

## Breaking Patterns of Disease

### Early-Life Clues May Predict Long-Term Health

Modern diseases often seem to occur in isolation, but many are now known to emerge from a complex web or pattern of conditions linked together by certain underlying biological mechanisms and processes. With the help of large disease databases, medical scientists have begun to discern how such patterns occur over the course of a lifetime. A new review focused on developmental immunotoxicology explores how this integrative perspective might inspire novel strategies for lowering the risk and prevalence of immune-based diseases influenced by environmental stimuli [*EHP* 118(8):1091–1099; Dietert et al.].

Many chronic diseases share three common features: 1) early-life exposures to chemical agents or pathogens, 2) evidence of immune



## An Uneven Path Forward

### The History of Methylmercury Toxicity Research

Organic mercury compounds were first described in the 1800s, with fatal cases of methylmercury poisoning reported in 1865. Early reports described a distinct set of symptoms of methylmercury toxicity, including altered sensation in the face and extremities, tunnel vision, deafness, loss of coordination, and impaired speech. Nearly a century later, against a backdrop of widespread environmental contamination, the clinical picture reappeared, and suspicions of additional harm to human health had developed. Yet it wasn't until 2009 that international agreement to control mercury pollution was reached. A historical review suggests that—as one early commenter observed—the tunnel vision, forgetfulness, and lack of coordination that symptomize methylmercury toxicity can also affect the conduct and interpretation of environmental health research [*EHP* 118(8):1137–1145; Grandjean et al.].

Methylmercury became commercially important as a crop fungicide around 1914. Worldwide use was accompanied by worker poisonings and several large-scale food poisoning incidents. The compound emerged as an industrial pollutant in the early 1950s around Japan's Minamata Bay, where contaminated seafood induced neurologic symptoms mirroring those reported in 1865. Epidemiologic evidence from Minamata, paired with a 1952 report from Sweden, indicated more severe disease from prenatal and early-life exposures, with symptoms including mental retardation, seizures, and impaired motor development. In the 1960s, advances in analytical technology permitted

insult or dysfunction, and 3) the appearance of disease biomarkers in exposed children although disease itself may not manifest until later in life. One example of interlinked disease conditions highlighted by the authors is metabolic syndrome, defined as the co-occurrence of at least three of five conditions: insulin resistance, obesity, high blood pressure, elevated triglycerides, and reduced HDL cholesterol.

Immune dysfunction is central to the underlying physiology of metabolic syndrome, and the authors posit that the seeds of such dysfunction may be planted in childhood. They describe pre- and postnatal exposures to environmental risk factors that produce postnatal lipid dysregulation and immune dysfunction. However, it is not yet known whether immune dysfunction is an underlying cause of metabolic syndrome or simply an associated or disease-facilitating characteristic.

The practical key to preventing metabolic syndrome may lie in treatments that address overall patterns and their progression, not just the initial presenting condition. “For those patterns of disease with immune involvement,” the authors write, “preventing the underlying immune dysfunction is the single most effective option to minimize the risk of one or more chronic diseases later in life.” This will require more information about risk factors for immune dysfunction that are encountered during development or childhood. Therefore, the authors also recommend that chemicals and pharmaceuticals be tested for developmental immunotoxicity end points; currently, safety assessments are based solely on adult exposures.

The authors say patterns of disease can be used to better predict, prevent, and treat diseases associated with an immune-related pattern of diseases, and may also serve as the basis for environmental protection and testing to prevent exposure to developmental immunotoxicants that may contribute to multiple interconnected diseases. But pattern-based evaluation, prevention, and treatment will require a shift from the prevailing single-organ approach to disease classification and management.

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chemical analysis of mercury species in environmental samples, resulting in the discovery of methylmercury biomagnification in the food chain and identification of environmental methylation of inorganic mercury in waterways. Methylmercury had become a worldwide problem, not simply a local issue.

Defining the scope of the problem, much less acting to address it, has involved a political, legal, and ethical maze set on an ever-evolving and still-incomplete scientific foundation. Initially, the inability to identify mercury species in the environment hampered researchers' efforts to link the presence of methylmercury with poisoning symptoms. That link also was blurred by a time lag of weeks to months between exposure and initial symptoms as well as slow recognition of the significance of experimental and wildlife data. Industrial suppression of toxicity data impaired accurate risk assessment, as did imprecise estimates of exposure, delayed recognition of low-dose effects, and use of adult data only.

Consequently, regulatory safeguards established in the 1960s and 1970s are now known to be inadequate, but improvements have been deferred in light of scientific uncertainties. For example, although it remains unknown whether a “safe” threshold exists for prenatal and early-life exposure to methylmercury, evidence of methylmercury damage to neurodevelopment has been accumulating since the 1950s. More research is certainly needed, the authors write, but prevention and correction of environmental health problems need not and should not be delayed by a desire for absolute proof.

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## Body of Proof Biomonitoring Data Reveal Widespread Bisphenol A Exposures

A review of more than 80 biomonitoring studies from nine nations suggests exposure to bisphenol A (BPA) is ubiquitous in people throughout the world [*EHP* 118(8):1055–1070; Vandenberg et al.]. Moreover, in samples of blood serum, median levels of unconjugated (biologically active) BPA were higher than levels predicted by toxicokinetic models that form the basis of U.S. regulations for the compound, reaching the range that has been shown to cause adverse effects in animals.

More than 8 billion pounds of BPA are produced each year, making it one of the world's most heavily used chemicals. BPA is used in baby bottles, drinking bottles, food storage containers, polyvinyl chloride, stretch films, paper, cardboard, medical equipment, and the epoxy resins lining most metallic food and beverage cans. BPA has estrogenic properties, and animal studies have linked low-level exposure to altered development of the male and female reproductive tract and brain as well as cancers of the mammary gland and prostate.

The authors analyzed 24 biomonitoring studies involving blood serum samples from healthy adults, adults with certain diseases, pregnant women, and fetuses or fetal tissues. Overall, these studies indicate exposure to unconjugated BPA is in the range of 0.5–10 ng/mL, with most studies suggesting an average exposure of 1–3 ng/mL. The latter concentrations are higher than those shown to cause effects in human and animal cell cultures.

The only data on BPA levels in children after birth is from studies of urine samples, most of which measured total (conjugated and unconjugated) BPA, but some of which measured unconjugated BPA separately from conjugated (inactive) BPA. The Centers for Disease Control and Prevention measured total BPA in urine samples from 314 children aged 6–11 years and 715 adolescents aged 12–19. Compared with adults, the younger children's levels were highest, and adolescents were in-between. Other smaller studies also showed that BPA concentrations were higher in neonates and young children than in adults.

Some of the studies measuring BPA in human blood were conducted using the enzyme-linked immunosorbent assay. Although this assay is considered less specific than the more precise analytical chemistry methods now favored for measuring BPA, the authors argue these studies are worthy of inclusion in their review because the concentrations they report are in line with what have been detected using the newer methods.

The paper also points out “significant deficiencies” in the two studies that have examined the toxicokinetics of BPA exposure in humans, which they say have been given undue weight in regulatory decision making. The authors note we don't yet know all the potential sources of exposure to BPA, which makes it impossible to predict toxicokinetics. Because the biomonitoring findings contradict the toxicokinetic studies, the authors recommend in a related commentary in the same issue [*EHP* 118(8):1051–1054; Vandenberg et al.] that biomonitoring data be considered in regulatory decision making whenever available rather than relying only on toxicokinetic models to estimate exposure.

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## Bringing the Bugs Back In Environmental Health Research Model Combines Toxicology and Infectious Disease

Although pathogens are known to modify the effects of toxicants, U.S. environmental health research currently focuses on physical agents and chemical toxicants—a focus that limits the field by ignoring the interaction between pathogens and toxic agents [*EHP* 118(8):1165–1172; Feingold et al.]. These authors present a conceptual paradigm that integrates infectious disease and toxicologic environmental health research, promotes cross-disciplinary education and communication, and elucidates a fuller body of environmental health risk factors.

Chemical toxicity often involves relatively direct effects of exposures on health outcomes, but infectious disease transmission typically is more complex, depending on factors such as dynamic environmental and ecologic systems, patterns of contact among populations, and host immune status. But interactions between pathogens and toxicants are undeniable. For instance, hepatitis B virus and aflatoxin individually increase the risk of liver cancer, but combined exposure to both agents increases risk far more than would

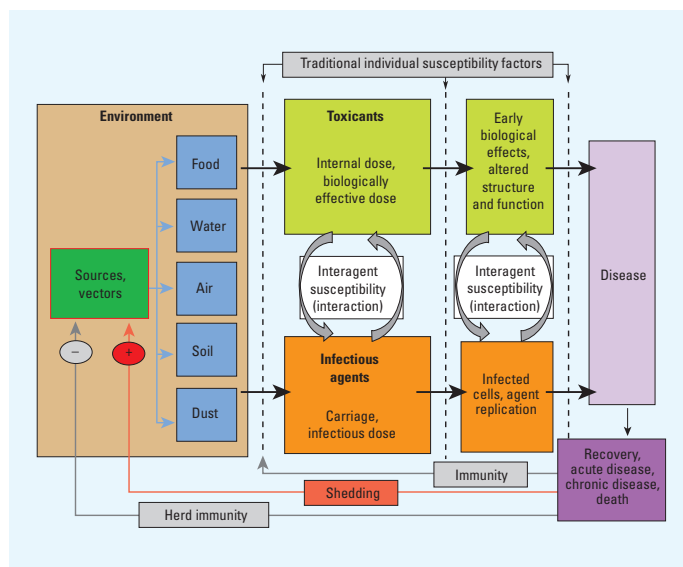
be expected based on effects of the two risk factors in isolation. And in the case of cervical cancer, although infection with human papillomavirus is believed to be necessary for the cancer to occur, smoking may act as a cofactor and increase the risk the cancer will occur in someone infected with the virus.

The authors identify multiple points between initial exposure and clinical disease at which toxicant–pathogen interactions can occur. They also describe approaches common to both areas of research. Both focus on upstream interventions to prevent disease by preventing exposure. Both areas also focus on spatial context (i.e., proximity to toxic or

pathogenic agents) and quantitative modeling to estimate exposure, and both use biomarkers to study exposure, susceptibility, and disease.

Fostering collaborations between researchers in these fields can lead to a better understanding of complex exposures and resulting diseases. “Classic reductionist thinking in toxicology focuses on ‘one toxicant, one outcome’ research,” the authors write. In contrast, they conclude, “If basic research is to increase our ability to predict the consequences of exposure to environmental chemicals, we must embrace nonreductionist thinking and design experimental models that emulate human experience.”

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**Pathogen–toxicant interactions may influence the progression from exposure to disease at multiple points.**