

SOCIAL AND POLICY IMPLICATIONS OF LOW-LEVEL EXPOSURES TO CHEMICALS¹

Nicholas A. Ashford and Claudia S. Miller

The Problem

There is mounting evidence that human exposure to chemicals at levels once thought to be safe (or presenting insignificant risk) could be harmful. So-called low-level exposures have been linked with adverse biological effects including endocrine disruption (1), chemical sensitivity (2), and cancer (3). In the 16th century, Paracelsus observed that *the dose makes the poison*. A more apt and modern revision might be that *the host plus the dose makes the poison*. Prior susceptibility of the host, whether inborn or environmentally induced, followed by other lifetime exposures, can cause irreversible injury. Humans in their most vulnerable developmental state, whether in the womb or during infancy, warrant special consideration, both in their own right and as sentinel indicators. The emerging science associated with low-level chemical exposures requires that we change both (1) the way we think about chemicals and health, including the adequacy of quantitative risk assessment, and (2) the solutions we devise to prevent and address chemically-caused injury.

Chemicals and Health

In his seminal work, The Structure of Scientific Revolutions, Thomas Kuhn described the process by which scientific knowledge evolves (4). His general observations are adapted here specifically to address the issue of emerging theories of disease (Table 1). New theories emerge only after much difficulty. At this point in time, we are just beginning to recognize the link between chemicals and a host of new public health problems that challenge the tenets of traditional toxicology and medicine. These include birth defects (and other damage) due to developmental toxicants; auto-immune diseases, including lupus, scleroderma, and Sjögren's Syndrome; certain 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, the unexplained illnesses of Gulf War veterans, chronic fatigue syndrome, fibromyalgia, and toxic encephalopathy; and, finally, new links to cancer, including childhood cancers.

These emerging public health problems are characterized by six common threads which provide a new perspective on disease: (1) They represent a departure from many classic diseases such as tuberculosis and heart disease in that *communication systems*

1. Published in Risk, Health, and Environment, NGO Background documents for the Third Ministerial Conference on Environment and Health and Parallel Healthy Planet Forum 16-18 June 1999, Maureen E. Butter (ed.), pp 31-34. First presented 1 August 1998 at the First International Conference on Children's Health and Environment, Amsterdam, the Netherlands, 11-13 August 1998.

or *networks*, rather than specific organs of the body appear to be the target. These include the *endocrine* system, the *immune* system, and the *neurological* system; (2) No *single* cause has been identified for each of these conditions. Further, there are often no clear biomarkers for either exposure or disease. Because of the current lack of clear biomarkers, classical epidemiology is less able to identify susceptible or sensitive subgroups; (3) Disease becomes manifest after two or more stages or events occur. For example, some cancer (and of course cancer is not a single disease) 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 two stages can involve different chemicals, radiation, or viruses. It has been hypothesized that Toxicant-induced Loss of Tolerance (TILT) leading to chemical sensitivity also proceeds via a two-stage process: (a) an initial exposure to high levels of certain chemicals (or repeated exposures at lower levels), followed by (b) triggering of symptoms by everyday chemical exposures at levels that do not appear to affect most people (2); (4) 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 after endocrine disruption can occur years later. Furthermore, the *timing* of the initial exposure can be crucial because there are crucial periods in the developmental process that are especially susceptible to damage. Chemical sensitivity reportedly can develop months after the initial exposure and remain manifest for years. Furthermore, 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; (5) The 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/disease (the dose-effect/response curve) is not monotonic--i.e., the extent of disease does not increase in a regular way as a function of dose. We have seen this vividly in the recent work of Fred vom Saal on the endocrine-disrupting effects of bisphenol A (5); and (6) Endocrine disruption (ED), TILT, and some cancers appear to represent a failure in functional and/or adaptive processes in important systems or networks as a result of chemical exposures at concentrations three to six orders of magnitude lower than those associated with classical toxic effects in normal individuals. Today, individuals may be exposed to multiple xenobiotics simultaneously, as in a sick building in which hundreds of volatile organic compounds might be present in the air.

Endocrine disruption (ED), TILT, and some cancers may be inter-related. ED disrupts normal development, and possibly the immune system, resulting in increased susceptibility to certain cancers. ED might also affect the neurological system, leading to increased susceptibility to sensitization by chemicals. TILT manifests as a loss of tolerance to everyday chemical, food, and drug exposures in affected persons, possibly leaving these individuals more susceptible to other disease. TILT may, in fact, represent a new theory of disease (2). Just as the general category of "infectious diseases" encompasses a diverse spectrum of diseases 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 Toxicant-Induced Loss of Tolerance, 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. The cause of the loss of protective function is not well understood.

Public Policy Responses

We have proposed that a systems-focused approach to disease best fits the pattern of these emerging illnesses of the 21st Century. It is our view that a systems approach likewise is needed as we fashion our public policy responses. The lack of clear biomarkers and the time lag between initiating exposures and ultimate disease make it technically, and increasingly politically, difficult to develop the extensive body of evidence needed to *regulate* many chemicals and industrial processes or to *compensate* the chemically injured. For this reason, we must seriously consider adoption of the *Precautionary Principle*, a concept endorsed at the UN Conference on Environment and Sustainable Development in Rio de Janeiro and already implemented in some European and U.S. regulatory systems. That is, we must act preventively in the face of uncertainty, erring on the side of caution. This requires education of the public, government, and industry, as well as political courage and conviction.

Over the past 25 years, scientific concern over emerging environmental or public health problems generally has begun with a suggestion -- sometimes a mere whisper -- that trouble was brewing. Those suggestions and whispers ultimately ripened into full-fledged confirmations that our worst fears were true. Examples include asbestos-related cancer, and the toxic effects of benzene, lead, and persistent pesticides. The frightening but enlightening reality is that with few exceptions the early warnings warranted heeding and the bulk of predictions were certainly in the right direction, if not understated. In retrospect, not only were our precautionary actions justified, but we waited far too long to take those actions. Endocrine disrupting chemicals present an opportunity to act more quickly than we have in the past, although some damage has already been done. Intervening now to prevent the next generation of developmentally or immunologically compromised or chemically intolerant persons, many of them children, is both possible and necessary.

Admittedly, there is considerable uncertainty about some aspects of endocrine disruption and other systemic damage or injury. We are told that this uncertainty places environmental legislators and regulators on the horns of a dilemma. They must risk making one of two types of mistakes: a Type I error is committed if they fail to regulate a chemical which turns out later to be harmful; a Type II error is committed if they regulate a chemical, imposing large costs on industry and the consumer, and the chemical later turns out to be safe. The Precautionary Principle argues for regulation when the scientific evidence is sufficiently compelling--but not perfect. It states a preference for avoiding a Type I error. As long as there is some scientific uncertainty, even if it is small, a potentially regulated industry is understandably more interested in avoiding a Type II error.

For the major stakeholders, these public policy responses suggest specific challenges. For industry it means a new kind of corporate stewardship that is in harmony with their customers' and the public's expectations that they will adhere to the Precautionary Principle, including the continuous seeking of less toxic, more sustainable technology to replace the old. For government it means a return to its role as a *trustee* of the environment, public health, and sustainability -- rather than serving as an *arbiter* or *mediator* of conflicts among the stakeholders. Further, government needs to address its interventions to all the stages of multi-stage disease, for example to promoters as well as initiators of cancer. For the media it means an increased commitment to understanding, reporting, and educating the public about the truth -- the *complex* truth-- which takes more than a sixty-second sound-bite or a 3-inch column. For the public interest/non-governmental organizations it means coalition-building and agendas that involve disparate groups, such as parents concerned with birth defects, advocates for toxic-free schools, and unions concerned with occupational exposures. For the international community it means a commitment to research and to multilateral environmental agreements, such as the proposal to ban Persistent Organic Pollutants (POPs). It will be important to ensure that such future agreements do not result in banning endocrine disrupting chemicals only to substitute chemicals with some other kind of harmful effect, or putting workers at significant risk in order to protect the general public. To win international approval, the strategy for EDs and other harmful chemicals must be one that ensures that less-developed nations have access to superior technology so that they can "leap-frog" into sustainable development. This is yet another reason to ensure that policies for science, technology, and regulation are coordinated. Finally, for private philanthropy it means greatly increased support for independent science, advocacy efforts for the environment, and education of the public.

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Nicholas A. Ashford, Ph.D., J.D. is Professor of Technology and Policy at the Massachusetts Institute of Technology. Claudia S. Miller, M.D., M.S., is Assistant Professor of Environmental and Occupational Medicine, University of Texas Health Science Center, San Antonio Texas. They are co-authors of Chemical Exposures: Low Levels and High Stakes, John Wiley, 1998.

STAGES OF A PARADIGM SHIFT (After Kuhn)

- M Ignore Departures From the Existing Paradigm**
- M Deny That an Anomaly Exists; Blame It On Faulty Observation Or Testing Error; Deride the Proponents of the New Paradigm**
- M Acknowledge the Anomaly, But Call It "Idiopathic"**
- M Try To Explain the Anomaly With The Existing Paradigm, Sometimes By Making Minor Adjustments.**
- M Seek Alternative Paradigms To Contradict or Minimize The One Proposed.**
- M Recognize Paradigm As Valid, But Within A Narrow Context Relegated To "Exceptions"**
- M Accept the New Paradigm As Offering Some Explanatory Power, But Retain the Old Paradigm, Too**
- M Discredit the Old Paradigm; Deride Any Attempt To Reinstate Or Rehabilitate Old Paradigm**
- M Accept New Paradigm With Enthusiasm**
- M Begin Again**

Source: Ashford & Miller Chemical Exposures: Low Levels and High Stakes, John Wiley Press, 1998.