Critical Biological Pathways for Chronic Psychosocial Stress and Research Opportunities to Advance the Consideration of Stress in Chemical Risk Assessment

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Emerging evidence suggests that psychosocial stress and toxicants may interact to modify health risks. Stress–toxicant interactions could be important in chemical risk assessment, but these interactions are poorly understood and additional research is necessary to advance their application.

Environmental health research can increase knowledge of these interactions by exploring hypotheses on allostatic load, which measures the cumulative impacts of stress across multiple physiological pathways, using knowledge about physiological pathways for stress-related health effects, and evidence of common target pathways for both stress and toxicants.

In this article, critical physiological pathways for stress-related health effects are discussed, with specific attention to allostatic load and stress–toxicant interactions, concluding with research suggestions for potential applications of such research in chemical risk assessment. (*Am J Public Health.* 2011; 101:S131–S139. doi:10.2105/AJPH.2011.300270)

IN RECENT RECOMMENDATIONS to the US Environmental Protection Agency (EPA), the National Academies of Science (NAS) stated that nonchemical stressors should be addressed in risk assessment and management when permitted by data. Specifically, the NAS suggested a focus on nonchemical stressors that may influence risk estimates, or that are influenced differentially by potential risk management options.[1] The NAS recommendations coincide with the growing scholarship on the role of psychosocial stress, a nonchemical stressor, in environmental health risk. Psychosocial stress has been examined as a risk factor in environmentally related diseases,[2–5] and as a risk modifying factor for chemical stressors in epidemiological studies[6–8] and toxicological studies.[9–11] It is also emerging as an important explanatory variable in theoretical research/analytical framework proposals to examine disparities, including racial/ethnic and income disparities, in environmental health risk and for diseases with environmental origins.[12–16]

The framework proposed by Morello-Frosch and Shenassa[14] is noteworthy because it explicitly integrates the stress-related concept of "allostatic load" into the traditional environmental exposure–disease paradigm. Allostasis is defined as a dynamic regulatory process wherein homeostatic control is maintained by an active process of adaptation during exposure to physical and behavioral stressors. Allostatic load is defined as the wear and tear on brain and body resulting from allodynamic overactivity as well as dysregulation of the mediators of allostasis. Morello-Frosch and Shenassa[14] posited that allostatic load interferes with normal functioning of protective toxicokinetic and toxicodynamic processes in ways that impair individual resilience and ability to recover from toxic insults; in other words, allostatic load confers some vulnerability to toxic exposures. How allostatic load may confer vulnerability to toxic exposures is poorly understood. Nevertheless, it is a fairly established concept in neuroscience, health psychology, and epidemiology, reflecting both co-occurring risk across multiple physiological systems and cumulation of such risk across time at the individual level after exposure to stressful circumstances.[17,18] To advance knowledge of stress–toxicant interactions and, therefore, the subsequent consideration of stress in chemical risk assessment, the next generation of environmental health research should explore hypotheses on allostatic load using knowledge about established critical physiological pathways for stress-related health effects, and evidence of common target physiological systems and pathways for both toxicants and stress. With a metric that captures multiple impacted systems, the integration of psychosocial stress in environmental health research and risk assessment can focus less on pathway-specific interactions and more on overall physiological or organ system vulnerability. Overall, this macro level focus on stress-induced vulnerability advances the adoption of emerging concepts in chemical risk assessment, such as the use of distributions of background vulnerability in dose–response assessment[1] to better inform risk-based decision-making.

In this article, these physiological pathways are discussed, concluding with suggestions for research to advance the consideration of stress in chemical risk assessment based on the concept of allostatic load. Specifically, this article (1) provides an overview of the neurobiology of stress in the context of pathways through which it contributes to adverse health effects, and with specific attention to the concept of allostatic load; and (2) highlights areas of cross-disciplinary research collaboration to advance knowledge about stress–toxicant interactions within the context of the potential applications of such research in chemical risk assessment.

PSYCHOSOCIAL STRESS AND CHEMICAL-RELATED HEALTH RISK

The experience of stress can vary considerably by race/ethnicity and income,[19–21] and certain types of stress experiences such as poverty seem to be of longer duration through the life course

and across generations for groups such as African Americans.[22] Individuals that experience excessive stress in their lives, as measured by multiple periods of poverty level income, are associated with earlier aging, more depression, and an earlier decline of both physical and mental functioning.[23] Timing of exposure to stress also may be an important consideration. Individuals who were abused as children experience an increased risk for depression, suicide, substance abuse, and earlier mortality and morbidity from a wide range of diseases.[23–25] Neighborhood conditions may also influence stress,[26,27] directly impact health,[28,29] or modify the effects of stress on health.[29] A more detailed discussion of this scholarship is beyond the scope of this article.

Psychosocial stress contributes to adverse physical health effects, including cardiovascular effects such as increased blood pressure and triggering of acute myocardial infarctions (MIs) and reversible cardiomyopathies,[30–34] immune system effects such as inflammation,[35] psychological and social effects such as increased postdisaster depression and anxiety disorders,[36] and even premature death.[37] These same physiological systems are adversely affected by exposure to chemical stressors. For example, particulate matter exposure is associated with cardiovascular morbidity and mortality,[36–45] and exposure to lead has been linked to increased risk of blood pressure and hypertension.[46–48]

Psychosocial stress may interact with chemical stressors to modify risks of adverse health effects. Coexposure to psychosocial stress and lead has been associated with impaired cognition[7,49] and higher risk of hypertension[50] in adults. Higher levels of chronic family stress have been associated with high inflammatory markers in asthmatic children at low levels of traffic-related pollution, leading investigators to hypothesize that the "role of chronic stress may be to lower the threshold at which physical exposures affect biological and clinical outcomes."[6] Increased susceptibility to the effects of traffic-related pollution and in utero tobacco exposure have been observed among children from chronically stressed households,[8] and statistically significant positive associations have been reported between measures of noise disturbance at night and doctor-diagnosed asthma in female children.[51]

Research findings in animal studies lend further support to the concept of chemical exposure–stress interactions. Concurrent exposure of dams to both lead and stress produced a pattern of hypothalamic-pituitary-adrenal (HPA) axis dysfunction with slightly different effects in male and female offspring.[9–11,52–55] Chronic stress caused by social conflict and defeat in rats enhanced the adverse respiratory effects of breathing air containing diesel exhaust and other fine particulates and irritants, and also potentiated white blood cell counts.[56] Reduced fetal weight and increased fetal toxicity were observed after joint exposure to perfluorooctane sulfonate and stress in pregnant mice, relative to previously reported studies of perfluorooctane sulfonate exposure alone.[57]

CRITICAL PHYSIOLOGICAL PATHWAYS FOR STRESS-RELATED EFFECTS

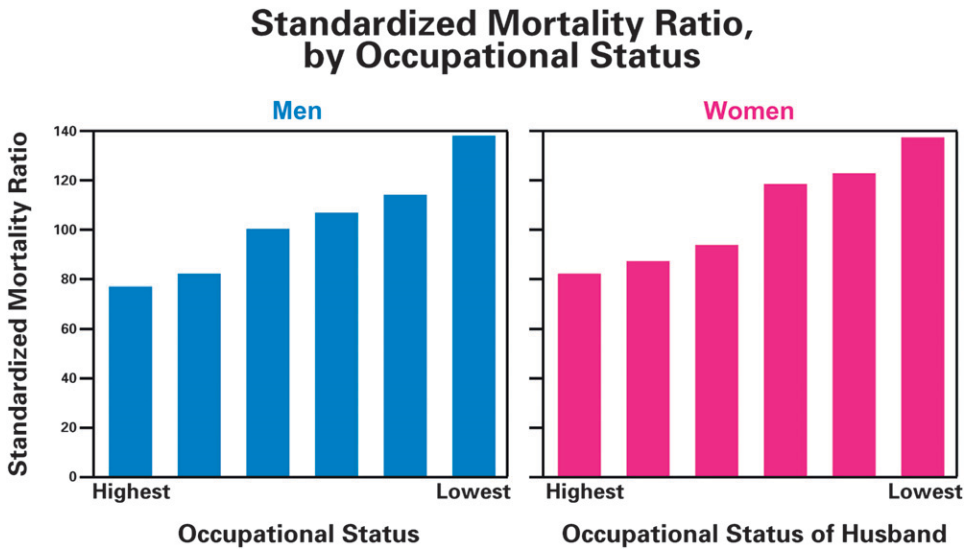
There is cumulative evidence that disparities in income, education, occupation, and other dimensions of socioeconomic status (SES) account statistically for appreciable variance in all-cause and disease-specific morbidity and mortality rates, as well as the prevalence of risk factors for chronic medical conditions[58–60] and prevalent psychopathologies of mood and substance abuse.[61,62] That health and longevity track a socioeconomic gradient cannot be explained entirely by material deprivation, illiteracy, or restricted availability of quality health care among individuals of lower SES.[59,63,64] Hence, several conceptual models of SES-related health disparities posited that additional life experiences inherent to socioeconomic position at the individual, familial, and community levels could influence well-being and disease risk through stress-related pathways.[59,63,65,66] For example, the chronic experience of low SES at the individual level could involve a number of issues causing stress, including enduring financial hardships, a sense of insecurity regarding future prosperity, and the possible demoralizing feelings of marginalization or social exclusion attributable to comparative social, occupational, or material disadvantage. Further, an individual's negative perception of her or his relative standing or ranking in a social hierarchy, formally termed subjective social status, might affect an individual's pattern of emotional, behavioral, and physiological reactivity to and recovery from life stressors, consequently impacting risk for ill health.[67–71]

Low SES is associated with shorter lifespan and increased incidence of a variety of diseases (Figure 1).

SES is thought to "get under the skin" via the brain (Figure 2), impacting its ability to regulate peripheral physiology, engage in adaptive social and health behaviors, experience and control emotions, and support cognitive functioning. Hence, a person who develops, matures, and ages in a household of low SES could become vulnerable to impairments in the functionality of stress regulatory systems of the brain and body, systems important for health.

Critically, such stress-related processes may unfold not only at the individual level, but also at the level of families and residential areas. For example, children who develop in lower SES households, in addition to being exposed to toxic substances and excessive noise and temperature variations, are more likely to live in unfavorable housing conditions and to be exposed to what have been termed "risky family" dynamics.[74] Such dynamics are characterized by conflict-laden relationships, aggressive and harsh parenting, and other forms of early life stress that may alter risk trajectories for ill health in later life.[74] Finally, individuals living in low SES neighborhoods may be more frequently exposed to stressful life events[75,76] in association with higher concerns over community crime, pollution, and crowding,[77] as well as unstable, effortful, and unrewarding employment opportunities related to persistent economic hardship.[78]

As the key target organ for stress and the effects of inequality, deprivation, and discrimination[18,72,78,79] (Figure 2), the brain not only processes inputs from the external environment, but it also controls adjustments of the body engendered by behavioral states like waking, sleeping, lying, standing, and exercising. These bodily adjustments promote adaptive activities, such as locomotion, and coping with aversive situations and discrete stimuli, such as noise, crowding, hunger, excessive heat



Note. SES = socioeconomic status. The standardized mortality ratio is the ratio of actual deaths to expected deaths. Note that there is an almost linear gradient with occupational status in the British Civil Service in which all persons have jobs and access to health care. The gradient indicates that there are aspects of income and education related to stress and lifestyle that are related to health and mortality.

FIGURE 1—Inverse relationship between SES and mortality ratio in Whitehall Study.[63,72,73]

or cold, and other threats to safety. Brain regions such as the hippocampus (memory), amygdala (fear, anxiety), and prefrontal cortex (decision-making, impulse, and mood control) are all affected by stress.[79]

The body has a set of mediators of stress and adaptation strategies that are activated by physical and psychological stressors and their interactions with each other. These mediators include not only hormones of the HPA axis, but also the sympathetic and parasympathetic nervous systems, and the pro- and anti-inflammatory cytokines. Each class of mediators regulates activity of other mediators and thus operates in a nonlinear network.[80] This network of mediators affects all tissue and organ systems, including the brain.[79] For most diseases, from diabetes to cardiovascular disease to cancer, inflammation is a key factor. Production of inflammatory mediators is stimulated by physical pollutants (e.g., from diesel exhaust), as well as by psychological stress.[81,82] Thus, psychological and physical stressors could potentiate each other through common physiological pathways such as inflammation.[79,81,83]

To further understand these regulatory processes, the key concepts of allostasis and allostatic load that complement the concept of homeostasis are introduced. Although it is true that physiological parameters like blood oxygen and pH are maintained in a narrow range (homeostasis), the cardiovascular system, metabolic machinery, immune system, and central nervous system all show a large range of activity as a function of the time of day and in response to external and internal demands (allostasis). Allostatic load affects the brain and the body and promotes ill health, involving not only the consequences of stressful experiences themselves, but also the alterations in lifestyle that result from a state of chronic anxiety and stress (e.g., eating too much of the wrong things, smoking, drinking, and sleeping badly).

Systems of allostasis that promote adaptation include the HPA axis, the autonomic nervous system, the metabolic system (including the thyroid axis, insulin, and other metabolic hormones), the gut, the kidneys, and the immune system (including the regulated network of cytokine producing cells throughout the body). The biological mediators of these systems (e.g., cortisol, sympathetic and parasympathetic transmitters, cytokines, and metabolic

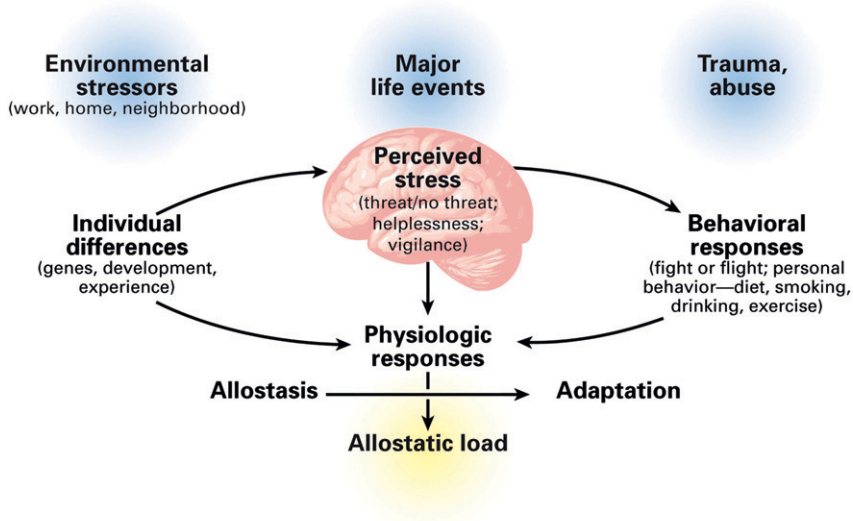


FIGURE 2—The central role of the brain.[18,72]

hormones) operate as a nonlinear, interactive network to maintain allostasis (Figure 3), in which mediators down- and up-regulate each other, depending on such factors as concentration, location in the body, and sequential temporal patterning.[80] Importantly, the activity of these mediating systems and mediators is closely coupled to psychological and genetic makeup, developmental history, and behavioral state of the individual.

STRESS-RELATED DYSREGULATION AND ADVERSE OUTCOMES

Adversity, including interpersonal conflicts, social instability, and other stressful experiences, can accelerate pathophysiological processes through adaptive systems of the body, increasing vulnerability for higher morbidity and mortality rates at the population level. The cardiovascular system is one of the most susceptible systems to stress. For example, blood pressure can increase because of job stress in factory workers, particularly in employees with repetitive jobs and time pressures,[84] and in British civil servants of departments undergoing privatization.[85] As further evidence, the stressful social collapse after the fall of communism in Eastern Europe led to cardiovascular disease being a primary cause for the increased death rate.[86] It is noteworthy that otherwise adaptive and brain-mediated stressor-evoked blood pressure surges have been linked to accelerated atherosclerosis,[87] as well as increased risk for MI.[88,89] Besides the adverse effects on the cardiovascular system, there are indications that metabolic disorders and abdominal obesity—contributors to cardiovascular disease—are increased at the stressful lower end of the socioeconomic gradient in Swedish men[90] and in the British Civil Service[63] (Figure 3). Finally, there is growing epidemiological evidence that impaired immune system function is also a likely target of stress processes within the context of socioeconomic position.[2,91–96]

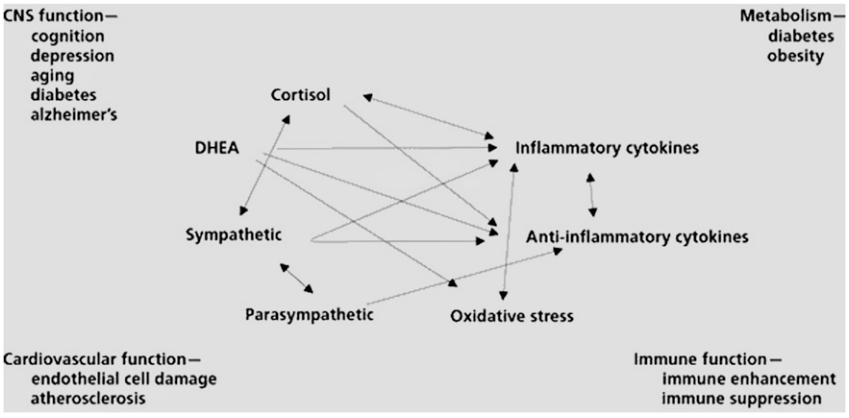
Stress-related processes impacting health within the context of SES can be viewed and understood by appreciating the marked differences that individuals show in response to adverse acute and chronic stressors.[97] In other words, individuals respond in different ways to adversity and threats (real or implied) to their safety and homeostasis. Mediators of allostasis, therefore, facilitate adaptation, whereas the parameters associated with homeostasis do not vary as a means of promoting adaptation. Importantly, variation in mediators associated with adaptation has long been appreciated, particularly beginning with the early work of Walter Cannon[98] on the human body. Allostatic systems are involved in coping and adaptation, and generally, they are most useful when they can be rapidly mobilized and then shut off when not needed. It is when their activity is prolonged or not terminated promptly that these systems undermine health. Moreover, the inability to engage allostatic systems when needed also produces a load on the body, because the normal protection afforded by these systems is lacking.

An important aspect of allostasis is the notion of anticipation, which can add to allostatic load. Although originally introduced in relation to explaining the reflex that prevents us from blacking out when we get out of bed in the morning,[99] anticipation also implies psychological states, such as apprehension, worry, and anxiety, as well as cognitive preparation for a coming event. Because anticipation can drive the output of allostatic biomediators (this is particularly true of hormones like adrenocorticotropic hormone, cortisol and adrenalin), it is likely that states of prolonged anxiety from anticipation can result in allostatic load.[100]

Other important aspects of individual responses in relation to allostasis and allostatic load are health damaging and health promoting behaviors, such as smoking, drinking, sleeping, eating a prudent diet, and regularly exercising, collectively called "lifestyle" behaviors. These may be embodied within the overall notion of allostasis (i.e., how individuals cope with a challenge) and they also contribute in some ways to allostatic load (e.g., a Western [high-fat] diet accelerates atherosclerosis and progression to type 2 diabetes; smoking accelerates atherogenesis; exercise and restorative sleep promote cognitive functioning and health).[80]

PHYSIOLOGICAL RESPONSES TO ALLOSTATIC LOAD

There are 4 types of physiological response that may contribute to and reflect allostatic load. The first type is related to frequent stressors, for example, blood pressure surges that not only trigger MI in susceptible individuals, but also accelerate atherosclerosis and prime the risk for MI when they are repeatedly expressed over the lifespan. Here, it is the frequency and intensity of the "hits" or events (e.g., high blood pressure surges) that determine the level of allostatic load engendered by this type. Frequent stress may lead to the other types of allostatic load



Note. CNS = central nervous system; DHEA = dehydroepiandrosterone.

FIGURE 3—The nonlinearity of the mediators of stress and adaptation.[80]

described as the body responds to repeated events by either failing to terminate neural and endocrine responses or failing to respond adequately.

The second type of allostatic load is the failure to habituate to repetition of the same stressor, leading to a persistent elevation of mediators like cortisol. This was first described in a subset of individuals who failed to habituate their cortisol response in a repeated public speaking challenge.[101] Later studies showed that such individuals had a low sense of self confidence, low self-esteem, and a smaller hippocampus, leading to stress-related behavioral and neurobiological processes.[102,103]

The third is the failure to terminate adaptive autonomic and neuroendocrine responses. Consider, for example, blood pressure elevations in repetitive, time pressured work[104] and that chronic, elevated levels of glucocorticoids accelerate obesity and type 2 diabetes. Moreover, persistent glucocorticoid elevation and/or excitatory activity in brain systems that regulate glucocorticoid secretion cause dendritic remodeling and neuronal death in the hippocampus and in other limbic brain areas. When these conditions persist over months and years, chronic overactivity of cortisol as well as other mediators of stress and adaptation through allostasis (see Figure 2) leads to allostatic load and promotes cumulative changes that lead to disease.

The fourth type of allostatic load is the failure to respond adequately to a challenge. Consider, for example, autoimmunity and inflammation that are associated with inadequate endogenous glucocorticoid responses, as in the Lewis rat[105] and possibly also in chronic fatigue syndrome and fibromyalgia.[106,107] Here, other biomediators of allostatic systems, such as inflammatory cytokines, show elevated activity, and this elevation may increase allostatic load because of inadequate HPA regulation, which normally "constrains" the activity of these biomediators. Posttraumatic stress is a form of psychopathology; it is yet another example of how an acute, but traumatic event leads to dysregulated HPA axis activity that may not respond adequately to acute challenge and may therefore promote comorbid physical disease.[108]

Measures of allostatic load hold promise for identifying populations that are already vulnerable because of psychosocial stress, and also for conducting the necessary population studies to elucidate the interactions between chemical stressors and psychosocial stress. The measurement of allostatic load involves tests that are normally used in physical examinations. Up to 14 different measures are collected and a point is awarded when an individual's value in a given test is in an extreme quartile for the population under study. The total points determine the overall allostatic load score.[109] As an example of how allostatic load scores are developed, the current allostatic load battery in the National Institute of Health's sponsored study called Coronary Artery Disease Development in Young Adults taps into autonomic nervous system, HPA, inflammatory, and acute phase measures as well as metabolic and cardiovascular parameters,[110] as shown in Table 1.

The allostatic load score has been very useful in predicting mortality over 7 years in the MacArthur Successful Aging study; it has also been useful in predicting decline of physical and cognitive functioning.[109] High allostatic load is also related to having few social ties and being isolated.[111] Racial differences are found in allostatic load scores between Black and White men and women, with individual biological markers showing different importance between Blacks and Whites and between men and women.[112] The racial differences may reflect, in part, effects of discrimination.[110]

DISCUSSION

From a neurobiological viewpoint, it is most important to recognize that there is a response network for stress—the network of allostasis that responds to psychological stressors—generated through the brain, the central organ of stress and adaptation. This network, or at least parts of it, respond to toxic agents (e.g., air pollution leads to inflammation, which, in turn, activates cortisol responses). Lead exposure may do the same; it certainly seems to alter cortisol[113] and is probably proinflammatory as are most toxicants (including radiation). Both cortisol and parasympathetic activity "attempt" to contain the inflammation, but sympathetic activity related to acute stress, sleep deprivation, and other stress enhances inflammation. Imbalances in the network because of chronic psychological stress and lifestyle (e.g., poor sleep, excess calories and obesity/diabetes, alcohol) cause the network to respond differently to toxic agents, and evidence so far (which is in need of more documentation) indicates that there is synergy and enhancement of, for example, the inflammatory response and further imbalance in the network. Over time, the imbalance in the network leads to allostatic load/overload that accelerates disease processes.

These points lead to the general conclusion that one cannot study toxic agents in a vacuum without considering psychological stressors and their impact on body physiology. Several opportunities exist to advance current knowledge of chemical–stress interactions in ways that are useful to chemical risk managers. For example, more data on differential dose–response relationships as a function of psychosocial stress levels can inform the selection of regulatory options to limit the

TABLE 1—Coronary Artery Risk Development in Young Adults Allostatic Load Measurement Battery[110]

Measure (biological medium)	Assayed for (change in biological marker)
Urine (12 h overnight)	Norepinephrine, epinephrine, cortisol
Saliva (6/d to map circadian variation)	Cortisol
Blood	Total and HDL cholesterol, glycosylated hemoglobin, IL-6, CRP, fibrinogen
Other measures	Waist/hip ratio, systolic and diastolic blood pressure, heart rate variability

Note. CRP = C-reactive protein; HDL = high-density lipoproteins; IL = interleukin.

concentration of chemicals in ambient media. This type of information can be generated through population studies in which toxic effect modification, because of allostatic load as a measure of the cumulative impact of stress, is a key hypothesis. This field of research can be advanced in present time and with limited resources using exploratory cross-sectional studies to investigate how allostatic load may change known relationships between exposure to environmental contaminants and adverse health outcomes, and using existing databases such as the National Health and Nutrition Examination Survey. The use of National Health and Nutrition Examination Survey data for allostatic load considerations has been illustrated by several authors.[112,114–116] This type of research can provide the basis for more in-depth confirmatory population studies. Also, knowledge that allostatic load confers enhanced vulnerability to chemical exposures can lead to the development of distributions of baseline vulnerability because of psychosocial stress using allostatic load as the measure. Data on baseline vulnerability can also be applied in dose–response assessments in risk assessment.[1]

Given that allostatic load requires measurement of biological parameters in the population, its wide deployment in policymaking may be limited by lack of data. For this reason, we advocate cross-disciplinary research mostly between the social and biological sciences to identify community level characteristics that correlate with and accurately predict allostatic load. As mentioned in the section Critical Physiological Pathways for Stress-Related Health Effects, SES may be a useful proxy measure of allostatic load because there is greater vulnerability to illness in lower SES populations. Additionally, there is evidence that children exposed to low levels of environmental toxins in higher SES, more well educated households may not experience the same health effects as children in more risky, adverse households.[117] The protective effects of a less adverse childhood on child development after toxic exposure is an area that could be explored. Community level data are easier to collect through the census and local scale surveys. These data are a potentially useful layer in screening and targeting tools designed to identify vulnerable or environmental justice communities. Several of these tools have already been developed or are being developed by environmental protection agencies and researchers.[118–121] Also, the ability to identify vulnerable communities or places can advance the evaluation of the impacts of regulatory policy options on these populations, and therefore aid the selection of protective regulatory policy.

How stress from fear of exposure to environmental hazards changes the allostatic load of populations living within the vicinity of sources or exposed to hazards is an unexplored yet important area of research. The prevalence and concentration of sources of environmental hazards are more common in racial minority and low income neighborhoods.[121,122] Populations that are chronically faced with these "technological disasters," which include contamination sites, are more likely to experience higher levels of chronic psychosocial stress.[26] Coping with such stress has to deal with threat perception, which is greater in racial and ethnic minorities in the United States[123]; minorities may experience a greater threat level because of issues such as greater proximity to location of a perceived threat, attachment to that location, and economic ties to the industry involved in the technological disaster.[26] Given that certain racial/ethnic minorities tend to have higher baseline allostatic load,[111] the effect of incremental psychosocial stress triggered by proximity to environmental pollution may mean that these groups are in the extreme right of the allostatic load distribution. Atypically high levels of allostatic load may not be captured in general population surveys. Therefore, the extent to which conditions of unusually high allostatic load impact health may not be adequately reflected in studies that use general population surveys. Assuming that the presence of sources of environmental hazards consistently predicts very high allostatic load, such a community vulnerability characteristic can serve as a useful layer in the types of risk screening tools alluded to in the previous paragraph.

Mechanistic studies are also necessary to advance understanding of chemical–psychosocial stress interactions in ways that can directly inform chemical risk management. One reasonable model would be to evaluate how psychosocial stress, measured by allostatic load, independently affects key biomarkers of the effects of a specific chemical. This research can inform assumptions that feed into the dose–response assessment for that chemical. With information from this type of study, risk assessors would have access to ample evidence to apply the concept of differential vulnerability to the process of identifying an exposure level that is without appreciable risk of harm. Finally, the nature of the interactions between various chemicals and stress is not fully elucidated and merits additional research in both the fields of epidemiology and toxicology.

Conclusions

In summary, bringing together the worlds of neurobiology, social sciences, epidemiology, and toxicology is the next frontier in terms of generating the necessary data to support suggested theoretical frameworks for considering psychosocial stress in risk assessment or management aimed at addressing environmental health disparities. Some of this work is already in progress in the form of emerging epidemiology and toxicology studies that explore the interactions between psychosocial stress and exposure to chemical stressors. We envision that the new directions proposed herein will lead to an influx of readily applicable data in a 3 to 5 year period. Specifically, we anticipate the generation of several types of pertinent data to advance the field, such as modified dose–response curves as a function of allostatic load and/or external measures of stress such as psychosocial hazards at the community level. Given that risk assessments do not currently account for effects of psychosocial stress in addition to toxic exposures that people experience in their communities, the inclusion of such data are likely to produce risk management decisions that are more informed and more health protective.

Finally, we recognize the need for more cross-disciplinary training and interaction for regulators, risk assessors, public health scientists, and other types of scientists whose research is obviously relevant to environmental health protection. This requires paradigm shifts in how training is structured in institutions of higher learning, and more importantly highlights

the need for regulatory agencies to increase their technical capacity in areas originally considered nontraditional, such as the social sciences. ■

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B.S. McEwen contributed material on stress and human physiology and allostatic load. P.G. Tucker contributed material on related stress studies in animal models. Both authors participated in the discussions, conclusions, and research recommendations.

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This article did not involve any research involving human subjects; institutional review board approval was not required.

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