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Defining and Intervening on Cumulative Environmental Neurodevelopmental Risks: Introducing a Complex Systems Approach

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Background: The combined effects of multiple environmental toxicants and social stressor exposures are widely recognized as important public health problems contributing to health inequities. However cumulative environmental health risks and impacts have received little attention from U.S. policy makers at state and federal levels to develop comprehensive strategies to reduce these exposures, mitigate cumulative risks, and prevent harm. An area for which the inherent limitations of current approaches to cumulative environmental health risks are well illustrated is children's neurodevelopment, which exhibits dynamic complexity of multiple interdependent and causally linked factors and intergenerational effects.

Objectives: We delineate how a complex systems approach, specifically system dynamics, can address shortcomings in environmental health risk assessment regarding exposures to multiple chemical and nonchemical stressors and reshape associated public policies.

Discussion: Systems modeling assists in the goal of solving problems by improving the "mental models" we use to make decisions, including regulatory and policy decisions. In the context of disparities in children's cumulative exposure to neurodevelopmental stressors, we describe potential policy insights about the structure and behavior of the system and the types of system dynamics modeling that would be appropriate, from visual depiction (i.e., informal maps) to formal quantitative simulation models. A systems dynamics framework provides not only a language but also a set of methodological tools that can more easily operationalize existing multidisciplinary scientific evidence and conceptual frameworks on cumulative risks. Thus, we can arrive at more accurate diagnostic tools for children's' environmental health inequities that take into consideration the broader social and economic environment in which children live, grow, play, and learn. https://doi.org/10.1289/EHP7333

Introduction

The combined effects of multiple environmental toxicants and social stressors are widely recognized as important public health problems, contributing to health inequities and potentially inadequate determinations of effect levels (Clougherty et al. 2014; Hicken et al. 2012; Morello-Frosch et al. 2011). Calls for federal and state environmental agencies to consider such cumulative risks in regulatory and policy decisions have been made by community advocates, stakeholders, and independent advisory bodies since the 1980s (NRC 1993; National Environmental Justice Advisory Council 2004; NRC 2008, 2009; Browner and Hansen 1997; U.S. EPA 1986), and significant research investments have been made to develop methods to assess the combined effects of multiple chemical and nonchemical exposures (National Institute of Environmental Health Sciences 2018; Payne-Sturges et al. 2018; Macdonell et al. 2013; Huang et al. 2018). However cumulative environmental health risks and impacts have received little attention from policy makers at state and federal levels in terms of developing comprehensive strategies to reduce these exposures, mitigate cumulative risks, and prevent harm. In fact, there is resistance to abandoning risk management decisions based on evaluation of chemicals in isolation from other stressors and risk modifiers, not because of the lack of evidence of such joint effects (Clougherty et al. 2014; Glass et al. 2009; Chari et al. 2012; Wright 2009; Appleton et al. 2016; Lewis et al. 2011), but rather because of the inability or unwillingness to formulate an approach that is necessarily multidisciplinary and captures the dynamic complexity to inform policy analysis (Payne-Sturges et al. 2018; Knudsen 2017; Harrison 2017). Thus, scientists are reduced to mapping the spatial concentration of chemical and nonchemical environmental stressors and conducting surveillance of chemical of exposures (e.g., through use of U.S. Environmental Protection Agency's EJ Screen and C-FERST, CalEnviro Screen, and NHANES biomonitoring) (Office of Environmental Health Hazard Assessment 2019; Zartarian and Schultz 2010; U.S. EPA 2019; Centers for Disease Control and Prevention 2018) and tinkering with traditional risk assessment (U.S. EPA 2003; Sexton 2015), which simply continues to confirm what we already know: *a*) near ubiquitous exposures to chemical mixtures even before birth; *b*) disproportionate exposures among low income and racial/ethnic minority communities; and *c*) persistent disparities in health. Where do we go from here? We recommend that a paradigm shift is essential that reimagines cumulative exposures and health effects research as well as policy and practice to move beyond the status quo. This is the context in which approaches like systems science, specifically system dynamics (SD), may be a more robust conceptual framework for devising policy solutions to address cumulative effects of multiple chemical, physical, biological, and social environmental stressors.

Research on children's neurodevelopment demonstrates the inherent limitations of current scientific approaches to cumulative environmental health risks. For example, children are often exposed prenatally and in early childhood to multiple chemicals and stressors that can adversely affect their cognitive abilities, academic performance, and consequent educational trajectories, adult health, wealth, and social status (Halle et al. 2009; Suor et al. 2015; Gee et al. 2012; Halfon et al. 2010; Evans and Kim

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2010; Morello-Frosch and Shenassa 2006; Evans and English 2002; Gray et al. 2013; Landrigan et al. 2010; Tulve et al. 2016; Trentacosta et al. 2016). The extent and breadth of such exposures are influenced by race/ethnicity and socioeconomic status (SES) that may contribute to pronounced health disparities for multiple outcomes, including school readiness and cognitive delay (Hackman and Farah 2009; Hillemeier et al. 2009; Brooks-Gunn and Duncan 1997; Entwisle 1999; Hair et al. 2006; Noble et al. 2005a; Burkam and Lee 2002). For example, concomitant exposures to maternal material hardship (e.g., unmet basic needs) and poor diet can heighten the toxic effects of air pollutant exposures on children's cognitive functioning (Rauh et al. 2004; Guxens et al. 2012). Although there is renewed attention among leading scientific, medical, and child health experts to improve children's overall environment to support healthy brain development (Bennett et al. 2016), current environmental policies still regulate only single contaminant /pollutant exposure [one slight exception is the assessment of aggregate pesticide exposures under the Food Quality Protection Act (FQPA) of 1996 (U.S. Congress 1996) for agricultural pesticide use (although FQPA has limitations, which are discussed later)] determined in the absence of any social/physical context, likely underestimating true health risks. Further, current risk assessment practice often fails to substantively account for the underlying dynamic complexity and the interdependent influence of sociostructural and interpersonal factors on neurodevelopmental risks over time.

The purpose of this article is to delineate how a complex systems approach can address such shortcomings in environmental health risk assessments and reshape decisions related to associated public policies. The concept of cumulative risks/impacts represents the synergistic health effects of the accumulation of multiple harmful environmental exposures. Therefore, we use SD, a systems science method that posits that the feedback structure of a system gives rise to its behavior (e.g., accumulations) to illustrate how insights can be gained, using combined effects of environmental chemical contaminants and social stressors on disparities in children's neurodevelopment as an illustrative example. Our objectives are to:

1. Provide a brief overview of the extant literature on children's multiple social and environmental neurodevelopmental risks.
2. Compare and contrast current approaches with a complex systems paradigm for evaluating factors that affect children's neurodevelopment.
3. Present a proof-of-concept SD model and describe how SD modeling can support the design of more robust effective policy responses to cumulative environmental risks and subsequent health impacts.

Children's Multiple Social and Environmental Neurodevelopmental Risks

Neurodevelopmental Disorders and Disability Trends over Time

Developmental disabilities affect 1 in 6 children in the United States, and the rate has increased over time (Zablotsky et al. 2019); these conditions include learning disabilities, sensory deficits, developmental delays, cerebral palsy, autism, and attention deficit and hyperactivity disorders (ADHD) (Zablotsky et al. 2019). Among these conditions, ADHD and learning disabilities have the greatest prevalence overall. Higher rates of developmental disabilities among children were associated with Medicaid insurance coverage (22%), family incomes below 200% poverty level (20%), low maternal education (17%), and male sex (22%) (Zablotsky et al. 2019). These measures, however, do not capture subclinical decrements in brain function that may be even more common (Grandjean and Landrigan 2014). Such disabilities can increase the cost for education and medical care, diminish quality of life, and reduce academic achievement, with profound consequences for societal welfare and productivity (Gould 2009; Grandjean and Landrigan 2014; Calderón-Garcidueñas et al. 2015; Bellanger et al. 2015; Lanphear 2015; McCann 2014). The estimated annual cost (medical care, lost economic productivity) of environmentally mediated neurodevelopmental disorders in U.S. children is $74.3 billion in 2008 dollars (Trasande and Liu 2011).

Social and Nonchemical Environmental Factors

Prenatal and early-life exposures to family and neighborhood disadvantage, physical stressors (e.g., substandard housing, crowding, and noise) and psychosocial stressors (e.g., family turmoil, violence, poverty, and household food insecurity) influence IQ (IOM 2000), language and cognitive development (Alaimo et al. 2001; Suor et al. 2015; Zaslow et al. 2009), socioemotional development (Evans and English 2002; Kleinman et al. 1998), and academic achievement (Alaimo et al. 2001; Lovasi et al. 2014). Childhood SES is an important predictor of neurocognitive performance, particularly of language and executive functions (Hackman and Farah 2009; Noble et al. 2005a, 2005b, 2012, 2015; Kishiyama et al. 2009; Halle et al. 2009). Psychosocial stress affects cognitive performance and prefrontal cortex and hippocampal regions of the brain (McEwen 2000a; Lupien 2006; McEwen 2000b). These effects may be mediated by nutrition, parenting styles, cognitive stimulation, chronic stress, and environmental contaminant exposures (Weiss and Bellinger 2006; Wright 2009).

Chemical Stressors

Numerous industrial chemicals [e.g., lead (Pb), organophosphate pesticides, phthalates, bisphenol A (BPA), methylmercury (MeHg), polychlorinated biphenyls (PCBs), arsenic, and toluene] are recognized causes of neurodevelopmental disorders and subclinical brain dysfunction (Grandjean and Landrigan 2006, 2014; Weiss 2000; Bennett et al. 2016). Experts conclude that there is no safe level of Pb exposure for children (Canfield et al. 2003, 2005). Developmental exposures to air pollution, a complex mixture of chemicals and particulate matter [fine particulate matter with aerodynamic diameter $\leqslant$ 2.5 μm ($PM_{2.5}$ particulate matter with aerodynamic diameter $\leqslant$ 10 μm (PM_{10}, polycyclic aromatic hydrocarbons (PAHs), NO_2, black carbon], also appear to contribute to neurodevelopmental disorders in children (Block et al. 2012; Calderón-Garcidueñas et al. 2014, 2015; Guxens and Sunyer 2012; Suades-González et al. 2015; Sunyer 2008; Sunyer et al. 2015; Weiland et al. 2011; Perera et al. 2009, 2014; Clifford et al. 2016; Brockmeyer and D'Angiulli 2016; Xu et al. 2016; Chiu et al. 2016; Payne-Sturges et al. 2019). PAH, a component of $PM_{2.5}$, has been associated with developmental delay (Perera et al. 2006); reduced IQ (Perera et al. 2009); symptoms of anxiety, depression, and inattention (Perera et al. 2012; Edwards et al. 2010); ADHD (Perera et al. 2014); and reduced volume of size of brain regions mediating information and impulse control (Peterson et al. 2015). Roadway proximity (Harris et al. 2015), traffic-related particulate matter (Suglia et al. 2008), and elemental carbon and NO_2 (Sunyer et al. 2015, 2017) were associated with decreased cognitive function. There is increasing evidence that prenatal exposure to traffic-related air pollutants (Volk et al. 2011; Becerra et al. 2013) and $PM_{2.5}$ (Raz et al. 2015) are risk factors for autism spectrum disorder (ASD) (Kalkbrenner et al. 2015).

Combined Neurotoxic Effects of Chemical and Nonchemical Exposures

Well-known disparities in environmental exposures important to children's health track along socioeconomic lines (Adamkiewicz et al. 2011; Brochu et al. 2011; Fann et al. 2011; Gray et al. 2013, 2014; Miranda et al. 2011; Morello-Frosch and Shenassa 2006; Morello-Frosch et al. 2011; Morello-Frosch and Jesdale 2006; Bell and Ebisu 2012; Landrigan et al. 2010; Hicken et al. 2012; Hajat et al. 2013, 2015; Salihu et al. 2012; O'Neill et al. 2007; Mohai et al. 2009; Evans and English 2002; Bullard et al. 2007). In addition, social and neighborhood conditions can modify associations between environmental contaminant exposures and neurodevelopment (Wright 2009). For example, poverty, maternal material hardship, and poor diet have been shown to heighten the toxic effects of air pollutant and other chemical exposures on cognitive functioning of children (Rauh et al. 2004; Guxens et al. 2012; Vishnevetsky et al. 2015; Chari et al. 2012; Hubbs-Tait et al. 2005; Lovasi et al. 2014; Appleton et al. 2016). Additionally, longitudinal studies of Pb exposure show synergistic effects with lower SES, thus demonstrating that higher levels of Pb exposure were associated with worse cognitive outcomes among children in families of low SES (Bellinger et al. 1988, 1990).

Laboratory studies provide additional support for cumulative effects of neurotoxicants and psychosocial stressors that can derive from their impacts on similar biological targets. Animal studies of pre- and postnatal air pollution exposures have demonstrated glial activation, white matter alterations, and negative effects on cognitive functions, particularly among males (Allen et al. 2014a, 2014b). Similarly, stress enhanced proinflammatory cytokine expression and associated neural damage in rats (de Pablos et al. 2006), and long-term exposure to psychosocial hazards was associated with structural and functional brain changes (McEwen 2000b; Sapolsky 1999). Studies of metal exposures (e.g., maternal and/or lifetime Pb exposures or developmental exposures to MeHg) have shown that toxic effects on offspring are enhanced when combined with prenatal stress exposures (e.g., maternal restraint, cold exposure), likely because both risk factors influence the hypothalamic pituitary axis and brain mesolimbic systems (Cory-Slechta et al. 2004, 2010; Virgolini et al. 2008; Weston et al. 2014). These metals are risk factors that co-occur or even occur successively with psychosocial and physical stressors in many human populations.

Environmental Health Disparities and Neurodevelopmental Effects

Children's neurodevelopment and functioning reflects interactions of multiple social determinants, environmental contaminant exposures, and nonchemical stressors at multiple levels (individual, family, community, national). Further, the impact of a neurotoxicant can differ depending on the developmental stage during which exposure occurs ("critical windows of vulnerability") and lead to lifelong consequences (Grandjean and Landrigan 2006). Maturation of the cortex during early development is intensive, and susceptibility to environmental insults is elevated (Grandjean and Landrigan 2006; Rice and Barone 2000). These research findings suggest intervening earlier in life or during childhood could lead to a greater reduction in health risk later in life (Grandjean et al. 2015). The enhanced exposures of racial/ethnic minority and low-income children to chemical and nonchemical neurotoxic environmental stressors reflect past and present economic, political, and regulatory decisions. We theorize that racialized and SES differences in children's exposures to neurotoxicants and related neurodevelopmental and cognitive effects are interdependently related to discriminatory practices/differential treatment in the siting of polluting industrial operations and traffic routes, education, employment, housing, health care, and community economic investments because of race and class, rather than presumed inherent genetic differences based on physical appearance (Link and Phelan 1995; Williams and Collins 2001; Morsey and Rothstein 2015; U.S. Department of Health and Human Services 2019; Weiss and Bellinger 2006; Bailey et al. 2017).

Grounded in social ecological models of health (Bronfenbrenner 1989; Diez-Roux 1998), Figure 1 presents an interdisciplinary conceptual framework for environmental health disparities (Gee and Payne-Sturges 2004) adapted for children's neurodevelopment, extending the traditional source–exposure–disease continuum to include the interaction of structural and community-level psychosocial stressors (e.g., violence, poverty) with environmental exposures to produce health disparities in outcomes such as cognitive delay and ADHD. "The framework shows that race and ethnicity are highly correlated with residential location, with minorities and whites often living segregated from one another" (Gee and Payne-Sturges 2004). Differential residential location as a result of institutionalized discriminatory practices in the housing market leads to differential exposure to health risks (Williams and Collins 2001; Morello-Frosch and Jesdale 2006; Casey et al. 2017; Mehra et al. 2019). Social vulnerability at community levels develops when neighborhood organizations (resources) may not be able to counterbalance zoning policies and tax incentives (structural factors) that encourage the entry of new polluting industries or that discourage the development of positive infrastructure, such as green space and access to healthy foods or quality early childhood education, enhancing community vulnerability/community stress (e.g., lack of economic and social opportunities, unsafe neighborhoods). Social vulnerability would also occur when community organizations are unable to address toxic emissions from past polluting industries. When personal coping cannot counterbalance these external insults, individual stress and illness may result. Additionally, parental stress can affect children and their neurodevelopment (Bolton et al. 2013; Cowell et al. 2015; Evans and English 2002; Fishbein et al. 2009; Johnson et al. 2016). The framework thus illustrates both positive and negative feedback conditions (i.e., neighborhood stressors and pollution both produce adverse health conditions, which could be counterbalanced by health-promoting neighborhood resources). Also, poor individual and community health may further weaken community resources, leading to a vicious cycle, as illustrated by the return loop from health to stress. Thus, there is a complex, dynamic interrelationship of multiple factors across the life course and heterogeneity in the distribution of these factors among children. This conceptual framework also illustrates how such factors may be arranged to create social structures that produce health inequities (Powell 2008; Elder-Vass 2010) and highlights the important contributors to children's environmental exposures and developmental outcomes that are often ignored in environmental health policy making. From our perspective, such a framework represents a significant challenge to traditional statistical methods and risk assessments and to environmental health policy makers at national and state levels to determine how to direct investments, initiatives, and regulatory actions to ultimately achieve the desired public health protections. Although such conceptual models such as those shown in Figure 1 can convey complexity, they can neither capture the magnitude or temporality of the influence of factors nor quantify the potential impacts of preventive interventions.

Current Environmental Policy Approaches for Neurodevelopmental Risks

Since the mid-1970s, quantitative risk assessment, a method to identify and measure the risk that a particular environmental

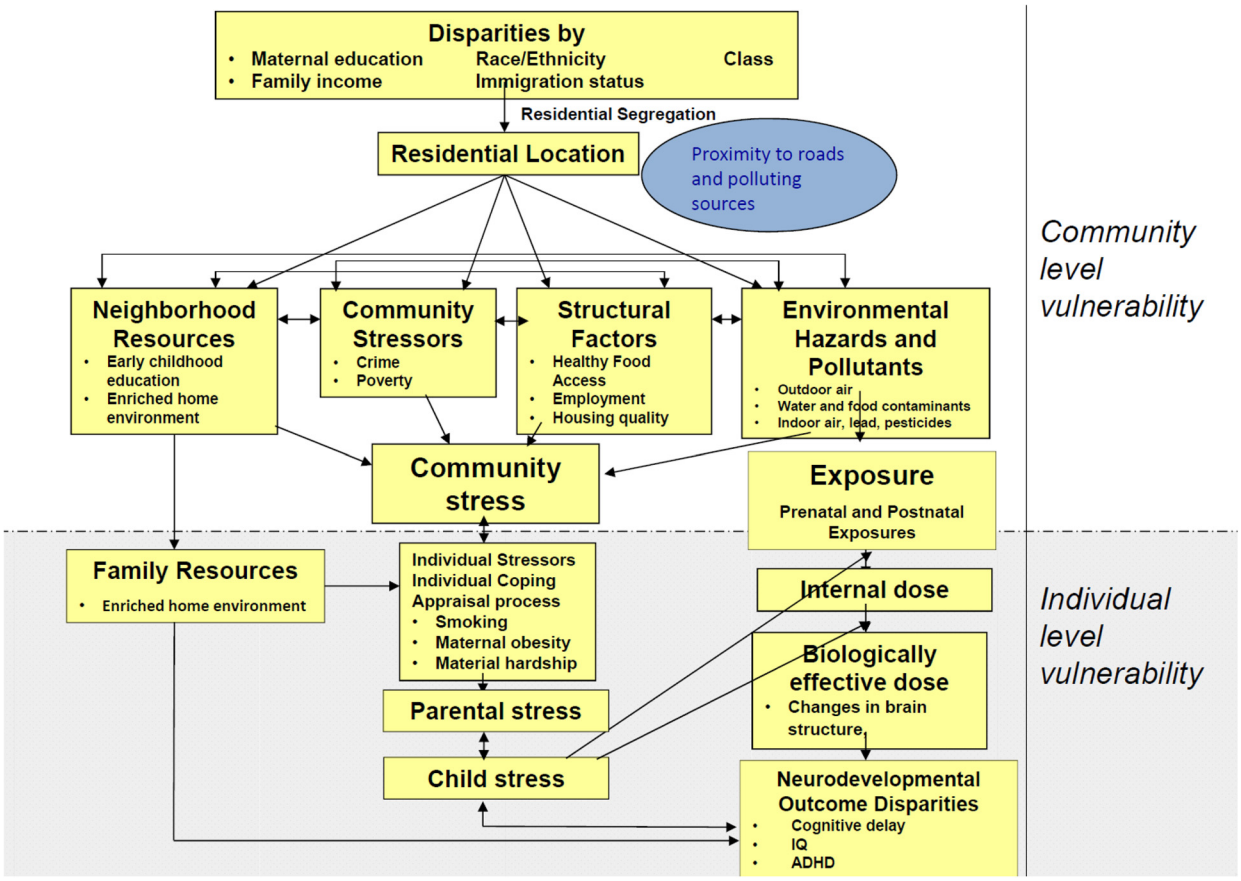

Figure 1. Exposure–Disease–Stress Framework for neurodevelopmental disparities. Modified from Gee and Payne-Sturges, 2004.

contaminant presents at a given exposure level, has been critical to many federal environmental regulatory and policy decisions (NRC 1983). Risk assessment consists of a four-step process: hazard identification, dose–response assessment, exposure assessment, and risk characterization (NRC 1983) based on probability theory, the law of averages, and linear regression modeling. It is a reductionist approach used mainly to assess and regulate *individual* chemicals. Although risk assessment has provided valuable guidance to the development of effective environmental policies, the limitations of chemical-by-chemical risk assessment to address real-world exposures have become increasingly evident (Israel 1994; Knudsen 2017). It was not until the 1996 FQPA that the U.S. Environmental Protection Agency (U.S. EPA) was statutorily mandated to consider aggregate exposure and cumulative risks of pesticides, at least those with common mechanisms of toxicity, and biological susceptibility in relation to human health—specifically among children—when regulating pesticide residues on foods, many of which are neurotoxic (U.S. Congress 1996). However, this requirement assumes a common mechanism of action and dose additivity and thus is highly limited in scope, omitting other mechanisms of toxic effects, synergistic effects, consequences of co-occurring nonchemical stressors, and convergence of downstream biological effects. Further, this paradigm does not examine upstream economic and social forces that underlie disparities in exposure to neurotoxic chemical stressors, thus limiting an environmental health policy maker's informed ability to consider intervention opportunities.

Broadening traditional risk analysis to include nonchemical stressors such as psychosocial factors (e.g., discrimination, poverty), physical agents (e.g., heat, noise) or biological stressors (e.g., pathogens), aggregate and background exposures, all relevant pathways and routes, and socioeconomic vulnerabilities was highlighted by the National Research Council report, "Science and Decisions: Advancing Risk Assessment," as "a move toward making risk assessments more relevant to environmental [health] decision-making and to the concerns of affected communities" (NRC 2009). Recent evaluations of statutory authorities suggest that the U.S. EPA could consider cumulate risks and impacts in regulatory decision making (Knudsen 2017; Alves et al. 2012). Yet, there has been no progress in this regard, with cited reasons including data deficiencies, inherent analytical complexities, lack of mechanistic understanding regarding stressor interactions, and lack of sufficient analytical tools (Sexton 2015; Payne-Sturges et al. 2018). Further, dominant narratives cited among U.S. EPA regulators are that "Environmental problems facing low income and minority communities are not that serious" (Harrison 2019) and that efforts to address inequities are beyond the purpose of the agency (e.g., "We do ecology, not sociology") (Harrison 2017), further constraining progress to protect public health from cumulative exposures.

Yet, the consequences of basing environmental health policies on *single* chemical risk assessment have been well argued (Cory-Slechta 2005; Israel 1994; NRC 2009; Wright 2009). A critical policy example relevant to children's neurodevelopment is the U.S. EPA's National Ambient Air Quality Standard for Pb. A reanalysis of the risk assessment shows that by not considering differential effects of Pb by SES, the current standard is underprotective of the most vulnerable children (Chari et al. 2012). The current standard of $0.15\ \mu g/m^3$ of Pb in ambient air, corresponding to a mean <2-point IQ loss for the nation's children, an IQ loss the U.S. EPA deemed acceptable. However, a >2-point IQ loss was estimated for children with low SES exposed at the U.S. EPA standard (Chari et al. 2012). Further, a small downward shift in the population mean would result

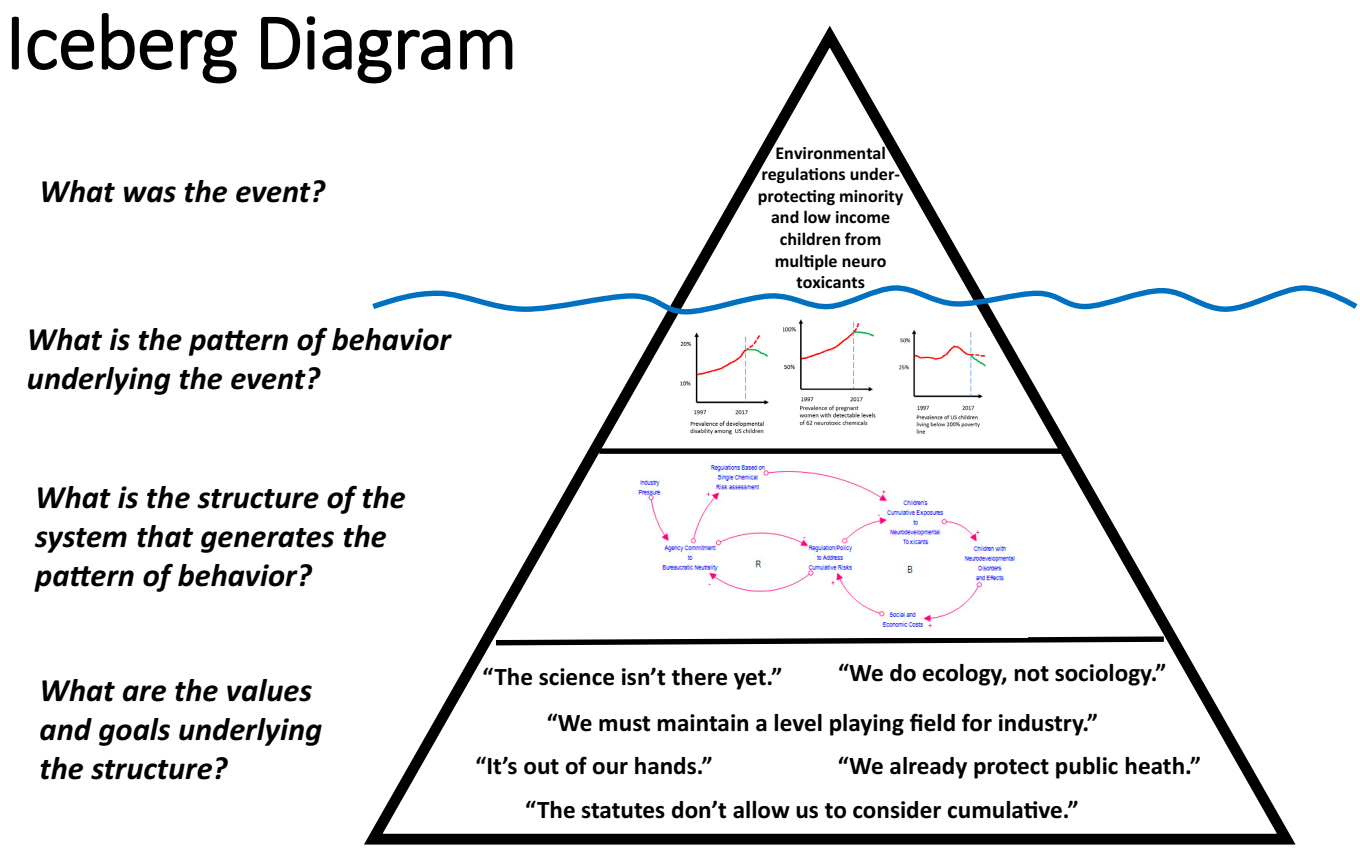

Figure 2. "The iceberg," a common systems metaphor, as applied to cumulative neurodevelopmental risks and impacts and environmental health policy. The iceberg is divided into four parts. Part 1: This part, the tip of the iceberg, is above the ocean surface and represents the event, such as the recognition that current environmental regulations are under-protecting minority and low-income children from multiple neurodevelopmental toxicants. Part 2: This part, just below the ocean's surface, depicts the pattern of behavior or time trends (AKA behavior-over-times (BOT) graphs) underlying the event. The first BOT graph is titled prevalence of developmental disability among U S children, plotting percentage, ranging from 0 to 20 in increments of 10 (y-axis), the second graph is titled prevalence of pregnant women with detectable levels of 62 neurotoxic chemicals, plotting percentage, ranging from 0 to 100 in increments of 50 (y-axis), and the third graph is titled prevalence of U S children living below 200 percent poverty line, plotting percentage, ranging from 0 to 50 in increments of 25 (y-axis) across years, ranging from 1997 to 2017 (x-axis). Part 3: Further below the ocean's surface, is the structure of the system that generates the pattern of behavior (BOTs) using causal loop diagrams of interlinking reinforcing and balancing feedback loops. Part 4: This final part is deep beneath the surface and represent the ultimate values and goals that underly the system structure that give rise to the patterns of behaviors (BOTs) which lead to the event or tip of the iceberg.

in an increase in the number of children with IQ levels consistent with intellectual or cognitive challenges, and a corresponding decrease in children with IQ levels considered "normal gifted" or "moderately gifted" (Lanphear 2015). Lower-income communities disproportionately exposed to Pb (Landrigan et al. 2010; Moody et al. 2016) may also be in areas with older housing stock, which contain Pb-based paint and Pb plumbing (Whitehead and Buchanan 2019); may also face higher levels of crime, violence, overcrowding (Evans and Kim 2010), and noise (Casey et al. 2017; Evans and English 2002); and have lower levels of educational enrichment (Johnson et al. 2016). The potential enhanced susceptibility of children of greater socioeconomic disadvantage to Pb is an important concern—especially because the U.S. EPA's IQ-loss framework (U.S. EPA 2008) specifically refers to the subset of children who would likely be exposed at the level of the standard. According to Chari et al., a Pb standard below a level of $0.10\,\mu g/m^3$ would be more protective (Chari et al. 2012). Further, the approach U.S. EPA used did not consider cumulative exposures of Pb from other sources (the 2008 revised National Ambient Air Quality Standards were developed using an "air-related IQ loss framework") (U.S. EPA 2008), especially among children with lower SES. This omission and its potential unintended effects are yet additional motivations for proposing a systems approach to developing environmental health policies.

However, the impacts of early-life exposures to neurotoxicants does not stop at childhood. Impairment in brain development in one domain could alter the trajectory of development in other domains, leaving a child poorly equipped to make good, future-oriented decisions and, consequently, because of poor academic success, facing restricted employment opportunities, material hardship, and other socioeconomic stresses (Bellinger et al. 2016). Further, changes in brain function occur throughout life, and some consequences of early damage may not even emerge until advanced age (Weiss 2000). Additionally, Pb-induced effects in one generation can have negative effects on the next generation, who may not have been exposed (Bellinger et al. 2016). These intergenerational effects are typically not considered in risk assessment. As a result, an environmental policy decision lacking consideration of cumulative risk modifiers and dynamic complexity may contribute to or exacerbate disparities not only in exposures but also health effects.

System Dynamics and Cumulative Environmental Neurodevelopmental Risks

Because children's neurodevelopment reflects a complex set of interactions of social and environmental factors (Bellinger et al. 2016; Bronfenbrenner 1989), including policy decisions, we

argue it is critical to move away from looking at isolated events and their causes and to examine the underlying system (system structure), made up of interacting parts, whose behavior creates these disparities. Figure 2 is based on a commonly used systems-thinking metaphor of the "iceberg." In public health we typically focus on the events, symptoms or health outcomes, the so-called tip of the iceberg (e.g., environmental regulations inadequately protecting minority and low-income children from exposure to multiple neurotoxicants and disparities in health outcomes), and we tend to narrow conceptual boundaries rather than expand them and to ignore feedback effects in favor of isolated linear cause-and-effect relationships (Rutter et al. 2017). To achieve lasting public health improvements, researchers, policy makers, communities, and other relevant stakeholders need to examine the patterns of behavior or trends that link symptoms over time and expose the underlying system structures that shape these trends and health outcomes.

Systems theory focuses on relationships and processes rather than singular, linear causation (Meadows 2008; Sterman 2000). Systems science methods enable investigators to simultaneously examine the dynamic relationships of variables at multiple levels of analysis while also studying the impact of the nonlinear behavior of the system as a whole over time (Sterman 2000). These methods can be used to develop policy analysis tools. Systems modeling is not new and is routinely used in fields such as corporate management, economics, engineering, physics, biology, and environmental resource management (Sterman 2000; Forrester 1961; Currie et al. 2018; Tidwell et al. 2004). Systems science is increasingly being recognized in the health sectors for its utility in mapping and understanding complex health problems, operationalizing research evidence, and systematically analyzing ranges of intervention and policy solutions (Luke and Stamatakis 2012; Atkinson et al. 2015; Calancie et al. 2018). Systems-oriented approaches have been successfully applied to examine trends and the impact of various interventions prior to implementation for specific conditions, such as influenza (Araz 2013), suicide prevention (Atkinson et al. 2015), cancer (Marcus 2007), cardiovascular disease (Hirsch 2010; Brittin et al. 2015; Knight et al. 2017), and diabetes and obesity (Hammond 2009; Hammond and Dube 2012; Luke and Stamatakis 2012; Johnston et al. 2014; Zhang et al. 2014; Gittelsohn et al. 2015; Freebairn et al. 2019).

SD modeling is one branch of systems science methods, which also include agent-based modeling and social network analysis. (Sterman 2000; Epstein 2006; Scott 2000; Wasserman and Faust 1994). A central tenet of SD is that the complex behaviors of organizational and social systems are the result of ongoing accumulations over time of people, material or financial assets, information, or even biological or psychological states (e.g., cumulative exposures, neurological functioning, number of Pb-poisoned children, number of children with cognitive delay) embedded within a set of balancing and reinforcing feedback mechanisms or loops (Homer and Hirsch 2006). Reinforcing feedback mechanisms amplify a change (e.g., living in poverty amplifies the negative effects of Pb exposure, which leads to limited economic opportunities and "feeds back" to further increase poverty), and balancing feedback mechanisms counteract a change (e.g., increasing timely assessment access to special educational services reduces the severity of effects of Pb-induced cognitive impairment and the need for further assessments). The dynamics of all systems arise from the interactions of multiple, interacting feedback mechanisms with changing influence (i.e., shifts of loop dominance) over time. Thus explanations in SD are from an endogenous perspective, meaning that it seeks to find explanations for system behaviors by understanding the internal structure of a feedback system rather than focusing on factors external to the systems (Richardson 2011). SD uniquely offers the practical application of these concepts through qualitative/informal causal maps and quantitative simulation modeling on a computer.

Causal loop diagrams (CLDs) are graphical representations of hypothesized causal relationships between factors, with specialized notation for representing balancing and reinforcing feedbacks (Sterman 2000). These SD qualitative models take the form of one or more closed loops to depict the cause-and-effects linkages, as shown in Figure 3. Reinforcing and balancing feedback loops are associated with behavior over time, such as patterns of exponential growth or decay. Series of feedback loops connected to one another can define system archetypes, such as virtuous/vicious cycles (amplification and reinforcement: a reinforcing process producing success or disaster), fixes that backfire (unintended consequences: the long-term negative consequences of a quick fix), or limits to growth (unanticipated constraints: limiting mechanism on spiraling growth) (Meadows 2008; Stroh 2015). The CLD depicted in Figure 3 represents causal hypotheses about cumulative environmental and social stressors that create disparities in neurodevelopmental outcomes in children. For example, the reinforcing feedback relationship "R3" illustrates the role of racial discrimination (e.g., in the location of polluting facilities and residential segregation) in increasing environmental exposures to neurodevelopmental toxicants among children. As exposure to multiple neurodevelopmental toxicants increases, neurological functioning decreases, which limits opportunities in later life as children become adults. Individuals with decreased neurological functioning may be further discriminated against in education, in housing, and in employment, which in turn decreases access to quality housing and less-polluted neighborhoods.

SD computational and simulation models, typically informed by CLDs, are articulated with stocks (e.g., number of children with learning disabilities, ADHD, or developmental delay) and flows (e.g., the rate of exposure, annual IQ loss) with balancing and reinforcing feedback structures, and such models consist of a set of coupled ordinary differential equations developed from a broad spectrum of relevant measured and experiential data, including exposure–response data from epidemiological studies and expert elicitation (Homer and Hirsch 2006). These quantitative models can accommodate nonlinearities by including interactions across variables at multiple levels and spatiotemporal scales; account for interrelationships, feedbacks, and interactions among these factors; and also provide insights into the emerging aggregate patterns that complex systems produce. Simulation models can be used to help policy makers understand a system and the impacts of various policy decisions before implementation. This feature addresses a major ethical issue in environmental health, where researchers cannot randomly assign populations to exposure scenarios that might be harmful. Programming tools that support SD modeling include STELLA (version 2.1; ISEE Systems) and VENSIM software (version 6.4; Ventana Systems). Models are considered to be theoretical representations of the complex problem and hence must undergo a validation process that includes determining accuracy of the model in reproducing real-world historical data patterns (behavior over time) to build confidence in the structure and predictions of a model.

Figure 4 provides an example of the output from our proof-of-concept SD simulation model of the CLD (Figure 3). The simulation model is implemented in STELLA Architect 2.0.1. The model simulates the growth of neurological functioning of birth cohorts from 2012 through 2017 for both an exposure group and a reference group. The model uses global population-level estimates of cumulative expressive language development by age for girls as a proxy for normal neurological growth curves (Ertem et al. 2018). Estimates are used to parameterize the continuous curves for fractional growth rates by age. Environmental exposures are then modeled as ratios that affect the factional growth rates where an environmental exposure of 2 will halve the

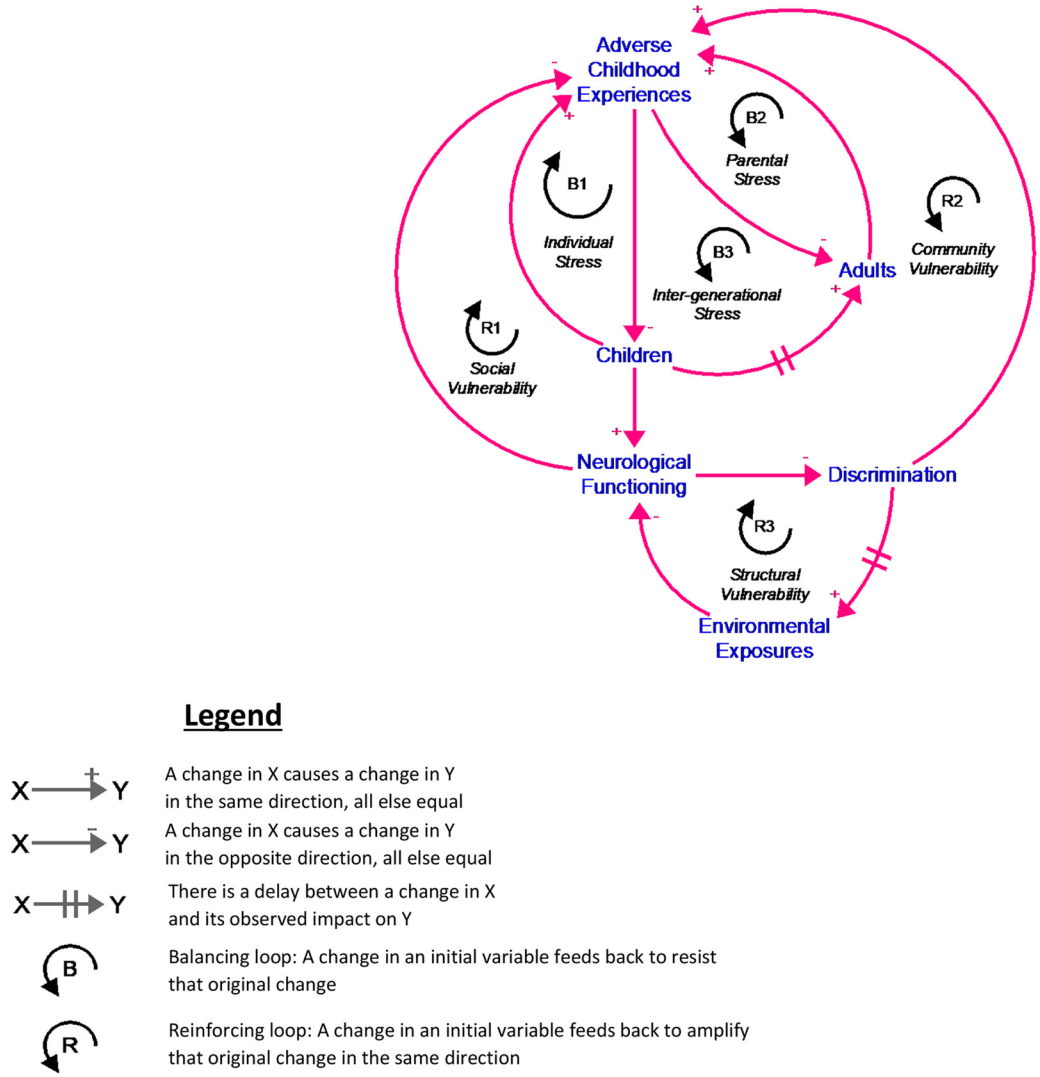

Figure 3. Example causal loop diagram on environment, social stressors, and neurodevelopment. Lines with arrows represent hypothesized causal relationships where polarities indicate the direction of influence. Double lines across the causal relationships represent temporal delays between causes and effects. Arcs with arrow heads indicate feedback mechanisms or loops where loops with "B" prefixes (B1, B2, and B3) represent balancing loops that counteract a perturbation, and "R" prefixes (R1, R2, and R3) represent reinforcing loops that reinforce a perturbation. Text in italics under the loop provides a short name for the feedback mechanism.

fractional growth rate. This approach allows for modeling environmental exposures that are sensitive to specific stages of children's neurological development. Disparities are represented as the mean difference in neurological function between the reference group and exposure group normalized by the reference group. For example, a mean difference of 0.1 means that the neurological functioning of the exposure group is 10% below that of the reference group. The choice to represent disparities in this form is based on the idea that developmental delays provide a reasonable proxy for the variables associated with discrimination and a larger set of vulnerabilities.

The output from the simulation model shown in Figure 4 illustrates a scenario where an environmental exposure from 2012 through 2015 (line 1 in Figure 4A) affects children's' neurological development. Initially, there are no developmental delays until the period of exposure. With exposure, the developmental delays and disparities rise. As the disparities increase, so too does the discrimination, which feeds back to amplify the effects of exposures. Once the exposures are removed, the developmental delays persist because children having passed a growth stage are not able to make up for the differences created by the environmental exposures. Figure 4B shows the corresponding simulated growth curves for the exposure group.

Policy Insights from SD Modeling

SD modeling assists in the goal of solving problems by improving the mental models we use to make decisions, including regulatory and policy decisions (Richardson 2011). In the context of disparities in children's cumulative exposure to neurodevelopmental stressors, unexpected insights about the structure and behavior of the system may be found, with the types of insights varying depending on which aspect of the problem is to be addressed through policy change (Hovmand 2014). This information in turn influences the type of SD modeling that would be appropriate, from visual depiction, i.e., informal maps, to formal quantitative simulation models. These insights can be enriched using participatory approaches that enable practitioners, decision makers across different sectors (e.g., housing, environmental management, transportation, education), researchers from multiple disciplines, and community members to learn together about cumulative exposures and children's neurodevelopmental

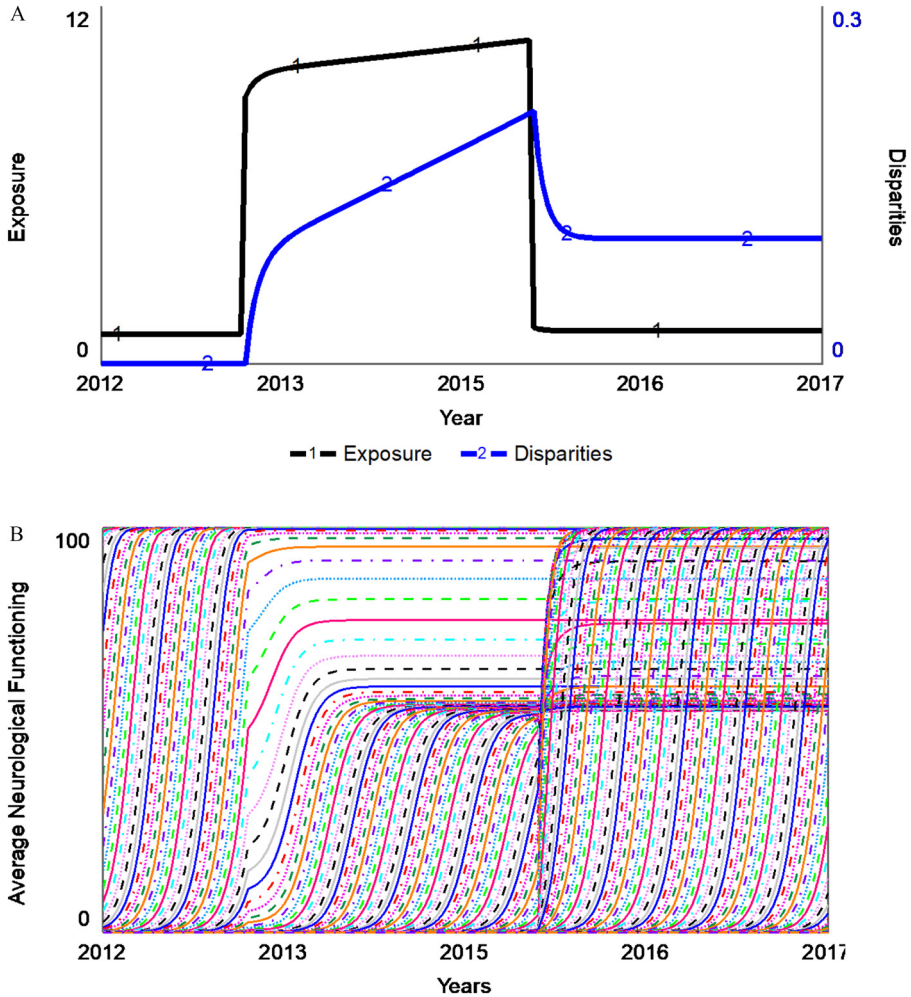

Figure 4. Output from proof-of-concept system dynamics simulation model (A) environmental exposure (line 1) and population level disparities (line 2) as difference in neurological functioning relative to reference group, and (B) average neurological functioning growth curve for each birth cohort from 2012 to 2017 where birth cohorts are 10 d wide. Note that the repeated pattern of line types (solid, dots, dashed) and colors in B are used only to help distinguish adjacent birth cohorts.

outcomes to build new concepts, insights, and practical innovations to identify high leverage points (Meadows 1999) for reducing the impact from cumulative exposures (Hovmand 2014; Cockerill et al. 2009).

An SD formal visual representation of a system can make our mental models more explicit and help stakeholders "see" that there is a system with interrelated components through systems pictures and CLDs (Hovmand 2014). Using SD could help the various stakeholders involved in children's neurodevelopment break out of their silos and bounded rationalities. Such insights allow stakeholders to probe others' thoughts about the system or shift from linear cause–effect views to a feedback perspective (Hovmand 2014). Recognizing opportunities to intervene (Meadows 2008) can lead to alternative system structures and to seeing ways that system transformation could occur. Deeper system insights involve developing more sophisticated and counterintuitive considerations about the system (Hovmand 2014). Formal simulation modeling can provide critical insights about which feedback mechanisms drive behavior patterns and elaborate consequences of nonlinear behavior and time delays in the system and what the consequences could be for decision makers, a first step to begin designing policies to shift these dynamics (Hovmand 2014). For example, short-term focus on reducing children's neurotoxicant exposures without also addressing social risk factors (e.g., access to high-quality early childhood education or improving incomes of families of lower SES) may not improve children's cognitive outcomes or close the achievement gaps as intended. A number of environmental statutes place broad mandates on the U.S. EPA to establish health-based standards that *a*) are "requisite to protect public health with ample margin of safety including susceptible populations" or do not tolerate "any" significant risk to public health or welfare; *b*) include technology-based provisions that do not tolerate risks that can be "feasibly" eliminated; and *c*) require risk–benefit provisions that find intolerable technologies, substances, or processes that pose "unreasonable" risk (Alves et al. 2012). In this context, we contend that the U.S. EPA does not need to impose social support such as providing access to health care, but the agency could do more to reduce hazards because people are more susceptible because they lack access to health care. Additionally, we contend that it should be incumbent on the U.S. EPA to work with other agencies who have the power to address conditions that are making people more susceptible or more vulnerable to environmental contaminants and pollutant exposures. The SD approach forces policy makers to move out of their silos and to take a more "both/and" approach rather than current "either/or" and "not at all" approaches.

Potential Challenges

SD has strengths and weaknesses. Its goal is to develop a scientifically based representation of the system for enhancing communication and understanding of the feedback system underlying dynamic behavior to develop efficacious policy solutions (Meadows 1999; Richardson 2011; Sterman 2018) that could address a topic such as how environmental exposures and social stressors affect children's neurodevelopment. Thus, the right selection and sequencing of group elicitation exercises to ensure representation of multiple perspectives is important. Although SD quantitative modeling represents hypothesized causal relationships regarding how diverse factors interact over time, the literature may or may not yet support those assumptions. Nevertheless, these models can help in consistent and rigorous consideration of implications of assumptions, allowing more complete and effective use of empirical evidence to better inform choices about CLD structure. The development of a useful SD simulation model requires a balance between comprehensiveness and comprehensibility (Hovmand 2014; Sterman 2000).

Although SD has historically been viewed as a "top-down," aggregate, or "lumped parameter" approach to systems modeling and has been contrasted with "bottom-up" individual-level modeling (e.g., discrete event simulations, agent-based modeling), this distinction is misleading and contributes to confusion in both the selection of methods and results. For example, there are examples in SD of individual-level models; aggregate-level models; and mixed, multilevel models including the embedding of agents represented by a feedback system within an environment (Sterman 2018; Hosseinichimeh et al. 2018; Osgood 2009).

The main distinction between SD and other methods is not the top-down vs. bottom-up approach (Sterman 2018), but the explicit emphasis on articulating the feedback mechanisms (Richardson 2011) and taking a continuous time, continuous variable orientation (Forrester 1961) to explicitly representing those feedback mechanisms, as opposed to the event-driven representation in methods such as discrete event simulations and agent-based models, where feedback mechanisms are implicit and emerge through interactions. The main implication of this distinction has to do with the complexity of implementing the model and computational requirements for simulation. As a system of ordinary differential equations, SD models can generally run much faster than an equivalent agent-based model of the system (Zeigler 1976). However, this speed comes at a cost in terms of representing actors in a system with many different attributes, the ability to efficiently represent larger social networks, and the requirement to have an explicit feedback theory (Rosenthal et al. 2020).

The development of an SD model to represent cumulative environmental neurodevelopmental risk should follow good modeling practices (Barton et al. 2020) and draw on a consistent set of variables across the literature for estimation of parameters and equations associating individual risk factors and environmental and social stressor exposures with neurodevelopmental outcomes. All data used to develop and test the model, including definitions of all variables, their units, ranges, expected values, and citations, should be compiled and documented to maximize accessibility of the model and supporting data (Sterman 2018; Rahmandad and Sterman 2012). Given the complexity of the system involved and the nature of social determinants, it is unlikely that all the model parameters and equations will have firm estimates from data or literature; therefore, sensitivity analyses are needed to test the robustness of model parameters and impact of uncertain parameters to make necessary changes following best practices from the SD field (Sterman 2000). Indeed, scientific efforts are needed to begin to quantify nonchemical stressors, including, for example, differences by the type of stress (Meehl 1990).

Another benefit of applying SD modeling process to cumulative risk is to highlight the most important data gaps. Systems science tools (including SD as described here) are best seen as a complement to (rather than a replacement for) existing approaches, with different strengths and weaknesses in comparison with conventional tools, and benefits are accrued when both are used together. For example, evidence from epidemiological and experimental research quantifying the effects of social stressors on children's neurodevelopment and knowledge drawn from literature on environmental sociology, public narrative, and organizational theory are needed to inform hypothesized mechanisms that generate inequalities in exposures and health outcomes. In the environmental policy realm, cost–benefit analyses may be needed. Policy levers identified using SD can be evaluated using any of the conventional approaches for cost–benefit analysis to estimate and compare the cost of one policy over another (Lyneis and Sterman 2016; Woodruff et al. 2018). Further it is important to note that all models, including traditional risk assessment and statistical models, are just one input into policy decisions and cannot remove uncertainty or the need for judgment.

Fundamentally, these models—whether using a system of ordinary differential equations or computer code for agent-based models—do not create certainty in the way one might expect from statistical distributions or confidence intervals. The fact that distributions and confidence intervals are often presented is misleading in that they do not help us forecast an outcome in the way we might want to predict the landfall of a hurricane or typhoon. They do, however, describe the distribution based on the assumptions, and for this, we can draw on sensitivity analyses to help us evaluate how sensitive our policies might be to our assumptions (Sterman 2000). In particular, what simulations do offer is a way to evaluate the policy impact of reducing uncertainty in our assumptions.

Researchers cannot escape the mathematical fact that as dynamic systems, there are certain fundamental limitations to what can be drawn from laying out our assumptions and simulating their implications (Meehl 1990). This should not dissuade researchers from using computer models because the alternative—trying to sort through an innumerable set of experiments empirically—is simply not feasible in terms of resources of time, people, and money (Forrester 1980). What researchers do need to be clear on, however, is the importance of having sufficient resources for conducting a rigorous and replicable program of sensitivity analyses (Osgood 2009). In our opinion, the best way to do this is to focus modeling efforts in ways that researchers can most efficiently explore the implications of their assumptions.

This efficiency becomes especially important when we consider the long time delays inherent to understanding the consequences of cumulative exposures. By the time when we might be confident based on empirical results about the systemic effects, it will often be too late to prevent their longer term consequences (Forrester 2007). As we have argued, simulation models, and SD in particular because of the fast execution speed and feasibility of both making assumptions transparent and conducting sensitivity analyses, provide a unique way to help people appreciate the impact of information delays on the dynamics of disparities and a means to more critically evaluate interventions as they unfold.

The approach we advocate for here and illustrate with the proof-of-concept model of a feedback theory focuses on a systematic approach to developing and appraising feedback theories (Meehl 1990). Specifically, the purpose of a model is generally to provide a simplified and interpretable explanation for reality. If models become so complex that it is no longer possible to readily appraise the core theory, conduct the needed sensitivity analyses, or interpret and communicate the results, then simulation models

have lost their scientific value. Hence, simulation models of feedback theories should be developed with a core feedback theory in mind, where the implementation of specific elements are treated as auxiliary theories, in much the same way measurement models are auxiliary theories to latent causal theories (Lakatos 1970). This approach allows researchers to disaggregate structures when policies are sensitive to a specific loop and aggregate details when they do not affect final results. In this way, investigators can systematically make scientifically informed choices about the appropriate level of aggregation and available resources for answering a policy question.

The time horizon for our proof-of-concept simulation model (2012 to 2017 or 5 y) is not sufficient to reflect the longer-term feedback effects of intergenerational stress and community and structural vulnerability. Although the choice of a short time horizon was made to more easily represent the individual growth curves, the approach was developed to be feasible for much longer time horizons in order to develop systemic explanations (Bunge 1997) that can be empirically tested for racial disparities. Being able to explicate mechanisms that reflect potential feedback interactions between environmental exposures, biological growth, and social repercussions over time is crucial to disentangling the effects of cumulative environmental exposures (Bunge 1997), especially during a time when we are appreciating and moving more toward precision medicine. Without this, we are likely to fixate on efforts that reduce precision medicine to biology while ignoring the potential explanations and opportunities for precision prevention and social supports.

Currently, application of SD to environmental health decision-making is limited, although there is growing interest (Currie et al. 2018; Prochaska et al. 2019). It is an emerging field. This may be a limitation, in that discussions about SD and environmental health are currently too generic with too few examples to learn from or compare against in terms of effectiveness of policies/decisions that resulted from the use of SD. Challenges associated with the application of SD in policy include siloed environmental health governance structures and the short time scale policy makers tend to operate within. In our view, having more evaluations of the SD in policy settings will help researchers and decision makers evaluate the merits of using SD. SD represents a significant potential bridge between environmental management and human health but needs further demonstration. As an initial step, we first focus in this article on the insights that could be gained by applying systems approach to a specific environmental health problem, children's cumulative exposure to neurodevelopmental toxicants. In this regard, we are contributing to advancing the application of SD to better understand the complex interactions of multiple chemical and social stressor exposures on population health.

Summary and Recommendations

There is a growing body of evidence and scientific consensus about the negative health impacts of multiple chemical exposures, including evidence about additive and synergistic effects of combined exposures to chemicals and social stressors. Unfortunately, policy solutions to address this public health problem lag behind the scientific consensus because environmental regulators continue to rely on *single* chemical risk assessment as the basis for making decisions. This status quo approach is being shaped by longstanding mental models among environmental regulators who separate and compartmentalize complex problems into policy domains to be addressed by other agencies or sectors. This approach directly contributes to fragmentation (Burke et al. 1997; Korfmacher 2019). Thus, we observe, environmental policy makers are blind to the consequences of their actions and to how what they do is disconnected from a larger whole. The "regulatory bureaucracy system" resists change, whereby traditional policy interventions based on single chemical risk assessment may be rendered ineffectual or worse, exacerbate disparities, potentially exacting a significant cost to public health, in our view. This is particularly salient in the case of children's exposure to neurodevelopmental toxicants that exhibit the characteristics of a complex adaptive system (e.g., increasing prevalence of neurodevelopmental disorders, heterogeneity by race and class, intergenerational effects and feedbacks).

Applying a systems science framework, specifically system dynamics, to cumulative neurotoxicant exposures in children, we argue, can illuminate a diverse array of relevant policy insights made possible by shifting the predominant mental models of environmental regulators and other stakeholders toward seeing the system structures that create and maintain disparities in cumulative chemical and nonchemical exposures and poor health outcomes. This more holistic approach we believe will help to identify effective policy levers for systems change (e.g., by reformulating goals; by weakening, strengthening, or altering or adding feedback loops). An SD framework provides not only a language but also a set of methodological tools that can more easily operationalize existing multidisciplinary scientific evidence and conceptual frameworks on cumulative risk. Using such approaches may allow us, as public health researchers and practitioners, to define more accurate diagnostic tools for children's' environmental health inequities that take into consideration the broader social and economic environment in which the children, live, grow, play, and learn. An SD approach can be used to demonstrate how the macro-level dynamics of cumulative neurodevelopmental exposures that have micro-level consequences for early child development can serve as a generalizable model that ensures decision-making on environmental policy includes appreciation for the social determinants of health as well as the historical and cultural contexts that shape our daily lives.

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