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Cumulative Environmental Impacts: Science and Policy to Protect Communities

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Abstract

Many communities are located near multiple sources of pollution, including current and former industrial sites, major roadways, and agricultural operations. Populations in such locations are predominantly low-income, with a large percentage of minorities and non-English speakers. These communities face challenges that can affect the health of their residents, including limited access to health care, a shortage of grocery stores, poor housing quality, and a lack of parks and open spaces. Environmental exposures may interact with social stressors, thereby worsening health outcomes. Age, genetic characteristics, and preexisting health conditions increase the risk of adverse health effects from exposure to pollutants. There are existing approaches for characterizing cumulative exposures, cumulative risks, and cumulative health impacts. Although such approaches have merit, they also have significant constraints. New developments in exposure monitoring, mapping, toxicology, and epidemiology, especially when informed by community participation, have the potential to advance the science on cumulative impacts and to improve decision making.

INTRODUCTION

Environmental regulations generally set limits for individual pollutants in air, water, soil, food, and other sources. Although this approach has been effective in controlling some exposures, it does not account for multiple pollutants from multiple sources and fails to incorporate nonchemical stressors and health vulnerabilities. Health disparities that disproportionately affect minority and low-income populations may enhance the vulnerability of these individuals to the effects of environmental chemicals. Cumulative exposures to environmental stressors, against a background of vulnerability, can result in heightened cumulative health risks and impacts across a population. Although the importance of cumulative impacts is conceptually obvious, the task of measuring and quantifying these impacts is enormously challenging.

Quantitative assessment of cumulative risk is impractical or impossible in many real-world situations because data on interactions among environmental stressors are unavailable, information on place- and population-specific exposures is lacking, and validated models relating exposure to effect for multiple chemicals and combinations of chemicals do not exist (58). The public health community has been faced with reconciling the need to assess cumulative impacts as part of an informed decision-making process in the absence of sufficient information and appropriate tools to adequately do so.

Numerous approaches have been used in different contexts to evaluate some aspects of cumulative exposures, cumulative risks, or cumulative impacts. These tools each have strengths and limitations and serve various purposes. Some approaches are more quantitative, whereas others are more qualitative; some involve more community participation than others do. We review evidence and mechanisms by which environmental exposures may interact with psychosocial and other stressors to exacerbate health impacts. Our main focus, however, is on methods that have been used to characterize cumulative impacts. Here we examine biomonitoring, health risk assessment, ecological risk assessment, health impact assessment, burden of disease, and cumulative impacts mapping as established approaches to evaluate aspects of this issue; we also review emerging approaches that may enhance the scientific understanding of cumulative impacts.

BACKGROUND AND EVIDENCE OF CUMULATIVE IMPACTS

Research and public health data have documented systemic disparities in the incidence and severity of diseases along socioeconomic and racial/ethnic lines (see **http://www.healthypeople.gov**). Many such diseases, including asthma, cardiovascular disease, adverse reproductive outcomes, and cancer, are associated with both social stressors and environmental factors. The interaction of environmental and social stressors has been referred to as a "double jeopardy" (31).

Four key concepts underlie cumulative impacts:

1. Health disparities are linked to social and environmental factors for many diseases;
2. Inequalities in exposures to environmental hazards are significant;
3. Intrinsic biological and physiological factors can modify the effects of environmental factors; and
4. Extrinsic social vulnerability factors at the individual and community levels may amplify the effects of environmental hazards.

These concepts have complex interrelationships and feedback loops. For instance, environmental exposures and social vulnerability can increase rates of health conditions, thereby heightening biological susceptibility to additional environmental exposures (40, 76). One example is the association between poor housing quality and exposure to indoor antigens from cockroaches or mold,

thereby increasing the risk of respiratory symptoms and in turn increasing host vulnerability to outdoor air pollutants such as ozone.

Vulnerability includes both intrinsic and extrinsic vulnerability. Intrinsic vulnerability includes genetic susceptibilities as well as underlying chronic health conditions. For example, people with low levels of the enzyme paraoxinase are more susceptible to adverse effects from exposure to organophosphate pesticides; paraoxinase levels have been reported to average fourfold lower in neonates than in adults, with a variation of up to 164-fold across individuals in a population (22).

Extrinsic factors, such as poverty, food insecurity, poor housing quality, linguistic isolation, exposure to violence, and poor neighborhood quality can heighten vulnerability to environmental agents. For example, low socioeconomic status may worsen the adverse effects of short- and long-term exposures to air pollution (46). Children exposed to violence in an environment with higher levels of air pollution had 1.6- to 2.4-fold higher rates of asthma diagnosis (13). Increased family stress is predictive of increased asthma symptoms from traffic-related pollution exposures in children (11, 60). Low neighborhood socioeconomic status may also amplify the risk of air pollution–related preterm births, lower birthweight, and adult mortality (20, 39, 50).

Allostatic Load

The concept of allostasis—meaning, "maintaining stability through change"—is one model for understanding the relationship between health outcomes, psychosocial stressors, and environmental exposures (35, 36). Allostatic load is the cumulative physiologic degradation that may result from chronic stress exposure and the accompanying long-term shift in homeostatic functions (57). The cascade begins with primary stress mediators such as catecholamines and cortisol, leading to primary, secondary, and tertiary outcomes. Cortisol levels have been used as a primary marker of allostatic load (32). Nonspecific secondary biomarkers of allostatic load include inflammatory, immune, metabolic, and cardiovascular responses (16). Some researchers have explored telomere length as a potentially useful tertiary biomarker of allostatic load (75). Data have shown that adverse childhood experiences increase allostatic load and inflammatory biomarkers later in life (17). Higher allostatic load, especially in childhood, has also been associated with a range of diseases, including myocardial infarction, asthma, mental distress, and overall disability (26).

Numerous socioeconomic factors contribute to allostatic load, such as residential crowding, noise, poor housing quality, exposure to violence, or experiences of racial discrimination (34). A study of African American residents of low socioeconomic status showed that walking past blighted vacant lots significantly increases heart rate, whereas walking past green lots lowers heart rate, indicative of environmental influences on allostatic load (61). Correlations between race/ethnicity, socioeconomic status, and allostatic load have been established (25, 56). Allostatic load may also amplify the adverse effects of environmental chemical exposures, such as lead exposure on risk of hypertension among adults and the effect of housing quality on asthma risk in children (27, 49, 55, 77).

ASSESSMENT METHODS FOR CUMULATIVE IMPACTS

Some cumulative impact assessment methodologies focus on populations or geographic areas, whereas others evaluate the impacts of emission sources, chemicals, policies, or programs (see **Table 1**). Few approaches to cumulative impacts aim to incorporate all types of stressors and vulnerabilities. Methodologies also differ in the degree to which they require quantitative or qualitative data, as well as the degree of community engagement they include (see **Figure 1**). These different approaches to cumulative impacts analysis are illustrated by six widely used approaches:

Table 1 Analytic dimensions for cumulative impacts analyses

Dimension	Analytic Characteristics
Context	■ Project-, policy-, program-, chemical-, or plan-based decision (e.g., identify consequences of a specific proposal or activity) ■ Geography- or population-based decision (e.g., identify overburdened areas or populations[a] to prioritize the allocation of resources)
Stressors	■ Chemical stressors (e.g., pollutants in air, water, soil, food, products) ■ Biological stressors (e.g., internal and external microbiome) ■ Social stressors (e.g., discrimination, poverty, violence) ■ Physical stressors (e.g., noise, radiation, housing quality)
Vulnerability	■ Intrinsic factors (e.g., age, existing health conditions, genome) ■ Extrinsic factors (e.g., socioeconomic vulnerability, access to health care)

[a]Communities or populations that may not necessarily share a common geography, such as agricultural workers or individuals who share similar social, occupational, and/or environmental exposures or a common disease/illness.

biomonitoring, health risk assessment, ecological risk assessment, health impact assessment, burden of disease, and mapping of cumulative impacts.

Biomonitoring

Studies conducted in the 1980s and 1990s evaluated multiple simultaneous chemical exposures in the population (59, 69). These studies demonstrated that people are exposed to numerous chemicals at any time and monitored multimedia personal exposures through air monitoring, assessment of chemicals in carpet dust, and surface wipe sampling. The expense and complexity of these "total exposure" studies made them difficult to continue longitudinally, and, in recent years, the focus has shifted toward biomonitoring. Although biomonitoring is a very efficient way

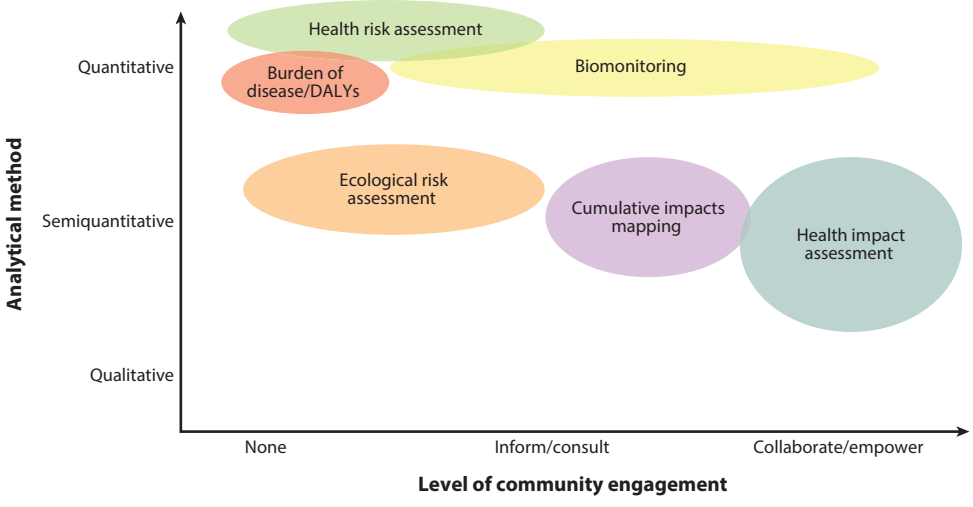

Figure 1

Cumulative impacts assessment tools: analytical method and levels of community engagement. DALYs, disability-adjusted life years.

to measure a large number of chemicals in humans, it does not effectively pinpoint sources of exposure, a benefit of earlier studies.

The capacity to monitor for chemicals and other biological markers in blood, urine, and biologic fluids has expanded dramatically in recent years. Studies have moved from measuring a handful of biomarkers for chemicals such as lead, mercury, and polychlorinated biphenyls (PCBs) to measuring ~265 chemicals in a representative subsample of the US population (9). Biomonitoring studies have demonstrated that almost everyone, including susceptible groups such as pregnant women, has hundreds of chemicals measurable in his/her body at any point in time, thereby proving the existence of cumulative environmental exposures (7, 72).

Data from the National Health and Nutrition Examination Survey demonstrated that mercury concentrations are significantly higher in Asians and Native American/Pacific Islanders (28). These findings are consistent with data showing higher rates of fish consumption in these groups. Other studies have shown higher concentrations of organochlorine pesticide metabolites in Latinos; these exposures have been linked to a higher risk of diabetes in this population (15).

Biomonitoring has shown co-occurrence of multiple chemicals of the same class, such as mixtures of organophosphate pesticides or phthalates, as well as multiple chemicals that act via similar biological mechanisms. For example, numerous estrogenic chemicals are present in samples, as are numerous neurotoxic agents. These findings suggest the need to evaluate combined exposures. Agencies such as the US Environmental Protection Agency (USEPA) and the California Environmental Protection Agency (CalEPA), which are engaged in cumulative risk assessment, are beginning to attempt to do just that.

Health Risk Assessment

Risk assessment seeks to quantify the probability of adverse health effects of chemicals at different exposure levels. Risk assessments traditionally examine one chemical at a time and often evaluate exposures through only one environmental medium, such as air or water. Such a narrow approach can be useful for deriving regulatory numbers, but it is likely to miss significant sources of combined risk. Risk assessments for cleanups of contaminated sites were among the earliest to evaluate the potential health risks of multiple chemicals. In the 1980s, several organizations developed toxic equivalence factors (TEFs) for dioxin and dioxin-like chemicals on the basis of their relative potency, allowing these chemicals to be assessed together rather than individually (68). This approach assumes that each chemical acts via the same biological mechanism and that doses are additive, which is not always the case. Although the early TEFs included only a few closely related chemicals and reflected an incomplete understanding of the toxicology, they became a model for later efforts to combine chemicals in risk assessments. Since the 1980s, the USEPA and CalEPA risk assessment guidance documents have included the assumption that cancer risks from exposure to multiple carcinogens are additive (10, 66). Exposures to multiple noncarcinogens are addressed generally by assuming that effects are proportional to the sum of the ratios of exposure levels to threshold guidance levels (hazard quotients and index). Overall sums greater than unity suggest the potential for health effects.

The environmental justice movement in the 1980s raised concerns about cumulative environmental exposures (5). In response, President Clinton signed an executive order on environmental justice in 1994 that required "[e]nvironmental human health analyses, whenever practicable and appropriate, [to] . . . identify multiple and cumulative exposures" (19). In 2003, the USEPA attempted to address the issue in its *Framework for Cumulative Risk Assessment*, which defined cumulative risk as "the combined risks from aggregate exposure to multiple agents or stressors" (67, p. 6). Although the Framework laid out a general approach to assessing cumulative risks, the

strategy has not proven easy to implement, and there are few examples of such risk assessments. One example was the cumulative risk assessment for the organophosphate pesticides, but that approach was focused on a group of chemicals thought to act via a common biologic mechanism (acetylcholinesterase inhibition).

In 2004, the National Environmental Justice Advisory Council (NEJAC), an advisory body to the USEPA, provided guidance about the short-term and long-term actions that the Agency should take to implement the concepts in its Framework (29, 44). The NEJAC urged consideration of nonchemical stressors and community vulnerability and called for community-based participatory research. Finally, the NEJAC pointed out the value of efficient screening and priority-setting tools that can be used by all stakeholders and the importance of qualitative information in domains where quantitative assessment is not viable in the near term.

In 2009, the National Research Council (NRC)'s *Science and Decisions: Advancing Risk Assessment* observed that "research and regulatory action related to cumulative risks have been conducted for decades without much advancement beyond chemical stressors in a small number of contexts" (43, p. 224). Noting the complexity involved, the NRC emphasized "a need for simplified risk assessment tools . . . [to] allow communities and stakeholders to conduct assessments and thus increase stakeholder participation" (43, pp. 10, 267). The NRC recommended focusing on evaluation of risk management options instead of on characterization of problems.

Health risk assessment is limited by the typical requirement that it generate a numerical estimate of risk. Data limitations make it very difficult to perform this task even on a single chemical, let alone on a combination of multiple stressors. It is worrisome that many assumptions built into risk assessment may bias toward underestimation of cumulative impacts. For example, risk assessments of noncarcinogens utilize a model that assumes a safe threshold in the population below which no health effects would occur. However, complex background exposures, when combined with differential vulnerability, may eliminate such thresholds.

Ecological Risk Assessment

Ecological risk assessment was developed in the 1990s. Unlike health risk assessment, ecological risk assessment incorporated the concept of cumulative impacts from its inception. The concept is founded on ecosystem science and the importance of the interrelationships of the plants and animals in a habitat. Ecological risk assessment evaluates the likelihood that adverse ecological effects occur as a result of exposure to one or more stressors (63). Ecological risk assessments are generally place-based and semi-quantitative or qualitative, rather than chemical-based and quantitative. Stressors include chemicals and other pollutants but also include such issues as the impacts of development, fishing, grazing, and the introduction of species. Effects are assessed on the ecosystem as a whole as well as on specific species of concern within the ecosystem.

The NRC provided insights on how ecological risk assessment could be adapted to human health assessment (42). One approach is to start by establishing the existence of a health concern, then determine the relevant stressors, and develop a conceptual model linking stressors and the outcome of concern (37). A conceptual community-based model could focus on the wide variety of sources in the community—chemical and nonchemical—that might affect outcomes in the initial screening-level analysis of the problem. A screening assessment would then reduce the number of stressors to those that might have the greatest influence based on analytical determinations, consultations with stakeholders, or both. The approach then emphasizes those sources that could be feasibly addressed.

A limitation of this approach is an overreliance on epidemiological studies that link environmental exposures and other stressors with outcomes (43). The advantage of this approach is a

broad scoping of chemical and nonchemical stressors, with the opportunity to surface a full range of options for consideration. For example, in an area with high rates of asthma and cardiovascular disease, an agency with the authority to reduce exposures to air pollutants and greenhouse gas emissions could focus on other related community improvements. Ideally, through the involvement of the community and other stakeholders, the process would enable decision-makers in partnership with communities to discriminate among options and construct feasible solutions. Although the application of ecological risk assessment to cumulative impacts in human communities may have potential, the methodology is in its infancy and has not yet been proven in practice.

Health Impact Assessment

Health impact assessment (HIA) shares certain commonalities with ecological risk assessment, as adapted to human communities. The roots of HIA, however, are not in risk assessment but in environmental impact assessment under the National Environmental Policy Act (NEPA) and similar state statutes. Such statutes have required cumulative impacts assessment since their inception. HIA emerged in the 1990s as an approach to evaluate human health consequences of decisions or projects, either under NEPA or as a stand-alone analysis (14, 70). The NRC defined HIA as "a systematic process that uses an array of data sources and analytic methods, and considers input from stakeholders to determine the potential effects of a proposed policy, plan, program, or project on the health of a population and the distribution of those effects within the population" (42, p. 46).

HIA considers impacts from environmental factors and from economic, political, social, and psychological contributions. A 1999 consensus paper from the European Center for Health Policy outlined the underlying conceptual framework of HIA, including a right to public participation (democracy) and the importance of understanding the distribution of impacts to populations with respect to gender, age, ethnic background, and socioeconomic status (equity) (18). Unlike health risk assessment, the ultimate outcomes of HIA are mostly qualitative (8).

An early HIA evaluated proposed oil and gas development on Inupiat communities in Alaska's North Slope (70). This qualitative assessment identified potential health risks that included multiple pollutant sources from oil processing, traffic, road dust, gas flares, and machinery. Potential exposure to pollutants from the consumption of marine mammals, fish, and game and nonpollution contributions including psychological and social pathology, injury, food insecurity, and infectious disease were also included. The information from an HIA can be very useful, but the generally qualitative nature sometimes makes it challenging for use in decision making. Furthermore, HIAs conducted in the context of evaluating multisource community impacts may become time-consuming and challenging to manage.

Burden of Disease

The original Global Burden of Disease (GBD) study was published in 1993 and included quantitative estimates for 107 diseases and 483 nonfatal health consequences (73). A 2013 update presents estimates of all-cause mortality, deaths by cause, years of life lost, years lived with disability, and disability-adjusted life years by country, age, and sex for 323 diseases and injuries, 67 risk factors, and 1,500 sequelae for 188 countries (24, 30).

Measuring and comparing the cumulative disease and injury burden in populations requires a composite metric that captures both premature mortality and the prevalence and severity of ill-health. The GBD study uses disability-adjusted life years (DALYs) to measure disease burden (41). The DALY is a time-based measure that combines years of life lost due to premature mortality and years of healthy life lost due to disability. The DALY approach has some advantages over

risk assessment in that it incorporates information on both the severity and the duration of health impacts, generates a metric that is more easily understandable and relevant than risk or probability, and creates a single unified metric that can be compared across communities or countries.

Environmental factors have long been included in the GBD, with a focus on infectious diseases, malnutrition, and water quality. Other factors that have been evaluated include indoor and outdoor air pollution, lead poisoning, tobacco use, and occupational exposure to carcinogens, particulates, and noise (3). The DALY has been used in several studies to comparatively and quantitatively assess the cumulative impact of environmental pollution (23). In one case study of an urban environment, researchers evaluated cumulative health risks associated with particulate matter and four volatile organic compounds in air and six pesticides in food (51). The researchers evaluated exposures in multiple microenvironments (e.g., home, school, vehicle) for three age groups. The DALY analysis indicated that indoor air pollutants are of particular health importance and that particulate matter is a major source of risk.

The GBD method is limited by major uncertainties about health outcomes, attributable risk associated with environmental diseases, and a failure to adequately address the multifactorial nature of disease (3). Many important stressors cannot be quantified using the GBD approach and are ignored in these assessments. Qualitative data cannot be effectively incorporated into a GBD analysis, thereby significantly limiting its utility. The GBD method also typically does not include community or public input.

Mapping Cumulative Impacts

Novel mapping approaches have been developed in recent years by environmental agencies and community-academic partnerships to screen for cumulative impacts. The uses of such tools include identifying areas of concern for environmental justice (1, 64); targeting Greenhouse Gas Reduction Fund monies generated through California's cap-and-trade program (6); and identifying areas to improve land use planning and regulatory enforcement (47, 53, 54). The key to this approach is the use of geographic information systems (GIS) mapping to integrate chemical and nonchemical stressors, vulnerability, and background risk factors in a semiquantitative manner. This strategy is consistent with the NEJAC and NRC's call for the development of tools that are simple and understandable to communities (43).

Developed by researchers in collaboration with environmental justice advocates and scientists from the California Air Resources Board, the Environmental Justice Screening Method (EJSM) maps cumulative impacts using a large set of health, environmental, and social vulnerability measures organized in five categories: (*a*) hazard proximity and land use; (*b*) estimated air pollution exposure and health risk; (*c*) social and health vulnerability; (*d*) climate change vulnerability; and (*e*) drinking water quality. The method results in a cumulative ranking based on all the census tract–level indicators, which is then presented visually as statewide and regional maps (54). In addition to calculating a total score, the EJSM enables investigators to examine each of the five categories separately, which facilitates uses tailored to various decision contexts. The EJSM effort included a process of ground-truthing results in which community partners, supported by researchers, gathered data about pollution sources and their proximity to concentrations of people, such as the elderly, young children, and people with chronic health conditions, who are most vulnerable to pollution (53).

The California Communities Environmental Health Screening Tool (CalEnviroScreen), developed by the California Office of Environmental Health Hazard Assessment, enables researchers to identify communities in California that are burdened by multiple sources of pollution and face different types of health and socioeconomic vulnerability (47). The tool's creation stems from

the CalEPA's Environmental Justice Action Plan, which called for the development of guidance on multimedia cumulative impacts to reduce pollution in communities that are most burdened. CalEnviroScreen was developed through a public process that included extensive community input and is composed of indicators that incorporate the following concepts:

- Contact with pollutants (exposures),
- Environmental threats and adverse conditions (environmental effects),
- Populations with biological traits that may magnify the effects of pollutants (sensitive populations), and
- Community characteristics that may increase vulnerability to pollutants (socioeconomic factors).

Potential data sources that represent each of these concepts were evaluated for relevance, accuracy, currency, and availability for analysis. The 2014 version of CalEnviroScreen is composed of 19 indicators, evaluated at the census tract scale and scored relative to other census tracts. Indicator scores are combined to calculate an overall cumulative impact score, allowing a relative comparison of the cumulative burden on communities (47).

NEW TOOLS FOR UNDERSTANDING CUMULATIVE IMPACTS

The methods described above have enabled significant progress toward improving the field's understanding of cumulative impacts, but each of these approaches has significant limitations. Some methods are useful at present only for screening-level evaluations; others are constrained by quantitative data limitations. No single method is tailored to the needs of all actors and decision makers, and multiple approaches will have utility.

It is timely to advance the science to incorporate emerging tools. In the field of exposure science, new sensor technologies offer the promise of portable—even wearable—monitors that can capture multiple human microenvironments in an integrated exposure assessment for one or multiple chemicals. Such monitors can be combined with cell phone location information and video capability to gather extensive information about environmental exposures. Some new sensors offer real-time exposure reporting, whereas others are slower but can sample for many chemicals at once.

Other advances in exposure science, such as nontargeted and semitargeted biomonitoring, remove the constraint of selecting test chemicals in advance. Nontargeted biomonitoring methods can identify novel priority compounds for confirmation and quantification through targeted analysis. This tiered approach to chemical biomonitoring can become an integral part of characterizing the "exposome" (71). Place-based biomonitoring could be done to develop geospatial cumulative exposure profiles. Mapping tools can also highlight areas of concern where targeted biomonitoring might be warranted. Communities living in areas impacted by pesticides or industrial emissions could collaborate in the development of biomonitoring and results communication protocols (38).

New tools in toxicology include mechanistic and predictive approaches, as well as rapid screening in vitro or in nonmammalian systems. The massive influx of new data from cell-based testing systems such as the USEPA ToxCast is one example of potentially valuable information (65). These systems allow researchers to detect perturbations in biological pathways involved in disease and may be an effective way of screening thousands of chemicals for potential toxicity. Because cell-based assays evaluate common biological pathways, they can generate new hypotheses about cumulative impacts. For example, such methods can identify multiple chemicals that interact with pathways that are relevant to diseases of interest. Cell-based systems allow investigators to screen toxicity from combinations of chemicals, potentially enabling quantitative assessment of mixtures. One characteristic of mechanistic toxicology is the focus on understanding how chemicals and other agents work at the cellular and tissue levels to perturb

biological pathways relevant to disease. This understanding may allow improved prediction of how multiple pollutants interact within the body to cause disease. This concept has been elaborated in a multipollutant risk assessment framework for air pollutants (4).

Another new development is the availability of highly diverse mouse populations designed to simulate human diversity. The Collaborative Cross is a panel of hundreds of different inbred strains with full genomic sequencing (62). The Diversity Outbred population is constructed of genetically unique individuals (12). These models offer information about gene-environment interactions, susceptibility, and the impact of individual or combined stressors on response. For example, diverse mice have illuminated genetic susceptibility to micronuclei formation for benzene, liver toxicity for trichloroethylene, and diet on intestinal cardiometabolic-related microflora (21, 45, 74). Co-exposures to arsenic and trichloroethylene have also been conducted (2). These experiments improve our understanding of combined stressors in susceptible groups. Toxicogenomics within these experiments may uncover underlying pathways related to susceptibility.

Human epidemiology has historically been hampered by long latency periods between exposure and disease. Biologic markers of effect from in vitro and metabolomic analyses are aiding molecular epidemiologic studies to become more predictive. Some researchers have taken the concept of effect biomarkers one step further by proposing that cumulative impacts may soon be measurable as "neighborhood-specific epigenetic markers" (48). The chemical modifications of DNA and chromatin that regulate gene expression (the epigenome) are known to be altered by environmental conditions (52). Advances in microarray technology are making it possible to detect epigenetic changes (33). It may eventually be possible to compare epigenetic patterns across different populations or communities and identify patterns that represent a marker of cumulative impacts in a population or group.

In the near term, case studies on chemical mixtures could help quantify health outcome variability in the population associated with social vulnerability factors. This information could help assess whether current safety factors used to derive risk-based standards to protect susceptible groups are truly protective of socially vulnerable populations. Ultimately, as science develops a better understanding of cumulative impacts, standard approaches in risk assessment may need to change to assure the protection of public health. Environmental and social stressors clearly converge in disadvantaged communities, and tools to measure these impacts are needed for improved decision making. The use of cumulative impact methods increases the likelihood that disadvantaged neighborhoods may receive critical attention, improving existing conditions and reducing future harm.

DISCLOSURE STATEMENT

The opinions expressed by the authors do not necessarily represent the views of the California Environmental Protection Agency or those of the California Office of Environmental Health Hazard Assessment. The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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LITERATURE CITED

1. Alexeeff G, Faust J, August LM, Milanes C, Randles K, Zeise L. 2010. *Cumulative Impacts: Building a Scientific Foundation*. Sacramento, CA: Off. Environ. Health Hazard Assess. **http://www.oehha.ca.gov/ej/pdf/CIReport123110.pdf**
2. Ball E. 2011. Conference highlights toxicogenomics, bioinformatics and computational biology. *Environ. Factor*. Oct. **http://www.niehs.nih.gov/news/newsletter/2011/october/science-conference/**
3. Briggs D. 2003. Environmental pollution and the global burden of disease. *Br. Med. Bull.* 68:1–24
4. Buckley B, Farraj A. 2015. Conceptual model for assessing criteria air pollutants in a multipollutant context: a modified adverse outcome pathway approach. *Toxicology* 335:85–94
5. Bullard RD. 1990. *Dumping in Dixie: Race, Class, and Environmental Quality*. Boulder, CO: Westview
6. CalEPA (Calif. Environ. Prot. Agency). 2015. *Greenhouse gas-reduction investment to benefit disadvantaged communities*. Updated Feb. 9, CalEPA, Sacramento, CA. **http://www.calepa.ca.gov/EnvJustice/GHGInvest**
7. Calif. Dep. Public Health, Dep. Toxic Subst. Control, Off. Environ. Health Hazard Assess. 2015. *Biomonitoring California's Results Database*. Updated Sept. 22, Biomonitor. Calif., Sacramento. **http://www.biomonitoring.ca.gov/results/explore**
8. CDC (Cent. Dis. Control Prev.). 2012. *Healthy places. Health impact assessment. What is the relationship of HIA to environmental impact assessment?* Updated July 25, CDC, Atlanta. **http://www.cdc.gov/healthyplaces/relationship.htm**
9. CDC (Cent. Dis. Control Prev.), Dep. Health Hum. Serv. 2009. *Fourth National Report on Human Exposure to Environmental Chemicals*. Atlanta: CDC. **http://www.cdc.gov/exposurereport/pdf/fourthreport.pdf**
10. CDHS (Calif. Dep. Health Serv.). 1985. *Guidelines for Chemical Carcinogen Risk Assessments and Their Scientific Rationale*. Sacramento, CA: CDHS, Health Welf. Agency
11. Chen E, Schreier HM, Strunk RC, Brauer M. 2008. Chronic traffic-related air pollution and stress interact to predict biologic and clinical outcomes in asthma. *Environ. Health Perspect.* 116:970–75
12. Churchill GA, Gatti DM, Munger SC, Svenson KL. 2012. The Diversity Outbred mouse population. *Mamm. Genome* 23:713–18
13. Clougherty JE, Levy JI, Kubzansky LD, Ryan PB, Suglia SF, et al. 2007. Synergistic effects of traffic-related air pollution and exposure to violence on urban asthma etiology. *Environ. Health Perspect.* 115:1140–46
14. Cole BL, Fielding JE. 2007. Health impact assessment: a tool to help policy makers understand health beyond health care. *Annu. Rev. Public Health* 28:393–412
15. Cox S, Niskar AS, Narayan KM, Marcus M. 2007. Prevalence of self-reported diabetes and exposure to organochlorine pesticides among Mexican Americans: Hispanic Health and Nutrition Examination Survey, 1982–1984. *Environ. Health Perspect.* 115:1747–52
16. Crimmins EM, Johnston M, Hayward M, Seeman T. 2003. Age differences in allostatic load: an index of physiological dysregulation. *Exp. Gerontol.* 38:731–34
17. Danese A, McEwen BS. 2012. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol. Behav.* 106:29–39
18. Eur. Cent. Health Policy. 1999. *Health Impact Assessment. Main Concepts and Suggested Approach. Gothenburg Consensus Paper. December, 1999*. Brussels: WHO Reg. Off. Eur.
19. Exec. Order 12898, 59 F.R. 7629. (Feb. 16, 1994)
20. Finkelstein MM, Jerrett M, DeLuca P, Finkelstein N, Verma DK, et al. 2003. Relation between income, air pollution and mortality: a cohort study. *Can. Med. Assoc. J.* 169:397–402
21. French JE, Gatti DM, Morgan DL, Kissling GE, Shockley KR, et al. 2015. Diversity outbred mice identify population-based exposure thresholds and genetic factors that influence benzene-induced genotoxicity. *Environ. Health Perspect.* 123:237–45
22. Furlong CE, Holland N, Richter RJ, Bradman A, Ho A, Eskenazi B. 2006. PON1 status of farmworker mothers and children as a predictor of organophosphate sensitivity. *Pharmacogenet. Genom.* 16:183–90
23. Gao T, Wang XC, Chen R, Ngo HH, Guo W. 2015. Disability adjusted life year (DALY): a useful tool for quantitative assessment of environmental pollution. *Sci. Total Environ.* 511:268–87
24. GBD 2013. Mortal. Causes Death Collab. 2015. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 385:117–71

25. Geronimus AT, Hicken M, Keene D, Bound J. 2006. "Weathering" and age patterns of allostatic load scores among blacks and whites in the United States. *Am. J. Public Health* 96:826–33
26. Gilbert LK, Breiding MJ, Merrick MT, Thompson WW, Ford DC, et al. 2015. Childhood adversity and adult chronic disease: an update from ten states and the District of Columbia, 2010. *Am. J. Prev. Med.* 48:345–49
27. Glass TA, Bandeen-Roche K, McAtee M, Bolla K, Todd AC, Schwartz BS. 2009. Neighborhood psychosocial hazards and the association of cumulative lead dose with cognitive function in older adults. *Am. J. Epidemiol.* 169:683–92
28. Hightower JM, O'Hare A, Hernandez GT. 2006. Blood mercury reporting in NHANES: identifying Asian, Pacific Islander, Native American, and multiracial groups. *Environ. Health Perspect.* 114:173–75
29. Hynes HP, Lopez R. 2007. Cumulative risk and a call for action in environmental justice communities. *J. Health Disparities Res. Pract.* 1:27–57
30. Inst. Health Metrics Eval. 2015. *Global Burden of Disease. GBD history.* Inst. Health Metrics Eval., Seattle, Wash. **http://www.healthdata.org/gbd/about/history**
31. IOM (Inst. Med.), Comm. Environ. Justice. 1999. *Toward Environmental Justice: Research, Education, and Health Policy Needs*. Washington, DC: Natl. Acad. Press
32. Juster RP, McEwen BS, Lupien SJ. 2010. Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neurosci. Biobehav. Rev.* 35:2–16
33. Lister R, Pelizzola M, Dowen RH, Hawkins RD, Hon G, et al. 2009. Human DNA methylomes at base resolution show widespread epigenomic differences. *Nature* 462:315–22
34. Lynch JW, Kaplan GA, Shema SJ. 1997. Cumulative impact of sustained economic hardship on physical, cognitive, psychological, and social functioning. *N. Engl. J. Med.* 337:1889–95
35. McEwen B, Seeman T, with Allostatic Load Work. Group. 2009. Allostatic load and allostasis. In *Allostatic Notebook*. Last revis. Aug. San Francisco: MacArthur Found. **http://www.macses.ucsf.edu/research/allostatic/allostatic.php**
36. McEwen BS. 1998. Protective and damaging effects of stress mediators. *N. Engl. J. Med.* 338:171–79
37. Menzie CA, MacDonell MM, Mumtaz M. 2007. A phased approach for assessing combined effects from multiple stressors. *Environ. Health Perspect.* 115:807–16
38. Morello-Frosch R, Brody JG, Brown P, Altman RG, Rudel RA, Perez C. 2009. Toxic ignorance and right-to-know in biomonitoring results communication: a survey of scientists and study participants. *Environ. Health* 8:6
39. Morello-Frosch R, Jesdale BM, Sadd JL, Pastor M. 2010. Ambient air pollution exposure and full-term birth weight in California. *Environ. Health* 9:44
40. Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. 2011. Understanding the cumulative impacts of inequalities in environmental health: implications for policy. *Health Aff.* 30:879–87
41. Murray CJL, Lopez AD. 1996. *The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020*. Cambridge, MA: Harvard Sch. Public Health on behalf of the World Health Organ., World Bank
42. Natl. Res. Counc., Comm. Health Impact Assess., Board Environ. Stud. Toxicol. 2011. *Improving Health in the United States: The Role of Health Impact Assessment*. Washington, DC: Natl. Acad. Press
43. Natl. Res. Counc., Comm. Improv. Risk Anal. Approaches Used by the U.S. EPA, Board Environ. Stud. Toxicol., Div. Earth Life Stud. 2009. *Science and Decisions: Advancing Risk Assessment*. Washington, DC: Natl. Acad. Press
44. NEJAC (Natl. Environ. Justice Advis. Counc.). 2004. *Ensuring Risk Reduction in Communities with Multiple Stressors: Environmental Justice and Cumulative Risks/Impacts*. Washington, DC: NEJAC
45. O'Connor A, Quizon PM, Albright JE, Lin FT, Bennett BJ. 2014. Responsiveness of cardiometabolic-related microbiota to diet is influenced by host genetics. *Mamm. Genome* 25:583–99
46. O'Neill MS, Jerrett M, Kawachi I, Levy JI, Cohen AJ, et al. 2003. Health, wealth, and air pollution: advancing theory and methods. *Environ. Health Perspect.* 111:1861–70
47. OEHHA (Off. Environ. Health Hazard Assess.). 2014. *California Communities Environmental Health, Version 2.0 (CalEnviroScreen 2.0) screening tool.* Updated Oct., OEHHA, Calif. Environ. Prot. Agency, Sacramento. **http://www.oehha.ca.gov/ej/ces2.html**

48. Olden K, Lin YS, Gruber D, Sonawane B. 2014. Epigenome: biosensor of cumulative exposure to chemical and nonchemical stressors related to environmental justice. *Am. J. Public Health* 104:1816–21
49. Peters JL, Weisskopf MG, Spiro A 3rd, Schwartz J, Sparrow D, et al. 2010. Interaction of stress, lead burden, and age on cognition in older men: The VA Normative Aging Study. *Environ. Health Perspect.* 118:505–10
50. Ponce NA, Hoggatt KJ, Wilhelm M, Ritz B. 2005. Preterm birth: the interaction of traffic-related air pollution with economic hardship in Los Angeles neighborhoods. *Am. J. Epidemiol.* 162:140–48
51. Ragas AM, Oldenkamp R, Preeker NL, Wernicke J, Schlink U. 2011. Cumulative risk assessment of chemical exposures in urban environments. *Environ. Int.* 37:872–81
52. Romani M, Pistillo MP, Banelli B. 2015. Environmental epigenetics: crossroad between public health, lifestyle, and cancer prevention. *Biomed. Res. Int.* 2015:587983
53. Sadd J, Morello-Frosch R, Pastor M, Matsuoka M, Prichard M, Carter V. 2013. The truth, the whole truth, and nothing but the ground-truth: methods to advance environmental justice and researcher-community partnerships. *Health Educ. Behav.* 41:281–90
54. Sadd JL, Pastor M, Morello-Frosch R, Scoggins J, Jesdale B. 2011. Playing it safe: assessing cumulative impact and social vulnerability through an environmental justice screening method in the South Coast Air Basin, California. *Int. J. Environ. Res. Public Health* 8:1441–59
55. Sandel M, Wright RJ. 2006. When home is where the stress is: expanding the dimensions of housing that influence asthma morbidity. *Arch. Dis. Child* 91:942–48
56. Seeman T, Merkin SS, Crimmins E, Koretz B, Charette S, Karlamangla A. 2008. Education, income and ethnic differences in cumulative biological risk profiles in a national sample of US adults: NHANES III (1988–1994). *Soc. Sci. Med.* 66:72–87
57. Seeman TE, Singer BH, Rowe JW, Horwitz RI, McEwen BS. 1997. Price of adaptation—allostatic load and its health consequences. MacArthur Studies of Successful Aging. *Arch. Intern. Med.* 157:2259–68
58. Sexton K. 2012. Cumulative risk assessment: an overview of methodological approaches for evaluating combined health effects from exposure to multiple environmental stressors. *Int. J. Environ. Res. Public Health* 9:370–90
59. Sexton K, Kleffman DE, Callahan MA. 1995. An introduction to the National Human Exposure Assessment Survey (NHEXAS) and related phase I field studies. *J. Expo. Anal. Environ. Epidemiol.* 5:229–32
60. Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. 2009. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. *PNAS* 106:12406–11
61. South EC, Kondo MC, Cheney RA, Branas CC. 2015. Neighborhood blight, stress, and health: a walking trial of urban greening and ambulatory heart rate. *Am. J. Public Health* 105:909–13
62. Threadgill DW, Miller DR, Churchill GA, de Villena FP. 2011. The collaborative cross: a recombinant inbred mouse population for the systems genetic era. *ILAR J.* 52:24–31
63. US EPA (Environ. Prot. Agency). 1998. *Guidelines for Ecological Risk Assessment*. Washington, DC: US EPA. **http://www2.epa.gov/osa/guidelines-ecological-risk-assessment**
64. US EPA (Environ. Prot. Agency). 2015. *EJSCREEN: Environmental Justice Screening Tool*. Updated Sept. 16, US EPA, Washington, DC. **http://www2.epa.gov/ejscreen**
65. US EPA (Environ. Prot. Agency). 2015. *ToxCast™. Advancing the next generation of chemical safety evaluation*. Updated Sept. 25, US EPA, Washington, DC. **http://www.epa.gov/ncct/toxcast**
66. US EPA (Environ. Prot. Agency), Off. Emerg. Remedial Response. 1989. *Risk Assessment Guidance for Superfund. Volume I. Human Evaluation Manual* (*Part A*). *Interim Final.* EPA/540/1–89/002. Washington, DC: Off. Emerg. Remedial Response, US EPA (Environ. Prot. Agency). **http://www2.epa.gov/sites/production/files/2015-09/documents/rags_a.pdf**
67. US EPA (Environ. Prot. Agency), Off. Res. Dev. 2003. *Framework for Cumulative Risk Assessment.* EPA/600/P-02/001F. Washington, DC: US EPA. **http://www2.epa.gov/sites/production/files/2014-11/documents/frmwrk_cum_risk_assmnt.pdf**
68. Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, et al. 1998. Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. *Environ. Health Perspect.* 106:775–92
69. Wallace LA, Off. Res. Dev., US EPA (Environ. Prot. Agency). 1987. *The Total Exposure Assessment Methodology* (*TEAM*) *Study*. EPA/600/6–87/002. Washington, DC: US EPA (Environ. Prot. Agency). **http://nepis.epa.gov/Adobe/PDF/2000UC5T.pdf**

70. Wernham A. 2007. Inupiat health and proposed Alaskan oil development: results of the first integrated health impact assessment/environmental impact statement for proposed oil development on Alaska's North Slope. *EcoHealth* 4:500–13
71. Wild CP. 2012. The exposome: from concept to utility. *Int. J. Epidemiol.* 41:24–32
72. Woodruff TJ, Zota AR, Schwartz JM. 2011. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. *Environ. Health Perspect.* 119:878–85
73. World Bank. 1993. *World Development Report 1993: Investing in Health*. New York: Oxford Univ. Press
74. Yoo HS, Bradford BU, Kosyk O, Shymonyak S, Uehara T, et al. 2015. Comparative analysis of the relationship between trichloroethylene metabolism and tissue-specific toxicity among inbred mouse strains: liver effects. *J. Toxicol. Environ. Health A* 78:15–31
75. Zalli A, Carvalho LA, Lin J, Hamer M, Erusalimsky JD, et al. 2014. Shorter telomeres with high telomerase activity are associated with raised allostatic load and impoverished psychosocial resources. *PNAS* 111:4519–24
76. Zeise L, Bois FY, Chiu WA, Hattis D, Rusyn I, Guyton KZ. 2013. Addressing human variability in next-generation human health risk assessments of environmental chemicals. *Environ. Health Perspect.* 121:23–31
77. Zota AR, Shenassa ED, Morello-Frosch R. 2013. Allostatic load amplifies the effect of blood lead levels on elevated blood pressure among middle-aged U.S. adults: a cross-sectional study. *Environ. Health* 12:64

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