



By Craig M. Pease

## Toxicity: You Can't Dial C For Cancer

EPA's Strategic Plan for Evaluating the Toxicity of Chemicals, released this spring, lays out an ambitious institutional shift in how the agency evaluates industrial compounds. Ultimately, these risk assessments are grounded in diverse environmental statutes which, though differing in language and detail, require EPA to answer the same underlying question: Which pollutants cause cancer and other human diseases, and at what levels?

The last half century has seen huge advances in biochemistry and molecular, genetic, and cellular biology. Though each advance was incremental, the sum total has been a revolution. The strategic plan presents the imminently sensible vision that, when undertaking risk assessments, we should exploit these scientific advances in molecular biology.

As it turns out, at one level EPA already does. For example, its dioxin risk assessment relied not only on data from human epidemiology (comparing cancer incidence in factory workers exposed to dioxin to the general population) and animal toxicology (comparing cancer incidence in rats exposed to dioxin, or not) but also on molecular information (dioxin binding to the Ah receptor). The strategic plan is novel when it envisions a future where, in contrast to the present, molecular information is primary, with human epidemiology and animal toxicology secondary.

This is a grand plan to meet the scientific requirements of environmental statutes. However, it is deficient when it exploits new data to answer an old question, posed by statutes often enacted decades before much of the molecular biology revolution. Implicit in the old question of which pollutants cause cancer is linear causation: toxin — in, cancer — out. Recent advances in molecular biology invite us to consider network causation.

A biochemical pathway mediating the human body's response to toxic chemicals is like a tiny Rube Goldberg machine. Actually, our biochemical networks are not a single one of the famous cartoonist's machines, but literally hundreds, interconnected to one another in complicated ways. Even with today's incomplete knowledge, it is clear that there is too much complexity to allow us to exhaustively catalog the relevant causation pathways. This is a qualitatively different world from making a telephone call, where there is a clear, single path between cause (dialing) and effect (person reached). There are too many biochemical paths, and it would take too long, and cost too much, to enumerate them all. And these paths cross and interact with each other in complicated ways. Further progress requires a paradigm shift.

These advances suggest we ask a different question: How can we best reduce the overall incidence of cancer? Cancer arises from the joint action of environmental toxins (some of which damage DNA, or alter its regulation), diverse endogenously produced toxins (some also damaging DNA), and numerous dietary nutrients (some critical to repair of damaged DNA). Layered on this are genetic differences among individuals in their biochemical networks.

Biochemist Bruce Ames (responsible for the Ames test, which assays potential carcinogens by testing whether they cause mutations in DNA) convincingly argues that American diets are broadly

deficient in various micronutrients found naturally in vegetables, fruits, whole grains and beans, and that are needed by the DNA repair pathways. Human epidemiology (e.g., studies comparing cancer incidence in Seventh Day Adventists to the general population) suggests that the correct shifts in the U.S. diet could reduce the incidence of cancer by roughly the same amount as entirely eliminating tobacco smoking. Yet the strategic plan proposes to evaluate "bad" chemicals (pollutants), while ignoring the "good" chemicals (dietary nutrients) impinging on the very same underlying biochemical networks.

To be fair, nowhere does the law deal gracefully with network causation. "But for causation" and "joint and several liability" allow legal decisions to be made in the face of multiple causes. While these rules are certainly useful, especially where there are only a handful of causes, they don't sensibly address the situation where there are hundreds of causes interacting in

only partly known ways. Similarly, the Food Quality Protection Act makes a useful advance when it requires EPA to simultaneously evaluate suites of chemicals

with a common mechanism of biochemical action, but is still firmly within the linear causation paradigm.

In the law, the verb "to cause" invariably implies linear causation. Yet networks are ubiquitous, not only in biochemistry, but also in ecology, communications, economics, and sociology (webs of interacting organisms, computers, financial agents and humans), all directly relevant to environmental law. Fully exploiting the ongoing advances in network science will require a revolution in environmental law and policy.

**Craig M. Pease**, Ph.D., a research scientist, teaches at the Vermont Law School Environmental Law Center. He can be reached at [cpease@vermontlaw.edu](mailto:cpease@vermontlaw.edu).

*Linear causation is out. Modern molecular biology looks instead at network causation*