh et al[141] measured prenatal and post-natal exposure to ETS, social stress factors, and Bayley Scales of infant development in 226 urban children enrolled during pregnancy and followed longitudinally. Prenatal ETS exposure was associated with a 5 point reduction in Bayley MDI scores. Material hardship was similarly associated with a 3 point reduction in MDI. However, the interaction of material hardship and prenatal ETS was associated with a further 7 point decline in MDI scores ($p=0.03$). In order to understand the basis of this finding, it is necessary to deconstruct the complex construct of SEP into its component features. These include nutrition, stress, other chemical exposures, and the social/physical environment. Some evidence can be marshaled to suggest a role for each of these features in the apparent effect modification of lead neurotoxicity by SEP.

Many studies have treated SEP solely as a confounder of the lead-health association[142]. Given the usual pattern of covariance between increased lead exposure and other risk factors

for adverse health states, there is no question that potential confounding by SEP must be considered, but careful consideration must be given, as well, to the possibility that treating SEP as a confounder could lead to bias. To the extent that blood lead level is an imperfect measure of lead exposure history, or is subject to misclassification bias, other factors (like SEP or race/ethnicity) may, in some circumstances, be better markers of cumulative exposure than a biomarker measurement. Secondly, lead exposure may be on the causal pathway between SEP and health. This arises from the social patterning of lead exposure along socioeconomic lines[42, 143] These considerations suggest that methodological tools such as directed acyclic graphs or techniques such as structural equation modeling might be useful in dissecting these complex relationships and controlling only those portions of the relationships that confound the exposure-outcome relationships of interest.

B.1.4.iii. Air Pollution

There is also a modest but consistent set of studies indicating that SEP modifies the effect of air pollution. For example, Forestiere and coworkers, using a city where it was the upper SEP subjects who had higher exposures, showed the effects of PM10 on daily death varied by SEP[144], a result consistent with other findings[145, 146]. There is also a small, but developing literature on other outcomes such as preterm delivery[147], or birthweight[129].

B.1.4.iv. Age

The elderly represent a particularly susceptible population, and the current growth in the number and proportion of older adults is unprecedented in the history of the United States. By 2030, the proportion of the U.S. population aged 65 and older will double to about 71 million older adults, or one in every five Americans. Cognitive decline in the elderly is also a growing burden. Recent estimates are that 6.4% of people over age 60 years in North America have dementia, and the number with dementia is expected to almost triple by the year 2040. Importantly, small changes in cognition are strong predictors of eventual development of dementia. Previous studies have also reported that heterogeneity in cognition is especially pronounced in the elderly compared to younger adults.[115] This raises the question of whether there are environmental causes of this heterogeneity. Air pollution exposure has been linked to increased inflammation in the brain,[148] and brain inflammation has been implicated in the development of Alzheimer's disease.[149]

The elderly are also at increased risk of cardiovascular disease, and air pollution has been shown to have differential effects on the elderly for a number of cardiovascular endpoints, including mortality[23, 150-152].

Children are also generally considered to be a subgroup at increased risk of toxicant-associated harm. Their greater vulnerability can be attributed to age-related differences in metabolism (e.g., greater absorption of toxicants from the gastrointestinal tract, reduced excretion, immaturity of detoxification pathways), developmental stage (e.g., ongoing development and organization of organs such as the central nervous system), and behavior (e.g., greater hand-to-mouth activity, greater relative dietary and respiratory intake of toxicants[153].

For example, children are more vulnerable with respect to air pollution because their lungs are only partially developed at birth and are not fully functional until about 6–8 years of age[154]. Infants are born with only one-tenth the number of alveoli of adults and an under-developed epithelium. Indeed, alveolar development begins only in the late 3d trimester[155]. There are approximately 24 million alveoli present at birth, which grows 10-fold to 257 million between birth and age 4[156]. This is postnatal development pattern is not merely a theoretical concern for air pollutants. Fanucchi and coworkers[157] exposed infant monkeys to 5 months of episodic exposure to 0.5 ppm of ozone. Compared to controls, O3-exposed animals had fewer airway generations, hyperplastic bronchiolar epithelium, and altered smooth muscle in terminal and respiratory bronchioles.

B.1.5. Other Environmental Agents

Evidence that co-exposure to other neurotoxicants (e.g., manganese, arsenic) increases the likelihood of lead-associated impairments is limited and comes mostly from animal models [158-161]. In humans, two studies[162, 163] reported that the slope of the dose-effect relationship between blood lead level and neurodevelopment in infants is steeper among those with higher blood manganese levels. In NHANES (1999-2006), adults whose blood levels of cadmium and lead were both in the highest quartiles had greater odds of albuminuria and reduced GFR[164].

B.2. Sources of Susceptibility (Differential Dose/Exposure)

The sections above describe how exposures to lead and air pollution may interact with other factors conveying risk, such as stress, SEP, genetics, and pre-existing disease. But in addition to interacting with such other risk factors, lead and air pollution often covary with them, resulting in a further skewness of the risk distribution.

Substantial socioeconomic and ethnic disparities in blood lead levels have been documented by the NHANES surveys since the 1980's[165] [166]. In recent decades blood lead levels have declined across all subgroups of the U.S. population and the magnitude of the subgroups disparities has diminished. Nevertheless, in the NHANES 1999-2002, the percentage of individuals with a level exceeding 10 µg/dL was greater among non-Hispanic blacks (1.4%) and Mexican-Americans (1.5%) than among non-Hispanic whites (0.5%). In analyses of NHANES data 1999- 2004, among children 1-5 years of age, the frequencies of blood lead levels greater than 10 µg/dL, by race/ethnicity, were: non-Hispanic black 3.4%, Mexican-American 1.2%, non-Hispanic white 1.2%. The frequency was greater among poorer children (poverty-to-income ratio ≤1.3)(1.8% vs. 0.8%) and among children on Medicaid (1.9% vs. 1.1%)The strongest risk factors for higher blood lead levels were residence in older housing, poverty, age, and being non-Hispanic black[167]

Other subgroups that have been identified as being at risk of greater blood lead levels include children of immigrant parents [168], international adoptees (MMWR, 2000), and refugee children [169]. It is uncertain, however, whether this reflects geographic differences in exposure opportunities (such as lead in folk and Ayurvedic medicines), genetic susceptibilities, or the prevalence of toxicokinetic modifiers.

Several genetic variants or polymorphisms thought to affect lead metabolism have been evaluated in terms of their influence on lead biomarker levels or their influence on lead-associated health effects. These include amino levulinic acid dehydratase (ALAD), the dopamine receptor D4, the HFE protein (hemochromatosis gene), apolipoprotein E (APoE), and peptide transporter 2. Several studies have compared lead biomarkers in individuals with the two co-dominant ALAD alleles (ALAD-1 and ALAD-2). There are substantial inconsistencies across studies, although some have reported that carriers of the ALAD-2 allele (1-2 or 2-2) have greater blood or cortical bone lead levels [51, 170-172]. One study of adults suggested that the plasma/whole blood lead ratio is greater in ALAD-2 carriers [173]. In a sample of Hispanic children, those homozygous for the peptide transporter 2 polymorphism had higher blood lead levels than those without or heterozygous for this polymorphism [172]. Another study showed that children who were carriers of the variant hemochromatosis or transferrin gene had significantly higher blood lead levels than wild-type children, and children carrying both variants were more likely to have a blood lead level >10 µg/dL[174] . Adult workers with the vitamin D B allele had significantly higher patella lead levels [175].

Systematic data are not available on the distribution of genetic variants of interest in relation to factors such as ethnicity and other demographic characteristics, and recent work

demonstrating the generally greater genetic variability within ethnic groups than between them suggests that this might not be a fruitful avenue of investigation in explicating differences between groups in toxicant-associated risks [176]. However, the prevalence of some variants do appear to vary substantially by geographic region. For example, ALAD-2 carrier status has a prevalence of 3% in Indian workers [170], 8% in Chinese children[177], and 16% in US men[50] . In another study, the frequencies of ALAD-2 allele were comparable in Asian and Caucasian samples but absent in African samples [178].

Based on epidemiologic associations, a variety of dietary variables have been proposed as modifiers of lead absorption or toxicity, most notably iron and calcium[179]. In the Normative Aging Study cohort of adult men, reduced dietary vitamin D was associated with increased bone lead levels, while decreased dietary vitamin C and iron were associated with increased blood lead level[180]. A study of children in the Philippines showed that higher folate and iron levels mitigated the inverse association between blood lead level and cognition [181].

B.2.1.i. Air pollution

There is strong evidence to support the view that socioeconomic position is strongly associated with increased exposure to a variety of air pollutants. This in itself, helps explain the differential distribution of lung related diseases in populations. For example, a study by Mohai [182]and colleagues found that Blacks and respondents at lower educational levels and, to a lesser degree, lower income levels were significantly more likely to live within a mile of a polluting facility. Similarly, traffic air pollution has been shown to be higher in persons of lower SEP[129, 183, 184]. In addition, exposure to pollution from concentrated animal feed lots varies by SEP and race[185]. And Woodruff and coworkers showed that ambient air pollution concentrations in general were higher in neighborhoods of pregnant women at higher risk for adverse pregnancy outcomes because of lower social conditions[186]. In one of the few studies to look at both indoor and outdoor air pollution concentrations, Baxter[187] found evidence that persons living in disadvantaged communities had higher exposure to both. They also showed that lower socioeconomic status not only was associated with greater exposure outside the home, but that factors associated with poverty such as cooking time, gas stove usage, occupant density, and humidifiers were contributors to higher indoor concentrations of PM2.5 and NO2. Using such covariation of exposures with susceptibility factors, a recent risk assessment showed a considerable disparity in the impact of air pollution on mortality in Mexico[188], and, relevant to cumulative risk assessment, showed the same disparity gradient for poor water quality and cooking fuel use.

B.3. Cumulative Exposure

The phrase cumulative exposure has been used to described two separate phenomena: a) long term sequelae of continuing exposure to a substance, and b) the cumulative burden resulting from exposure to many stressors. That cumulative burden may be enhanced by interactions among the different stressors, as described above. Prior research in the Normative Aging Study and other cohorts has demonstrated a link between cumulative lead exposure (as measured by bone lead) and heart rate variability,[83] hypertension,[189, 190] ischemic heart disease[191, 192] and death[193]. Several frameworks have been established to conceptualize cumulative exposure to all stressors over the life course. These include Geronimus's concept of weathering[17, 18] and more recently, the concept of allostatic load[13, 14]. Both approaches attempt to capture the cumulative wear and tear that occurs as a result of long-term exposure to multiple stressors as reflected in increased vulnerability and decreased reserve capacity. In environmental science, Zartarian summarizes various efforts undertaken by the EPA to assess cumulative exposure in communities including the "Cumulative Communities Research Program" within the National Exposure Research Laboratory[194] Additional tools have been developed in "life course epidemiology", although a great deal more work is needed to further refine these ideas. As Menzie et al argue, a key requirement for thinking about cumulative exposures is the development of clear conceptual frameworks[195]. Complications arise when there are interactions among multiple exposures, or when there are latencies in the onset of biological effect.

Lead exposure shows strong socio-economic gradients, which are in turn associated with higher stress, and is higher in black Americans, who have a higher prevalence of renal disease. Hence, if, as suggested above, lead also has a multiplicative interaction with those risk factors, the distribution of lead associated risks, or of cumulative risks, can become highly skewed. Similarly, if as noted above, air pollution exposure is more common in populations with higher rates of diabetes, hypertension and obesity, and those conditions modify the effects of exposures, cumulative burdens may become large.

B.4. Markers of Cumulative Exposure

Assessing cumulative burden from multiple stressors is difficult, and consideration of this issue could be advanced if a biomarker of cumulative burden were available. Telomeres are regions of non-coding DNA at the ends of chromosomes that protect against structural degradation, inappropriate recombination, and end-to-end fusion of chromosomes.[196, 197]

Telomere length declines with each successive cell division and thus serve as a measure of biological aging.[198] In addition to aging in general, shorter telomeres are associated with various chronic diseases, including diabetes,[199] hypertension,[199-202] atherosclerosis,[203] coronary artery disease,[204, 205] heart failure[206] and increased cardiovascular risk.[207, 208] Evidence from in vitro[209-211] and human studies [199, 210] suggests that oxidative stress and inflammation accelerate telomere shortening. Reduced blood DNA telomere length has been also related to cumulative long-life exposure to tobacco smoking.[212, 213]Recently, exposure to traffic pollution has been associated with reduced telomere length[214]. It is too early to tell if this could be a useful biomarker either for susceptibility or cumulative burden, but the possibility deserves greater attention.

C. Methodological considerations

This next section addresses a partial set of methodological issues that might arise if the issues raised above were to be taken into greater account. There are a number of other issues we do not address here having to do for example with problems in the measurement of lead dose. A rich literature on measurement issues in lead research exists [139, 215-218] Instead, we focus here in issues related to the further elucidation of issues related to differential vulnerability and susceptibility.

C.1. General overview of methodological issues.

C.1.1. Methods for exploring interactions

A key issue in modeling interactions between environmental exposures and measures of susceptibility, whether social, genetic, or due to disease status, is that the variables often exist on multiple levels, with potentially different meanings. It is clear that in addition to individual level SEP, contextual aspects of place affect people's health, and potentially, their response to exposure. Hence, a well off person residing in a geographic area that is predominantly poor will be exposed to the same excess of fast food, deficits of fresh fruits and vegetables, safe recreational areas and drug stores, as the poorer residents. This may affect their health, and their response to environmental contaminants. The presence of environmental contaminants may similarly, vary geographically, and this spatial patterning may effect exposure. For example, within city variation in airborne particles is predominantly driven by traffic particles, while cross-city, or cross time variations may be more due to secondary particles. These are not necessarily equally toxic. Similarly, soil lead declines with distance from a smelter, but some soil lead is from past emissions of leaded gasoline, or lead paint residues. These may vary on

different spatial scales, and have different bioavailability. Hence statistical modeling needs to recognize the presence of different scales of variation, both spatial and temporal.

C.1.1.i. Hierarchical Mixed Models

One approach that lends itself to examining these issues is the Hierarchical Mixed model. Where appropriate, such as where multiple measurements of each outcome are available for a subject (or for an area), it allows us to identify whether there is variation in baseline health across subjects (via the random intercepts), whether there is variability in response to exposure (via the random slopes), and to examine what individual level or area level, or temporal level factors modify baseline levels or responses. That is, if some subjects have higher blood pressures than average, and others lower than average, the repeated measurements of the first subject will all tend to be higher (or lower) than predicted and hence the residuals (measured – predicted) will all tend to have one sign, rather than varying randomly about zero. We may also have correlations over space. Suppose the jth observation in subject i and subject i´ depends on the spatial distance between them for example. The spatial patterning of residences by social status, ethnicity, etc. may induce such a structure. Again, there may be period effects or trends which may make observations in the same year more alike than average. Mixed models can be used for binomial outcomes such as health events, or rates, but it is easiest to focus on continuous outcomes to illustrate the point. That model assumes:

$$Y_{it} = (\beta_0 + u_i) + \text{covariates} + (\beta_1 + v_i) X_{it} + \varepsilon_{it}$$

$$u_i = \gamma_0 + \gamma Z$$

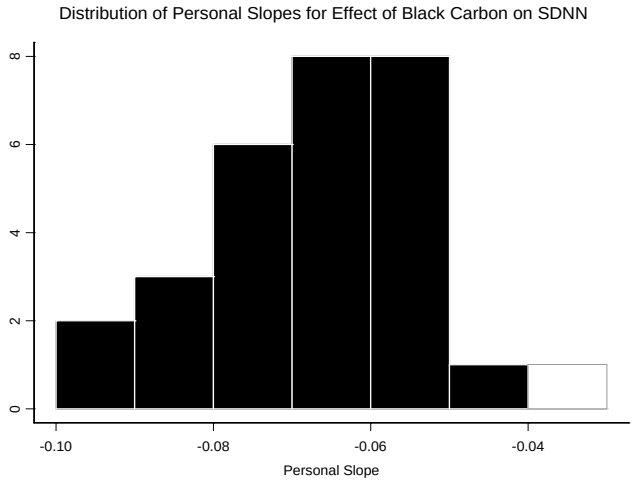
$$v_i = \lambda_0 + \lambda\, Q$$

Where i denotes a level of aggregation: usually subject (but census tract or year are also common), t denotes repeated measures, where present, u_i is the difference from the overall mean in subject i, and v_i is the difference from average response to pollution (X) for subject i, Z and Q are variables that explain some of the susceptibility. If i represents subject, for example, than the variables in Z and Q may be subject level, may be neighborhood level (for example median household income in a Census block group), or may represent periods. Similarly, we could decompose, where appropriate X. For example, we might let

$$X_{it} = Z_t + (X_{it} - \ddot{\ddot{X}}_t) + (\ddot{\ddot{X}}_t - Z_t)$$

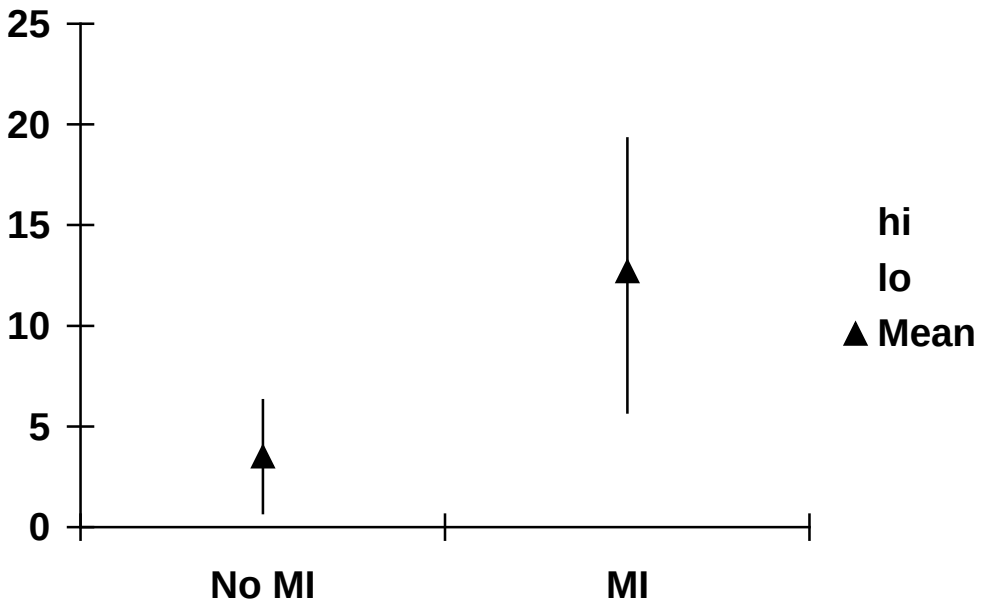
Where Z_t is the air pollution reading from a central monitor, $\ddot{\ddot{X}}_t$ is the average of the personal exposures of all the subjects on day t, and X_{it} is the exposure of the ith subject on day t. In this framework we replace the single coefficient (β_1 above) with 3 coefficients—one representing the effect of area level pollution, one the effect of the difference of individual level exposure from the

mean exposure of the population on that day, and one the difference of population mean exposure from the monitored exposure. The latter is usually classical measurement error, but the first two can legitimately be different and tell different stories about exposure at different levels.



For example, the above figure, taken from a repeated measures study of air pollution and heart rate variability in an elderly panel in Boston, shows the distribution of the random slopes (vi), which is clearly skewed. This is explained by the next figure, showing that a past myocardial infarction modified the association. The modifiers in multilevel modeling can be area based as well as based on individual characteristics. For example, Zeka et al showed that birth weight was influenced by SEP, by traffic exposure, and by interactions between the two[129]. Another example is Glass et al. [102] who used multilevel models to examine how the toxicity of lead is exacerbated by living in neighborhoods high in psychosocial hazards.

Percent Decrease in SDNN for IQR Change In BC



C.1.2. Methods for addressing risk chaining

While standard regression methods are widely used to investigate both main and interaction effects, such models rely on the standard assumptions that go with such models. Among them, the assumption that each separate predictor variable is "distinct" in the sense of having the capacity to arise (or be experimentally set) without regard to the other variables entered. As described in the classic paper by Gordon [219], this property of distinctiveness is a matter of the larger theory guiding model building, and not simply a property of the data or study design. Risk chaining refers to the connectedness of multiple risk factors in time and space as a function of the arrangements of these variables in the world. For example, if a factory releases multiple pollutants into the air, water and land, measurements of each individual

pollutant are not distinct from one another (due to arising from a common source). If the correlation among those exposures is high enough, it will not be possible to treat them all as independent variables. In such cases, new metrics that combine multiple exposures (for say exposures that operate through a common biological pathway) can be generated. Alternatively, various clustering approaches can be used to identify distinct groupings of exposures, treating them either as latent or manifest constructs (see [195]). Beyond regression approaches, these model constraints can be relaxed and the data explored for both clustering and interactions with fewer assumptions using decision tree and machine learning approaches[220], including kernal machines[221]. Finally, new methods drawn from engineering and computer science in systems dynamics offer ways of analyzing complex chains (or disease production algorithms) that can not be seen given the assumptions imposed by standard regression models [45, 222, 223].

C.2. Alternative approaches to quantification of inequity

C.2.1. Underlying Issues.

Thus far we have demonstrated that there are social, medical, and genetic factors that modify risk, but have provided little quantitative evidence for how important this could be for the equity issues. Doing so will require a measure. There are well-established methods to quantify the inequality of distribution of outcomes that can be brought to bear on this issue. For example, Levy et al quantified the risk reduction and equity considerations of alternative methods for reducing mortality risk associated with coal burning power plants[224, 225]. He showed alternative control strategies on two dimensions: efficiency (essentially risk divided by cost) and equity. Equity was quantified using the Atkinson's Index, a measure of the inequality in the distribution of risk. This presupposes no judgment about what an acceptable inequality is, it merely quantifies the level. By plotting multiple alternatives policies on the two dimensional scale of efficiency and equity this approach provides decision makers with the necessary information to make decisions based on their judgments of appropriate societal tradeoffs. Moreover, by making the tradeoffs explicit rather than implicit, it encourages the appropriate public discussion during rulemaking that will allow decisions to reflect societal values.

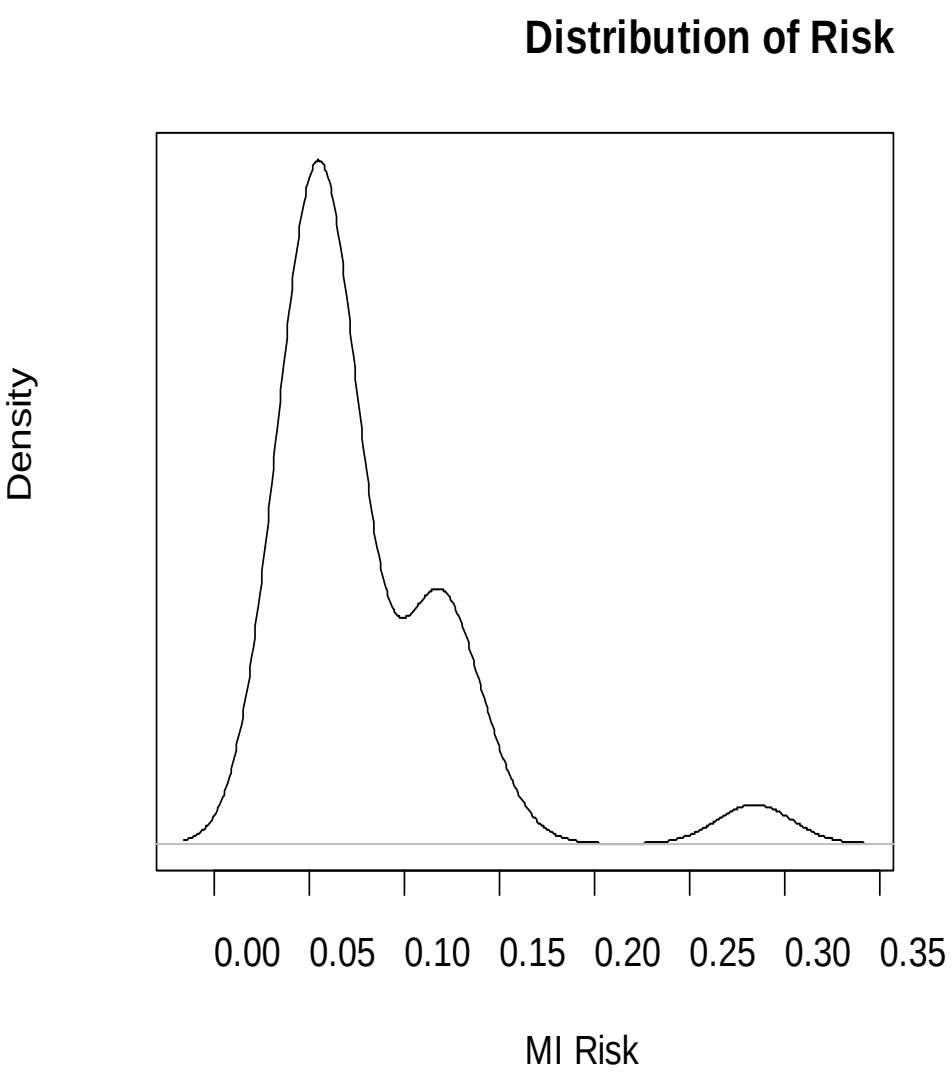
Another approach was taken by Su and coworkers, who adapted the "concentration index" from social science as a measure of inequality[226]. Using small geographic scale units they quantified the inequality in the distribution of risk from three pollutants, aggregated either on a multiplicative or additive scale, and applied it to a real world scenario in Los Angeles. While their metric was not risk per se, but the ratio of risk to, for example, an ambient standard, the approach could be adopted to an absolute risk scale, and clearly demonstrates the ability to

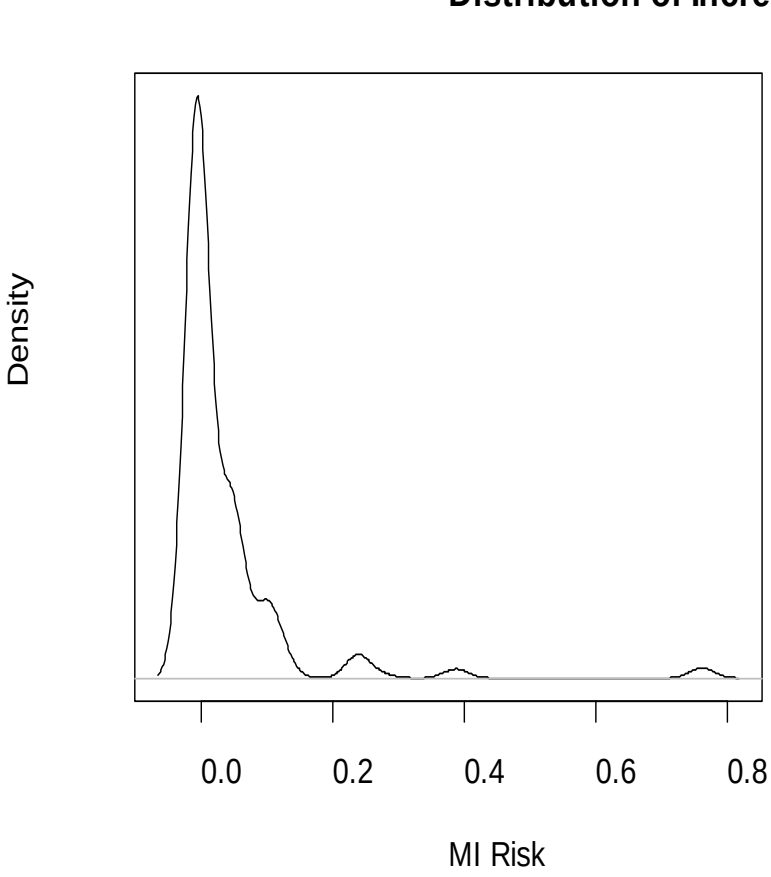
examine distributional issues in the context of assessing cumulative exposure in the sense of multiple exposures.

Other dimensions may be necessary as well. A quantification of the inequity in the distribution of risks among *individuals* may be insufficient if the risks are also inequitably distributed among *groups* those individuals belong to. These groupings could be geographic, as in the example in A.6, race-ethnicity, persons with special diets, etc.

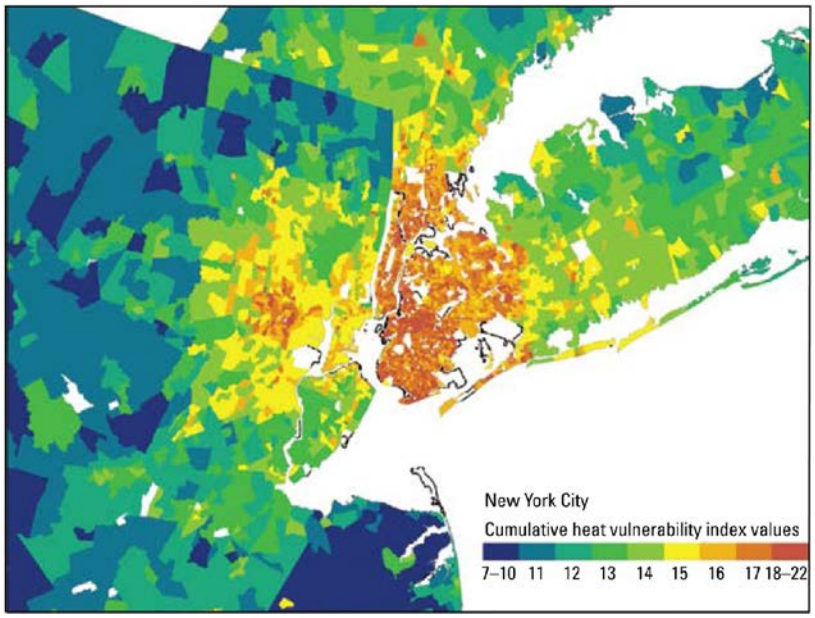
C.2.2. Approaches and examples

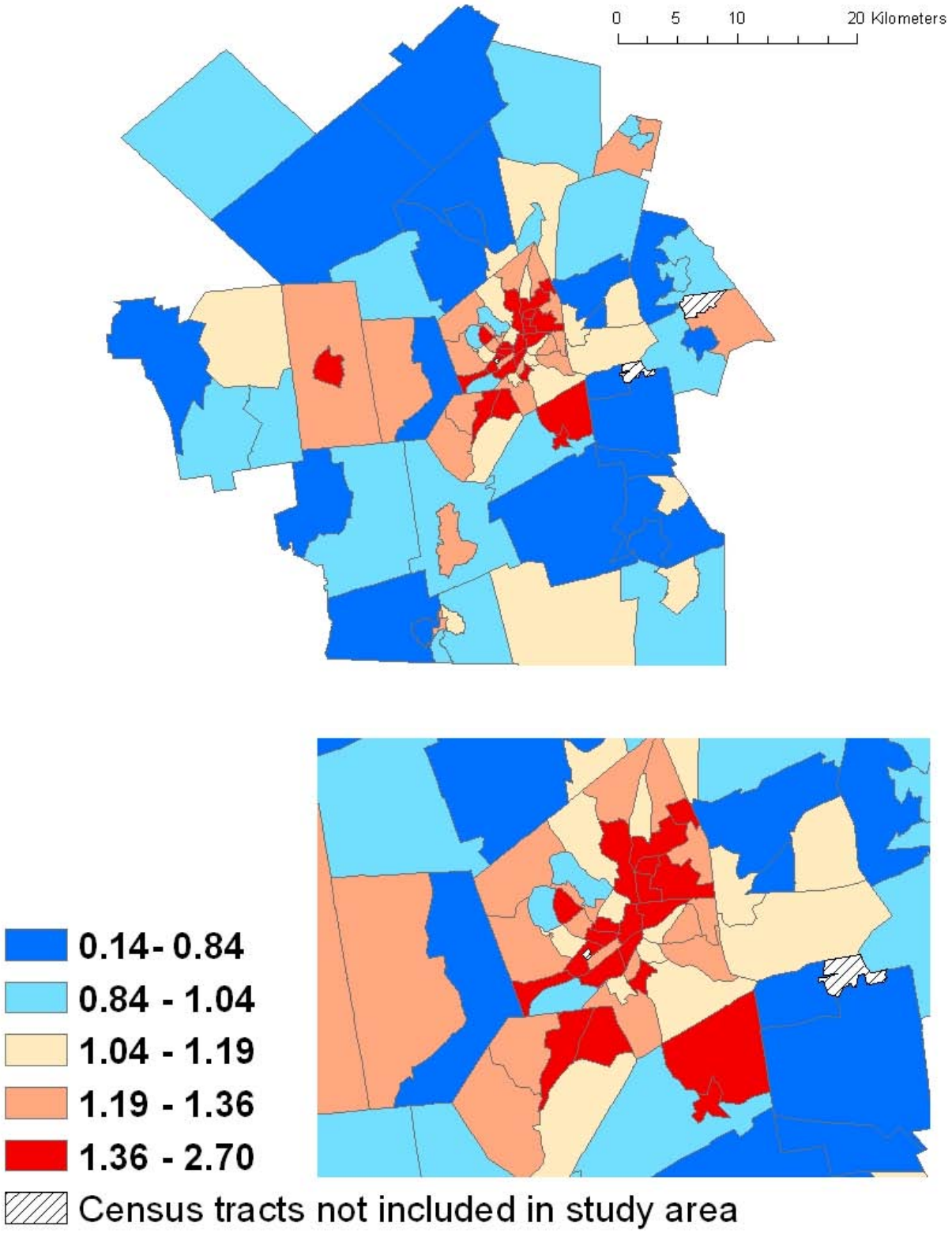
To illustrate this further, we now provide some examples. First, consider a hypothetical, but reasonable scenario, based on the literature. The underlying risk of having a heart attack varies by income, and we have taken estimates from Banks et al for this[227]. From the same source, we obtained estimates of how diabetes prevalence varies by income. Finally, from a recent paper from Denmark[228], we take the relative risk for heart attack given diabetes to be 2.4. Given that, we can simulate the distribution of the probability of a heart attack in a hypothetical population of one million. If we then further assume that diabetes doubles the particle associated risk of having a heart attack (plausible given the interactions between diabetes and at least short term effects of particles), and that 20% of the population have genetic factors, independent of diabetes, that also double the particle associated risk, and finally, that the risk for a 10 $\mu g/m^3$ increase in annual average PM2.5 is 1.2, we can then examine the distribution of incremental risk. Figure A, below, shows the baseline risk of heart attack in the population, under the simulated scenario. Figure B shows the distribution of incremental risk. Note that while the average incremental risk is only a few per hundred (still vast compared to the risk that EPA tolerates for cancer), for a small portion of the population the incremental risk is about 0.7. Are we really happy to impose a 70% risk of having a heart attack on a subset of the population?



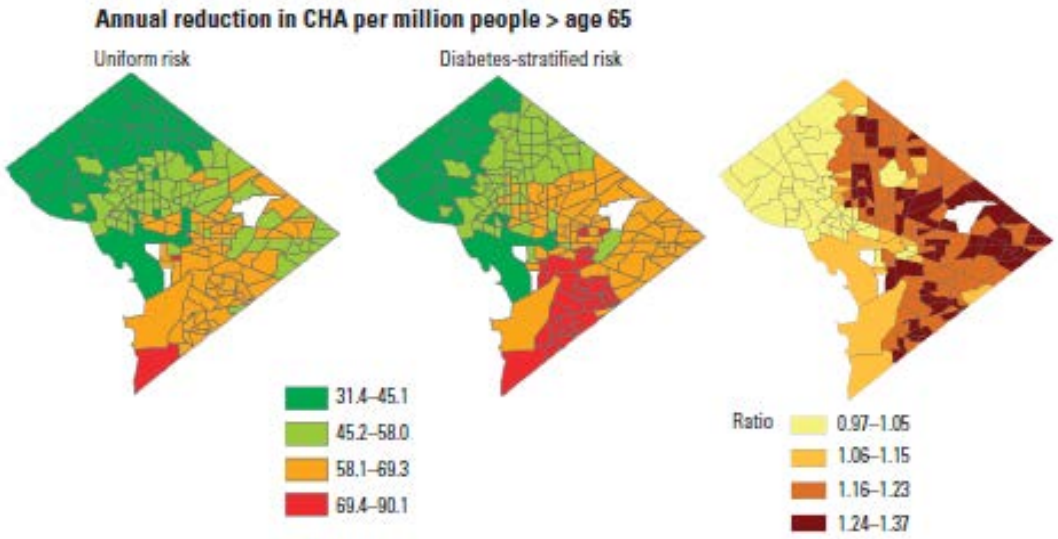


So far, this just examines the distributional effects of modification by medical and genetic conditions, but geographic concentration of risk is also a key concern. Two figures illustrate how this can affect equity concerns. The first, from Reid et al, examined the geographic distribution of factors shown to modify the effects of high temperatures on mortality, to produce a map of temperature vulnerability on a census tract scale. It demonstrates geographic vulnerability varies substantially within a small area. Such neighborhood scales variations in vulnerability cause particular equity concerns. A similar pattern is illustrated in Worcester County, MA, where Tonne and coworkers found a factor of three range of variation in heart attack risk by census tract, again with clustering of the tracts at highest risk. The figure shows the incidence rate of MI in each census tract for the county as a whole, and below that, for the central area, relative to the community average rate, after adjustment for age, race, and sex.





Finally, Levy and coworkers examined the geographic distribution of risk of emissions from coal burning power plants in Washington DC assuming uniform risk, and then taking into account modification by income or diabetes[229]. The figure below shows the annual reduction in cardiovascular hospital admissions as a rate per million, assuming uniform risk in the population and stratifying by diabetes, and taking into account the differential numbers of diabetics in different census tracts in Washington. The last figure is the ratio of the two risks. This indicates that taking into account the differential spatial patterning of diabetes, and the differential vulnerability we find substantial inequity by geography in the particle associated risk.



C.2.3. Transgenerational Risk

In a follow-up study of women exposed to dioxin in Seveso, Italy, Baccarelli and coworkers reported neonatal blood TSH concentrations and the risk of elevated TSH showed graded responses with distance from the site of the accident, even in births many years after the exposure occurred[230]. To even investigate this hypothesis required a long term follow-up of a cohort of children born to residents of Seveso, after the accident. This need for long term follow-up after exposure has ceased, and possibly transgenerational follow-up represents a challenge for epidemiologic studies.

D. Conclusions and recommendations

If continued progress is to be made in explicating these complex phenomena, future studies of toxicant exposure-risk relationships must invest the resources necessary to measure individual and contextual factors that might modify these relationships. Risk assessments need to move from an RfD approach to estimating attributable risk and the distribution of that attributable risk, in order to allow the assessment of inequity and to allow risk mangers to have quantitative measures of both overall risk and the distributional aspects to use to in reaching judgments. Environmental rulemakings are often supposed to provide protection to the population subgroup most vulnerable to a toxicant (and thus, by extension, be protective for all other subgroups). The reality is that in most cases we do not know which subgroups are the most vulnerable or, if we do, subgroup is defined very broadly, such as the fetus in the case of methylmercury, or young children in the case of lead. Based on the evidence we have marshaled, however, it is likely that not all fetuses are equally sensitive to methylmercury or that all young children are equally sensitive to lead. If the perspective that we are advocating were incorporated into epidemiology studies and subsequent risk assessments, the definition of the most vulnerable subgroup would therefore become much more specific and, therefore, much more useful in terms of targeting preventive strategies for reducing toxicant-associated morbidities. But first, more studies must be conducted to provide the necessary data on factors that modify vulnerability.

D.1. Unpacking the risk assessment black-box

In most risk assessments conducted for the purpose of identifying an acceptable level of exposure, various uncertainty factors (UF) are applied to effect levels derived from empirical studies. These are necessary to address inter-species extrapolation (if the critical effect level is based on a nonhuman model), human variability in vulnerability (which is usually interpreted as pertaining to toxicokinetic/toxicodynamic variability), absence of data on long-term sequela, or other gaps in the available database. The specific value assumed for an UF varies, but often a generic default value of 10 is used. Most models regard this variability as stochastic, and not explainable given the data. A main recommendation implied by our paper is the need to move to modeling those sources of variability using data. What we have proposed in this paper is a strategy for understanding, at a more precise quantitative level, human (or inter-individual) variability in vulnerability. In essence, we have begun to address how the workings of the “black box” that represents this variability can be understood. We have shown that considerable

progress has been made in understanding the myriad factors that influence the magnitude of an individual's external dose to a toxicant, the association between the external dose and the internal (or absorbed) dose (i.e., toxicokinetics), and the biological response at the critical target organs to the internal dose (i.e., toxicodynamics). That is, epidemiologic studies designed to identify susceptibility often do so—the goal is quite achievable. In the short run, EPA should incorporate those findings into quantitative risk assessment now while encouraging the research that will allow the approach to be extended to more pollutants in the future. Moreover, we have shown that the distribution of these important factors is not random within the population. Rather, they co-occur in patterns that result in some subgroups of the population bearing a disproportionate burden of the health morbidities that can be attributed to toxicants.

D.2. Acknowledging the need for social justice in risk assessment

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 which we have more mature tools of investigation. We cannot, however, escape that fact that the clustering of high and low exposure regimes in particular environments also represents social, political and economic processes at work [231]. While less familiar and harder to study, these "upstream" factors are important drivers of disparities in health outcomes. 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 CFCs is an important historical example. But beyond the caliber of the science, we recognize a moral imperative to augment risk assessment approaches in the pursuit of greater social justice [232, 233]. 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 [234]. But it also means treating inequities in the delivery of exposure as a fundamental problem that requires explanation and action.

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