

VIEWPOINT

## Low-Level Chemical Exposures: A Challenge for Science and Policy

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Once thought to be safe, there is mounting evidence that human exposure to chemicals at low levels can be harmful. The exposures are linked with adverse biological effects, including endocrine disruption (1), chemical sensitivity (2), and cancer (3). Prior susceptibility of an individual, whether inborn or environmentally induced, followed by other lifetime exposures, can cause irreversible injury. Unfortunately, although emerging scientific knowledge associated with these exposures indicates a need to change the way we think about chemicals and health, new theories are slow to emerge.

We are just now beginning to recognize the link between chemicals and new public health problems that challenge the tenets of traditional toxicology and medicine. These include birth defects and other damage due to developmental toxicants, autoimmune diseases (including lupus, scleroderma, and Sjogren's Syndrome), chronic conditions in children (such as attention deficit hyperactivity disorder, depression, and asthma) that have become more prevalent in the past few decades, chemical sensitivity including its overlaps with sick building syndrome, unexplained illnesses of Gulf War veterans, chronic fatigue syndrome, fibromyalgia, toxic encephalopathy, and new links to cancer, including childhood cancers.

### Problem characterization

These emerging health problems are characterized by common threads that provide a new perspective on disease.

**Nature:** They are a departure from classic diseases such as tuberculosis and heart disease. Communication systems or networks—including the endocrine system, the immune system, and the neurological system—rather than specific organs of the body, appear to be targeted.

**Cause:** No single cause has been identified for each of these conditions.

Often there are no clear biomarkers for either exposure or disease. Consequently, classical epidemiology is less able to identify susceptible or sensitive subgroups.

**Stages:** Disease becomes manifest after two or more stages or events occur. For example, some cancers may proceed first by initiation—a mutation that alters the genetic material of the cell—followed by the promotion of cancer cells to a recognizable tumor. These stages can involve different chemicals, radiation, or viruses. It has been hypothesized that Toxicant-Induced Loss of Tolerance (TILT), a new theory of disease, leading to chemical sensitivity, also proceeds via a two-stage process: an initial exposure to high levels of certain chemicals (or repeated exposures at lower levels), followed by triggering of symptoms by everyday chemical exposures at levels that do not appear to affect most people (2). **Time:**

The time between the first and subsequent stages of disease can be long enough to obscure the connection between exposures and ultimate disease. The latency of chemically caused cancer is measured in years. Observable reproductive system failure can occur years after endocrine disruption. Chemical sensitivity reportedly can develop months after the initial exposure and remain manifest for years. The timing of the initiating doses appears important. Loss of tolerance does not always require a high initial dose; smaller doses, strategically timed, might also cause pathological loss of tolerance.

**Nonclassical explanation:** Classical approaches and models used in both toxicology and epidemiology, premised on single agents disrupting individual organs, do not explain these diseases. Moreover, the relationship between the initiating exposure and ultimate health effects is not monotonic. This is illustrated in the recent work of Fred vom Saal on the endocrine-disrupting effects of bisphenol A, as discussed in Hileman's article (5). Endocrine disruption (ED), TILT, and some cancers appear to represent a failure in functional and adaptive processes in important systems or networks as a result of chemical exposures at concentrations 3 to 6 orders of magnitude lower than those associated with classical toxic effects in normal individuals. Moreover, individuals exposed below "safe" thresholds to multiple xenobiotics simultaneously, as in a sick building, are affected.

**Disease processes:** Endocrine disruption (ED), TILT, and some cancers may be interrelated. ED disrupts normal development, and possibly the immune system, which results in increased susceptibility to certain cancers. ED might also affect the neurological system, leading to increased susceptibility to sensitization by chemicals. TILT manifests itself as a loss of tolerance to everyday chemical, food, and drug exposures in affected persons, possibly leaving these individuals more susceptible to other diseases. Just as the general category of infectious diseases encompasses a diverse disease spectrum involving different organisms (which affect different organs via different specific disease mechanisms), TILT may arise from different chemical exposures (which, like the infectious diseases, could affect different organ systems via different specific disease mechanisms). With TILT, key systems of the body appear to lose their ability to adapt to low-level chemical exposures. Finally, cancer proceeds when adaptive, homeostatic repair

processes and the immune system no longer function as they should, although the cause of this loss of protective function is not well understood.

#### Framework for response

A systems-focused approach to disease is needed to fashion policy responses. Lack of clear biomarkers and the time lag between initiating exposures and ultimate disease make it technically and politically difficult to develop evidence needed for regulating many chemicals and industrial processes or to resolve compensation issues. We must therefore consider adoption of the Precautionary Principle (acting preventively in the face of uncertainty), erring on the side of caution. Applying the Precautionary Principle requires stakeholder education, political courage, and conviction. Concern that new problems-such as asbestos-related cancer, and the toxic effects of benzene, lead, and persistent pesticides-are emerging generally has begun with only a modest suggestion of evidence. When strengthened by further information, concern grows. Often, early warnings warranted heeding: Predictions were in the right direction, if not understated. Unfortunately, although precautionary actions were justified, too much time elapsed before they were implemented, and harm occurred. Some damage has already been done by endocrine-disrupting chemicals, but a growing recognition of the need to address problems now presents an opportunity to act quickly. Some aspects of endocrine disruption and other systemic damage or injury remain uncertain, and potentially regulated industries are opposed to costly controls. Nonetheless, rapid intervention to prevent the next generation of developmentally compromised or chemically intolerant individuals is possible and advisable. Uncertainty and economic concerns may appear to pose a dilemma for environmental legislators and regulators (they may fail to regulate a chemical that is later discovered to be harmful, or they may, at cost to industry and consumers, regulate a chemical and later find that the chemical is safe to use), but potentially harmful chemicals should be regulated when scientific evidence, although imperfect, is compelling.

A policy response consistent with a precautionary view presents specific challenges: Policies must be harmonized and coordinated among the major stakeholders. A new corporate stewardship is required, one that is harmonized with the customers' and the public's expectations that companies will adhere to the Precautionary Principle. Rather than serving as an arbiter or mediator of conflicts among stakeholders, government must return to its role as a trustee of the environment, public health, and sustainability, and direct its interventions and research support to all phases of multistage diseases, for example, to promoters, as well as initiators of cancer. Media representatives must accurately report the complex evolution of scientific understanding. Public interest groups and nongovernmental organizations should strengthen linkages among disparate groups and continue their role as educators and advocates for precautionary protections. The international community must commit to a program of relevant research and to the establishment of multilateral environmental agreements, such as the proposal to ban persistent organic pollutants. These agreements should not result in banning endocrine-disrupting chemicals by substituting chemicals that produce other harmful effects or that put workers at significant risk, and the strategy for dealing with endocrine disrupters and other harmful chemicals must ensure that less developed nations have access to needed technologies.

#### References

- (1) Colborn, T.; Dumanowski, D.; Myers, J. P. *Our Stolen Future*; Dutton Press: New York, 1996.
- (2) Ashford, N. A.; Miller, C. S. *Chemical Exposures: Low Levels and High Stakes*; Wiley & Sons: New York, 1998.
- (3) Davis, D. L.; Telang, N. T.; Osborne, M. P.; Bradlow, H.; *L. Environ. Health Perspect.* 1997, 101 (3), 571-576.
- (4) Kuhn, T. *The Structure of Scientific Revolutions*, 3<sup>rd</sup> ed.; University of Chicago Press: Chicago, IL, 1996.
- (5) Hileman, B. *Chem. Eng. News* 1997, 75 (12), 37-38.

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