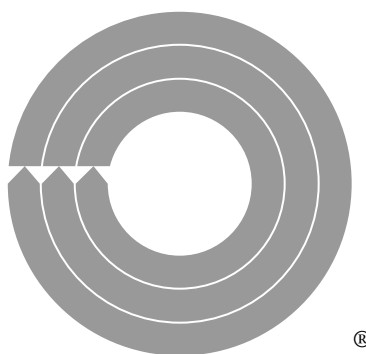


# RENEWABLE RESOURCES JOURNAL



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## CONTENTS

News and Announcements .....	3
Articles:	
“Emerging” Chemicals as Pollutants in the Environment: a 21st Century Perspective .....	6
<i>Christian G. Daughton</i>	
Meetings, Workshops & Symposia .....	24
International News .....	29

# ABOUT RNRF

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## Purposes

The Renewable Natural Resources Foundation (RNRF) was incorporated in Washington, D.C., in 1972, as a non-profit, public, tax-exempt, operating foundation. It was established to:

- Advance sciences and public education in renewable natural resources;
- Promote the application of sound scientific practices in managing and conserving renewable natural resources;
- Foster coordination and cooperation among professional, scientific and educational organizations having leadership responsibilities for renewable natural resources; and
- Develop a Renewable Natural Resources Center.

The foundation represents a unique, united endeavor by outdoor scientists to cooperate in assessing our renewable resources requirements and formulating public policy alternatives.

## Membership

RNRF's members are professional, scientific and educational organizations interested in sustaining the world's renewable natural resources. The foundation is governed by a board of directors comprised of a representative from each member organization. The directors also may elect "public interest members" of the board. Board members are listed on the back cover of the journal. Individuals may become Associates for an annual contribution of \$50 or more.

## Programs

RNRF conducts national meetings, congressional forums, public-policy round tables and briefings, and international outreach activities. It also conducts an annual awards program to recognize outstanding personal, project and journalistic achievements. More information about RNRF's programs is available at [www.rnrf.org](http://www.rnrf.org).

*Renewable Resources Journal*, first published in 1982, promotes communication among RNRF's represented disciplines. The journal is provided to the governing bodies of RNRF member organizations, members of the U.S. Congress and committee staffs with jurisdiction over natural resources, federal agencies, and universities. Tables of contents of all volumes of the journal are available at RNRF's web site.

## Center Development

The Renewable Natural Resources Center is being developed as an office and environmental center for RNRF's members and other nonprofit organizations. The Center is located on a 35-acre site in Bethesda, Maryland, where lawns and forested buffers provide an exceptional work environment. The site is the former family estate of Dr. Gilbert H. Grosvenor, of the National Geographic Society.

The master site plan for the Center contemplates additional construction—including a 16,500 square foot conference and common-services facility. Organizations may either lease or purchase their offices. The Center currently has approximately 52,500 square feet of office space.

### MEMBER ORGANIZATIONS

American Fisheries Society

American Geophysical Union

American Meteorological Society

American Society of Civil Engineers

American Society of Landscape Architects

American Water Resources Association

Estuarine Research Federation

International Society of Arboriculture

Society for Range Management

Society of Environmental Toxicology and Chemistry

Society of Wood Science and Technology

Soil and Water Conservation Society

Universities Council on Water Resources

The Wildlife Society

# “Emerging” Chemicals as Pollutants in the Environment: a 21st Century Perspective

Christian G. Daughton

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*Editor's Note—Pesticides, pharmaceuticals, industrial chemicals, nanoparticles, and personal care products are being detected increasingly throughout the environment. These substances are being detected in tissues of humans, terrestrial animals, amphibians, and fish. We believe that a basic understanding of existing and potential threats posed by these substances has become prerequisite knowledge for natural resources managers, professionals in related disciplines, and those in government whose decisions affect monitoring and regulatory activities. Thus, we have dedicated this issue of the Renewable Resources Journal to an expansive overview of the extent and nature of challenges we face. The next issue of our journal will extend the examination by presenting findings and recommendations stemming from*

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*Daughton is chief, Environmental Chemistry Branch, U.S. Environmental Protection Agency. This article has been subjected to peer review. The United States Environmental Protection Agency through its Office of Research and Development funded and managed the research described here. It has been subjected to the agency's administrative review and approved for publication as an EPA document.*

*RNRF's upcoming Congress on Assessing and Mitigating Environmental Impacts of Emerging Contaminants, scheduled for December 1-2, 2005, in Washington, D.C.*

## Abstract

Defying comprehension is the complexity of the chemical sea that surrounds, sustains, and constitutes all life. From this sea, never-ending challenges are faced by organisms striving to defend against those multitudes of chemicals that cause cellular stress or harm. Biological mechanisms have evolved for maintaining organism homeostasis during contact with these harmful substances. Most of these chemical stressors have long existed or are produced by myriads of human activities. However, for those chemicals that are relatively new to the world, the mechanisms for homeostasis maintenance are not necessarily adequate. Chemicals for which organisms have had the least time to adapt are those that only recently have emerged as environmental contaminants.

Essentially limitless combinations of a very small set of atomic elements can yield a seemingly infinite number of unique chemicals—a universe known as “chemical space.” Although thousands of chemical pollutants or con-

taminants are regulated under international, federal, and state programs, these represent but a minuscule fraction of the universe of chemicals that occur in the environment as a result of both natural processes and human activities. This array of chemical pollutants (or occupational hazards) might at first seem large, but it pales compared with the universe of known chemicals, and would become insignificant if compared with those chemicals yet-to-be identified, waiting to be synthesized, and that are just now “emerging.” A key assumption is implicit in the limited and selective lists or menus of chemicals targeted by regulations—namely that these are indeed the chemicals responsible for the most significant share of risk to ecological integrity, economic impairment, and human health. Given the myriads of other chemicals that are ignored or escape notice by regulatory processes, a multitude of questions can be posed regarding society's relationship with chemical pollutants, particularly with respect to whether a more holistic understanding of risk might be required. With the immense size of the chemical universe, this is a daunting challenge. How would we know when we have narrowed the chemical universe to the most significant hazards worthy of our attention? Not necessar-

ily will the continued emergence of new pollutants pose the biggest challenge. A larger unknown might be the occurrence of myriads of chemicals that remain hidden from our view. Perhaps more daunting will be gaining a better understanding of the unanticipated ways in which these substances can interact with the environment and the creation of a new paradigm for their management or stewardship. Adding yet additional challenge is the emerging realization that society is averse to exposure to certain chemicals, even in the absence of any hazard, simply because these chemicals occur where they are not expected or desired—the chemical equivalent of “weeds.”

Outlined in this paper is a sampling of some of the many alternative perspectives regarding chemical pollutants (especially those that are new to our attention—the so-called “emerging” pollutants) and their ramifications for biological systems and society’s values. A primary objective in presenting these alternative views of chemical pollution is the hope of catalyzing dialog and debate regarding new approaches for its management, not to make recommendations for implementing solutions.

## Introduction

Tremendous investments continue to be made in the prevention, control, and mitigation of environmental pollution by chemicals. Nevertheless, how can we be sure that these are the most important chemicals with respect to protecting humans and the ecology? Do we sufficiently understand the processes that dictate exposure to these pollutants and its aftermath? Is the introduction of new chemicals to commerce outrunning our ability to fully assess their significance in the environment or to human health?

This article is intended to foster discussion aimed at establishing a more holistic view of xenobiotic exposure

and its ramifications. More emphasis needs to be placed on non-regulated pollutants, especially those considered to be “emerging.” Over the last few years, the appellation “emerging” has been applied to chemical pollutants with such frequency that its meaning is becoming confused. In reality, those pollutants that are truly “emerging” (for example, those that have just gained entry to the environment because they are new to commerce) are sometimes confused with those whose environmental presence just has been

elucidated but which have long been present. There are a number of different perspectives from which to view the many dimensions of “emerging” (Daughton, comp. 2005a). One example is that of PPCPs (pharmaceuticals and personal care products; see Daughton, comp. 2005b), which include many substances that long have been present in the environment but whose presence and significance only now are beginning to be elucidated. “Emerging” also sometimes is intended not to refer to the pollutant itself, but

**Table 1. Some Groupings of Chemical Pollutants. Confusion results from their intersections and acronyms.**

<i>Grouping</i>	<i>Grouped According to:</i>
<b>EDC</b> (Endocrine Disrupting Chemical) <b>CMR</b> (Carcinogenic, Mutagenic, toxic to Reproduction)	toxicological mode of action or endpoint
<b>PBT</b> (Persistent, Bioaccumulative Toxic) <b>vPvB</b> (very Persistent, very Bioaccumulative) <b>POP</b> (Persistent Organic Pollutant)	environmental properties (e.g., ease of degradation or fat solubility)
<b>PPCPs</b> (pharmaceuticals and personal care products)	type of intended usage
<b>“priority pollutants,”</b> and other regulated pollutants	legislative enactment (e.g., CERCLA)
<b>xenobiotics, exotics</b>	foreign versus endogenous
<b>toxicants, toxins, toxics</b>	overall toxicity (note: “toxins” are a special subset that are proteins; “toxics” is jargon for “toxicants”)
<b>“emerging”</b> contaminants/pollutants	novelty, fad, timeliness, or new concern
<b>HPV</b> (high production volume chemicals)	quantity (manufactured/imported in U.S. in annual amounts >1 million pounds)

rather to a newly hypothesized concern regarding an old pollutant. For example, pollutants that long have occupied our attention can gain new notoriety with the revelation of new aspects of their occurrence, fate, or effects; the production of acrylamide during the cooking of certain foods is but one example.

A source of on-going confusion is the proliferation of acronyms for the different categorizations of chemical pollutants. Various groupings of chemical pollutants (see Table 1) have evolved, and each looks at chemicals from a different perspective. Each group tends to contain some but not most of the chemicals from other groups; each group slices the chemical universe pie in a different dimension. In this sense, members of “emerging” pollutants can each belong to others of these groups.

The discussion that follows will highlight some of the less appreciated aspects of chemical pollution (with “emerging” pollutants as a common thread) and place these in the context of hazard and exposure, and whether risk can be assessed more holistically.

### The Chemical Universe and Exposure 101

An ever-expanding universe of unique chemicals, untold numbers of which have yet to be recognized or revealed, continually perfume our environment and contact living systems. Multitudes of chemicals originate both from natural processes and from anthropogenic sources, including synthesis-by-design of new molecular entities and inadvertent formation of by-products from these syntheses or from the molecule’s destruction (incineration is an example). Sometimes, the chemicals produced by humans are the same as those produced in nature (this has led to long-standing confusion over the meaning of “organic”). Many of these chemicals have existed through-

out the course of life on Earth. Some are inherently harmful, some are essential for sustaining life, and others share both characteristics depending on their concentrations or when exposure occurs during the course of an organism’s development or natural rhythms. Exposure, however, is not sufficient for toxicity. All organisms have evolved a complex repertoire of defense mechanisms for coping with exposure to those chemicals foreign to their normal existence (xenobiotics). Living systems have developed protective, defensive, or adaptive mechanisms for minimizing exposure or even the toxicity of many of the otherwise harmful, naturally occurring chemicals. For those “new” chemicals that only recently have emerged, however, and to which biological systems never have been exposed, these defensive mechanisms sometimes can be inadequate.

***Chemicals Are Chemicals, But They Are All Different.*** Whether from nature or from industry, chemicals are chemicals—both naturally occurring and anthropogenic. However, their characteristics and properties can differ dramatically. The quantities in the environment and the toxicities of individual chemicals span an extraordinarily broad range. The types and quantities of individual chemicals in a wide array of environmental compartments (soil, sediment, water, air, biota) also vary dramatically over time. Their presence is not necessarily static, often varying temporally and spatially in both absolute amounts and in relative proportions. Concentrations of chemicals in any one sample can range from percent to parts-per-million to less than the yocto-molar range—a span exceeding 20 orders of magnitude. The interactions of living systems with chemicals (part of the study of “exposure”) can result in myriads of biological responses or changes (“effects”), ranging from adverse to benign to even beneficial. Chemical exposure is an extraordinarily complex and dynamic

process, which takes place under continually changing conditions. Exposure, for example, can range from short-term contact with a small, select group of chemical stressors (“toxics”) at relatively high concentrations (acute exposure), to extended durations of exposure with lower concentrations (chronic) of multitudes of chemicals in extraordinarily complex mixtures. Effects can range from overt, where adverse consequences are elicited quickly (e.g., from a lethal dose), to subtle, where effects are not readily apparent or easily measured (e.g., slight but gradual shifts in mental health and behavior). Some stressors can elicit delayed effects that become apparent only weeks, months, or years after an initial exposure (delayed onset toxicity). The relative concentrations of stressors can change continually. Likewise, the types and vulnerabilities of biological receptors that interact with the stressors also can change (as a function of the organism’s overall health status). Windows of particular vulnerability can exist during certain critical times, such as specific development stages and biological rhythms. Chemicals of environmental concern can have origins from both purposeful human activities as well as from nature. One of many examples includes the endogenous estrogenic and androgenic steroidal hormones synthesized and excreted by humans and other mammals, the plant-produced phytoestrogens consumed in our diet, and the anthropogenic, synthetic versions of these naturally occurring chemicals such as ethynylestradiol (synthetic analog of estradiol; an extremely potent active ingredient in reproduction regulators).

***Legal or Illicit Chemicals—All in the Pollutant Family.*** The environment does not discriminate between pollution from legal or illegal chemicals. Whether the pollutant is chlordane, codeine, or cocaine, whether methylmercury or methamphetamine, biologi-

cal receptors interact without regard to the chemical's legal standing or its source. All can impart effects. Even so, the legal standing of chemicals seems to affect the degree to which they are studied. For example, while prescription and over-the-counter pharmaceuticals have gained much attention as pollutants since the late 1990s, little effort has been devoted to uncovering the environmental prevalence of illicit drugs, such as cocaine or any of the numerous amphetamines. The first reports of illicit drugs occurring as trace pollutants in environmental waters recently were published by Jones-Lepp et al. (2004) and Zuccato et al. (2005).

***Real or Fake—It's All the Same.*** "Exotic" chemicals that are found in the environment might seem, on first examination, to originate from human activities. An accurate perspective, however, also must recognize that some of these chemicals have natural sources. Microorganisms (bacteria, fungi, and algae) and plants are highly versed at synthesizing a bewildering array of chemicals, most of which might at first seem to be foreign to living systems. Many possess extreme acute and chronic toxicity. Indeed, many of these chemicals are involved in the unrelenting chemical warfare and signaling that occurs between organisms. Natural abiotic processes (such as sunlight and natural combustion such as forest fires and lightning) also are capable of catalyzing the formation of other xenobiotics. Some chemicals (even certain persistent organochlorines, including certain dioxins) can originate from both natural and human activities.

With this very brief and oversimplified overview of the intersection of the universe comprising chemicals with the world of biological systems, a number of questions can be posed with respect to how this nexus can be managed to minimize risk to the environment and human health. We also can explore some of the many facets of this inter-

section in more detail to reveal potential oversimplifications of the various tenets we long have held, and how we might want to alter these to better accommodate reality.

***Regulated Pollutants: Minor Ingredients in a Small Slice from the Whole Risk Pie?*** Since the 1970s, the impact of chemical pollution has focused almost exclusively on lists (or menus) of conventional pollutants, especially those collectively referred to as "persistent, bioaccumulative toxicants" (PBTs) or "persistent organic pollutants" (POPs); see Table 1. This relatively small number of primarily con-

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ventional, regulated pollutants, however, represents but one piece of a much larger universe of potential pollutants—one of largely unknown scope. That biological systems can suffer exposure to countless chemical stressors, only a small number of which are regulated, poses many currently unanswerable questions regarding risk. As of August 2005, over 26 million organic and inorganic substances (excluding biosequences such as proteins and nucleotides) had been indexed by the American Chemical Society's Chemical Abstracts Service in their CAS Registry (CAS, 2005a). One-third of these

(nearly 9 million) were commercially available, representing a 12 percent increase over the prior year. In contrast, fewer than a quarter million (240,000) were inventoried or regulated by government bodies worldwide (CAS, 2005b).

***"Chemical Space."*** While the known universe of organic chemicals might seem large, the universe of potential organic chemicals (those that possibly could be synthesized and those that already exist but which have not yet been identified) is unimaginably immense. So-called "chemical structure space" essentially is unexplored. If chemical space is defined as comprising all possible structural configurations up to a certain nominal molecular size, it is estimated to contain between  $10^{30}$  and  $10^{200}$  unique structures, depending on how the estimate is calculated and the upper boundary for the molecular size (Bohacek et al., 1996; Dobson, 2004). The types of possible organic chemicals essentially are limitless in their ever-expanding structural universe. The efforts of synthetic organic chemists, using advanced combinatorial chemistry and exploring new forms of matter such as nanomaterials and superatom clusters, are only beginning to reveal the complex dimensions of chemical space. The ramifications for risk assessors and regulators indeed are profound. Historically, we only have studied and regulated the tip of the chemical space iceberg.

***Looking Glass to Parallel Chemical Worlds—Stereochemicals and Chirality.*** Strewn about in chemical space are parallel chemical worlds, where certain molecules (those with asymmetrical structures) exist in multiple forms whose mirror images are not superimposable. Known as chiral molecules, one of the simplest examples is bromochlorofluoromethane, which contains a single carbon atom bonded to four different elements (hydrogen, bromine, chlorine, and fluo-

rine). Pairs of chiral molecules are known as “enantiomers” or as “optical isomers.” Chirality (“handedness”) plays critical roles in the environmental chemistry and toxicology of myriads of chemicals. A chemical comprising chiral forms can have properties of two or more distinct chemicals (depending on its number of points of asymmetry), but each having the same composition and two-dimensional structure. Chiral chemicals composed of equal parts of their optical isomers are known as racemates. Isomers of more complex chiral molecules that possess at least two stereogenic centers can either be enantiomers or diastereomers (stereoisomers that are not mirror images). Isomers of achiral molecules possessing at least two stereogenic centers are called meso isomers (stereoisomers that are superimposable). A ubiquitous pollutant notorious for its complex stereochemistry is the flame retardant hexabromocyclodecane (HBCD), which comprises six enantiomeric pairs and four meso forms, a total of 16 stereoisomers, all having identical compositions but different chemical properties.

Many synthetic chemicals (e.g., certain pesticides) are regulated as their racemates or isomeric mixtures. Of most significance, however, is that the environmental fate and toxicity of the individual isomers can differ, sometimes dramatically. For example, one isomer might be more readily degradable, while the other persists. One might have much greater toxicity (or beneficial effect), while the other can have completely different effects (or none at all). The well-known drug thalidomide is but one example, where one of its enantiomers has the designed effect of sedation but the other is a potent teratogen (causes fetal malformations). Countless other examples would show how the different forms of stereochemicals can have different and unpredictable ramifications with respect to exposure and effects. This is

one reason that the pharmaceutical and pesticide industries have been moving toward the design of optically pure chemicals that cannot racemize among enantiomers. A significant major question, however, is how a regulatory system can best deal with stereochemical mixtures, especially when it can be extremely difficult to distinguish between them during environmental monitoring.

**Chemicals Unlike Themselves.** For those chemicals with optical isomers, the seeming paradox exists where chemically identical molecular structures can have wildly different chemical or biological properties. Nanoscale chemicals (also called nanoscale particles or materials) constitute another potentially immense class of chemicals where an analogous conundrum exists; superatom clusters (whose atoms take on the properties of other elements) are another example. Nanoscale materials (which are much larger than most molecules, but with one dimension smaller than 100 nanometers) are distinguished by having chemical and biological properties that differ profoundly from those of their chemical constituents. The size and shape of nanoscale materials (which, for example, dictates very large surface-to-volume ratios, which in turn have enormous potential for catalyzing reactions) impart unique properties.

Regulatory conundrums result from the fact that although the constituent chemicals already might be regulated, the nanomaterial does not resemble or act like its constituents. This problem is exacerbated further by the fact that natural weathering processes could yet further alter these materials, producing “structurally undefinable ubiquitous xenobiotics” (SUDUX), which may not be measurable for monitoring purposes. The potential is unknown for nanoscale pollutants resulting from nanomaterial weathering to create exponentially more xenobiotics, an un-

known portion of which may be new to organisms.

**Whither the Bull’s Eye—Are We Aiming at the Correct Target?** Two distinct approaches can be used by analytical chemists to gage or probe the molecular make-up of an environmental sample and hence reveal some of its toxicological hazards. The prevalent, most cost-effective approach uses “target” analysis, where the chemicals considered for measuring (known as “analytes”) are preselected from a standardized “menu.” This is the approach that necessarily drives the environmental monitoring dictated by regulatory priorities—where various chemicals are “listed.” The second approach is through non-target “characterization,” where the universe of chemicals that might compose a sample are all subject to discovery by the analyst—the analysis does not begin with predefined notions as to what the search will encompass or what it might reveal. This approach, which is used in “environmental forensics,” is much more time consuming and costly. The latter approach can uncover the presence of many more chemicals than can targeted analysis, but even it eventually is subject to the gross limitations of even the most advanced analytical tools, which still are incapable of revealing the structures or even the presence of incalculable numbers of chemicals in any environmental or biological sample.

Even though chemical characterization does not account for an unknown portion of organic chemicals. These comprise those chemicals that cannot be detected or identified. Significantly, these unidentified or unidentifiable compounds almost always comprise an unknown fraction of all those present, so the toxicological significance of their presence is rarely known. These unidentified chemicals are neglected, ignored, omitted, or overlooked because of any number of limitations or idiosyncrasies of the many tools employed by the analyti-

cal chemist (see Figure 1 in Daughton, 2003a). The salient question is whether any significant risks for living systems are associated with the target analytes, with the non-targeted chemicals, or both. Exactly where is the toxicological target, and are we aiming for the bull's eye? The proliferation of new anthropogenic chemicals coupled with the continued discovery of new chemicals produced in nature will continue to challenge analytical chemists and regulators alike. On the other side of the coin, however, one can argue that those very few chemicals that we monitor in the environment, and to which we know organisms are exposed, also can be viewed as serving as surrogates for the presence of untold numbers of other chemicals possessing similar physicochemical properties. By regulating one (e.g., via removal during waste treatment), untold others coincidentally are controlled.

**Analytical Chemists—The Regulator's Worst Friend?** Analytical chemistry plays a key role in expanding and refining our ever-changing perspective of the chemical sea in which we find ourselves. As the power of analytical chemistry increases, the types of chemicals that can be detected and identified increase, and the limits of concentration at which they can be measured continually are lowered. By ever expanding the horizon of the known chemical universe, analytical chemists unwittingly add to the burden of responsibility for risk assessors and regulators. Lowering the limits of detection challenges our concepts of “purity,” “zero,” and “safe,” which must then be revised. The extraordinarily wide range of concentrations at which chemicals can occur imposes seemingly insurmountable hurdles for risk communicators. The lay public's bewilderment with the jargon required for expressing these concentrations has fostered the perception that essentially all concentrations are the same—whether they are minuscule or large. The number of

chemical contaminants at “trace” levels can exceed those present at higher levels. Largely stemming from this ability to reveal ever more pollutants, environmental analytical chemists often are perceived as problem makers—not as problem solvers. It becomes increasingly difficult to assess risk and to design regulatory programs for new and moving targets. Where should regulatory limits be placed? Does “zero” even exist? The chemicals of potential concern comprise the broad spectrum of anthropogenic chemicals (those purposefully synthesized and indirectly produced by human activities) as well as “natural products” (those created both by natural physicochemical or biological processes). Using drinking water to illustrate, the gasoline oxygenate additive MTBE (methyl-tert-butylether), tris (4-chlorophenyl)methanol, and halogenated disinfection by-products (DBPs) are three of countless examples of widespread anthropogenic contaminants. Arsenic and geosmin (the off-flavor bicyclic alcohol produced by certain algae and fungi) are examples of naturally occurring contaminants. Some chemicals (e.g., DBPs and acrylamide) can originate from both natural and anthropogenic processes. Multitudes of questions languish unanswered. Is a new paradigm required for more efficiently and effectively assessing and protecting the world from whatever risks might be posed by those stressors comprising the chemical sea in which all life forms must sustain their homeostasis?

**Chemical-by-Chemical Regulation: Thoroughfare or Dead-end for Protecting Ecological and Human Health?** An ultimate question is whether the approaches that have evolved over the last half century for regulating chemicals will be sustainable. The challenge increases as analytical chemists and toxicologists continue to redefine and expand the scope of concern by discovering more poten-

tial chemical stressors, at lower and lower concentrations. Add this to the work of synthetic chemists designing new chemicals with abilities to impart new types of biological effects, sometimes at exquisitely low concentrations. The approaches used worldwide all rely on assessing hazard on a chemical-by-chemical basis (through various “listing” processes). Some recent progress has been made toward considering “cumulative” and “aggregate” regulation of certain groups or classes of chemicals. Examples of such a group are those that share a well-defined mechanism of action, or to which we are exposed from multiple routes or origins, including the cholinesterase inhibiting organophosphorus and carbamate pesticides.

To illustrate the substantial (and perhaps insurmountable) challenges to the sustainability of a chemical-by-chemical approach for regulating the occurrence of pollutants in the environment, consider the particularly diverse spectrum of ubiquitous pollutants that originate from the daily activities and actions of countless individuals—the PPCPs. There are myriads of other anthropogenic chemicals whose occurrence in the environment originates from the behavior and activities of consumers. Using PPCPs as an example, as of August 2005, more than 140,000 bioactive compounds were in various phases of drug research and development (Prous Science, 2005). The rapid evolution of the “omics” revolution undoubtedly will feed an expansion of new drug entities that already has been underway (Daughton, 2003a). New drug entities, many with mechanisms of action never before encountered by biological systems, can be expected to enjoy continued introduction to commerce. All will have the potential to enter the environment merely as a result of their daily use (e.g., introduction to surface and ground waters via excretion, bathing, or disposal to sewage systems).



By following a road mapped out by a chemical-by-chemical approach, do we risk going in the wrong direction or heading for a dead end? Will target-lists (or menus) of pollutants blind us to more important pollutants, including truly emerging pollutants? Target chemical menus can never be sufficiently large to satisfy our appetite to minimize potential risk. By restricting ourselves to a single slice from the risk pie, are we getting the best toxicological value for our investment of resources in environmental monitoring?

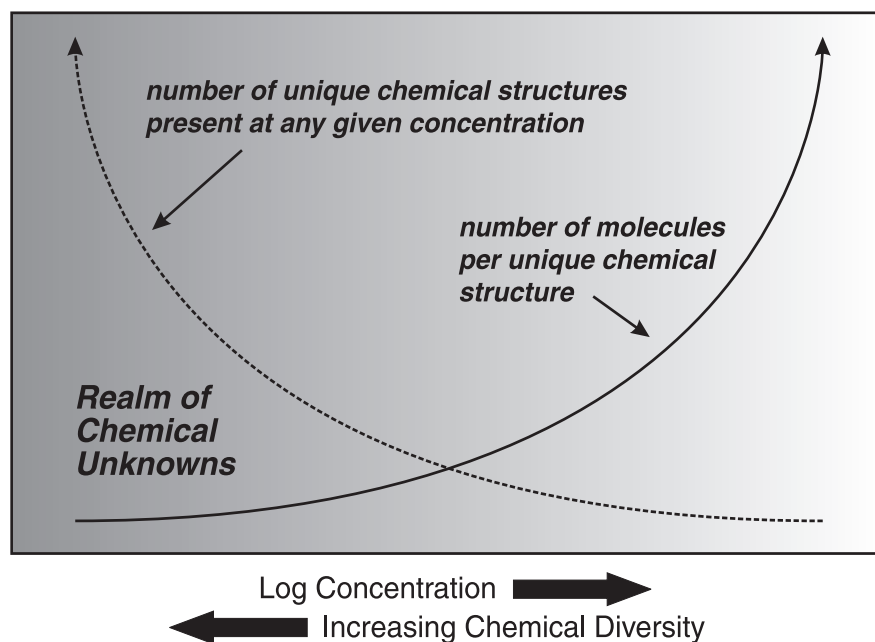
**Ubiquity and Ubiquity: Everything Can Be Found Everywhere.** One might surmise that the number of chemicals that can be found in any environmental sample increases as the detection limits achievable by chemists are reduced. Perhaps exponentially more types of chemicals occur at incrementally (or exponentially) lower concentrations. Those chemicals with distinct chemical structures that are detected (or are detectable) compose the minority of the total number of unique chemicals present in any sample. In other words, most of a sample's identified contaminant molecules are associated with a minor part of the overall chemical diversity of a sample—the majority of the molecules in a sample belong to a minority of the unique structures present. On the other hand, the majority of the unique chemical structures present (i.e., the highest diversity of chemical types) comprise a minority of the total molecules present. The realm of chemical unknowns increases at lower concentrations (Figure 1) because modern analytical technology cannot yet identify these countless chemicals.

At a certain range of infinitesimally low concentrations, we may be approaching the off-the-cuff truism: "Everything can be found everywhere." With this concept of chemical diaspora, the notion of "pristine" is relative. What then when molecules of vastly different types of chemicals can be

found in just about any type of sample? What challenges will be faced by risk communicators, toxicologists, and risk assessors. Will the way in which risk is perceived be altered dramatically, will chemical exposure be more accepted as a fact of life, or will risk perception become a major obstacle for our increasingly technological world?

in concentration by and accumulation in lipids and fat; bioconcentration then leading to bioaccumulation via the food chain); and (3) possess acute or chronic toxicity in their own right. While each of these factors is unquestionably significant and has contributed to the notoriety of certain pollutants (i.e., the "dirty dozen"), less appreci-

### Higher Abundance of Unique Chemical Structures at Lower Concentrations?



**Figure 1: Increasing Chemical Diversity at Lower Concentrations. The realm of chemical unknowns also expands at lower concentrations.**

#### Alternative Perspectives Regarding Chemical Pollution

**Persistence, Bioaccumulation, Toxicity—the Only Talents for Hazardous Chemical Celebrities?** Over the years, a consensus view has emerged of three factors that purportedly dictate the highest propensity for adverse effects from exposure to chemical stressors. Such stressors need to: (1) possess structural stability (which imparts environmental persistence from long half-lives); (2) be lipophilic and thereby more amenable to passively crossing cellular membranes (resulting

ated is that they are not necessarily required for a chemical to pose risks in the environment. These three factors deserve further consideration with respect to their restrictiveness in defining risk.

**Reassessing “Persistence”—the Weak Become Stronger.** One of the three hallmarks distinguishing those environmental pollutants that are the focus of regulatory actions is environmental persistence, which results from resistance of chemicals to structural alterations (e.g., the making and breaking of covalent bonds) by biological or physicochemical transformation. Ex-

posure to chemicals that easily are transformed was thought to be insignificant. Possible outliers to this requirement, however, are those unknown numbers of pollutants that are conveyed to open waters by sewage treatment plants and septic systems. The continual release of these pollutants gives them a “pseudo-persistence” in any aquatic or marine environment, regardless of their structural instability. This alternative view was first formulated with respect to PPCPs (see p. 761 in Daughton, 2003a), many of which can have a continual environmental presence, regardless of environmental half-life, simply because their degradation is offset by constant replenishment.

***Reassessing Bioaccumulation and Toxicity—“Me Too” Chemicals.*** Bioaccumulation is dictated largely by a chemical’s lipophilicity (fat solubility). Many pollutants, once ingested, rely on passive transport across the gut wall or across the dermis, facilitated by lipid solubility. Lipophilic chemicals gain access to intracellular domains by passive diffusion within cellular lipids. This process serves to continually extract trace residues of these chemicals from the environment until significant levels have bioconcentrated. Subsequent consumption of this contaminated tissue by organisms in higher trophic levels of the food chain serves to further concentrate these chemicals, leading to biomagnification. This is the classic way in which ubiquitous pollutants such as the organohalogenes gain significant presence in biological tissues and disperse worldwide. It also is why seemingly insignificant, minute levels of these pollutants in the ambient environment can be important to regulate. Less recognized, however, is that certain hydrophilic chemicals (those that readily dissolve in water) also have the potential to bioconcentrate. Some of these chemicals can be transported actively via cellular systems whose purpose it is to ac-

tively carry (transport) chemically similar endogenous chemicals important to the cell’s function. Others can gain indiscriminate, promiscuous intracellular access in the absence of high lipid-water partition coefficients by other mechanisms. Some examples of these mechanisms are provided below.

One example of an alternative route for bioaccumulation is illustrated by certain drugs that are transported actively, including ones that are hydrophilic. In fact, one of the current strategies under investigation for improved drug delivery is the design of drugs that capitalize on active transport (see Daughton, 2003a). This property could allow such chemicals, as water-soluble pollutants, to bioconcentrate, seemingly in defiance of predictions based on lipophilicity. A second example involves the small, subcellular scale of nanoparticles, which can facilitate their promiscuous entry to intracellular domains, thereby circumventing cellular defenses. The size and conformation of these materials alone (rather than their actual chemical composition) holds the potential to adversely affect biological systems, such as via surface-mediated effects (e.g., sorption and catalysis) or the ability to evade host defenses by freely penetrating or permeating cellular membranes. Certain nanoparticles may have the potential to indiscriminately concentrate within their porosities or on their surfaces a wide spectrum of chemicals and thereby serve as Trojan horses for ferrying their chemical hitchhikers across biological membranes (facilitated transport), irrespective of cellular defensive barriers such as efflux pumps (cellular “bilge pumps”). Indeed, this ability is being pursued in the design of more effective approaches to drug delivery. Moreover, simply the sorption of endogenous proteins to nanoparticles within an organism could theoretically elicit an immune response as a result of altering the native conformation of the exposed protein. Dis-

cussions regarding the possible environmental ramifications of nanomaterials are just emerging (e.g., CBEN, 2005).

***Hazards from “Non-toxic” Chemicals.*** Although generally recognized that any chemical can pose a risk when exposure occurs at a sufficiently high dose (“the dose makes the poison,” Paracelsus), certain chemicals pose risks even when exposure is at levels where overt effects cannot be measured from exposure to the chemical in isolation from other toxicants. These “indirect” chemical stressors possess no inherent toxicity of their own at benign exposure levels but they can potentiate or amplify the toxicity of other chemical stressors. An example of this phenomenon involves the cellular efflux pump systems, which are evolutionary conserved across taxa and which particularly are important for aquatic organisms as a defensive mechanism against toxicant exposure. These systems also are called multi-xenobiotic transporters, and confer resistance for the organism to a wide array of ordinarily toxic substances (Daughton, 2001). These efflux pump systems serve to physically remove xenobiotics that gain entry to a cell, as well as waste products generated during normal metabolism. They roughly are analogous to bilge pumps on ships. By preventing sufficient exposure, efflux systems allow an organism to maintain its homeostasis in an environment surrounded by pollutants that might otherwise prove toxic. A wide number of chemicals, however, have the ability to inhibit these efflux enzyme systems (the best known examples are certain drugs), thereby allowing access to the cell by any extracellular toxicants that previously had been excluded by the pumps. Toxicity testing currently has no way to account for these so-called “non-toxic hazards.”

Another example of indirect toxicants includes certain manufactured nanoparticles. These substances can

have extraordinarily large surface-to-size ratios. Even if not possessing toxicity of their own, their surface areas nonetheless possess high potential for catalyzing reactions involving other chemicals. This single characteristic of the nanoscale imparts nanomaterials with properties that differ dramatically from those of their “macro” counterparts made from the exact same elemental constituents. Whether the products of these catalyzed reactions are toxic themselves, damaging free radicals (oxidized chemicals with unpaired electrons) frequently are produced as by-products. Nanoparticles, in this sense, are examples of indirect toxicants, where exposure to the parent chemical alone is insufficient for adverse effects.

***Living Systems Not Just Victims, but Also Creators, Perpetuators, and Vectors of Pollutants.*** Nearly all organisms, ranging from microorganisms, plants, and wildlife to humans, actively and passively are involved in exposure to xenobiotics. While exposure holds the potential to elicit adverse consequences, these same organisms also can create chemicals that serve as stressors for others, either purposefully (e.g., natural products biosynthesized for establishing allelopathy—chemical warfare between plants) or inadvertently (e.g., methylation of mercury). Less appreciated, however, is that organisms also can serve as vectors for distributing pollutants worldwide. So-called “biotransport” of lipid-soluble pollutants by migrating wildlife can occur, for example, via bird droppings (Blais et al., 2005).

***Not Everything That Can Be Measured Is Worth Measuring, and Not Everything Worth Measuring Is Measurable—Chemicals in Hiding.*** The data collected from water monitoring can be biased in two ways: i) limitations in the actual analytical protocol or the measurement technology, and ii) a consequence of ignoring large classes of potential chemical stressors as a re-

sult of the exigency to focus on lists of preselected analytes (“target-based” analysis). The use of water monitoring data based on “free” (dissolved) concentrations to predict total environmental loads of a particular pollutant has the potential to yield misleading values that are biased low (perhaps even by orders of magnitude). This is true particularly for those pollutants that reside in alternative physicochemical forms that serve as hidden reservoirs,

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*Rarely is any organism exposed to but a single chemical stressor at any time, in isolation from all others. Development of a real-world understanding of exposure involves organisms continually interacting with mixtures of multiple or multitudines of stressors.*

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such as excreted metabolic conjugates (which can be reconverted back to their parent forms) and residues tied up as ligands or reversible precipitates or sorbed to suspended particulates or sediments. In reality, a multitude of chemicals can be overlooked, ignored, or omitted by environmental monitoring for any number of reasons.

***Maybe Gone but Not Forgotten.*** It is not just the original (“parent”) chemical that may play a significant role in the environment. Often of significance are the transformation products that result from its metabolism

(animal, plant, and microbial) and the products from abiotic processes such as sunlight and chemical-mediated reactions. Some parent chemicals can yield a multitude of so-called “break-down” products or “degradates.” Just because the original “parent” chemical might be gone, does not mean that its presence is no longer felt. Natural metabolism and engineered waste treatment processes can create a plethora of transformation products, many of which can have bioactivity of their own, sometimes greater than that of the parent chemical. Carbamazepine, for example, is an anticonvulsant drug that occurs frequently in open waters (from treated sewage), but its metabolism yields a host of products that also can occur (Miao and Metcalfe, 2003). These types of transformed chemicals usually remain hidden from all probing except by the curious analytical chemist.

With respect to obtaining a holistic view of risk, target-based environmental monitoring necessarily yields a distorted, filtered view of environmental occurrence by purposefully and inadvertently neglecting an unknown (and perhaps substantial) portion of unidentified constituents (see Daughton, 2003a). In the final analysis, consideration should be given to a quip, adapted from a purported Einstein quotation, “Not everything that can be measured is worth measuring, and not everything worth measuring is measurable” (Daughton, 2003a).

***Interfaces and Microenvironments—Where the Action Is.*** We tend to examine the obvious places, such as open bodies of water, for pollutants and how they behave in the environment. Nevertheless, the less obvious niches also can prove significant. As one example, interfaces and their associated heterogeneous microenvironments at the junctures of dissimilar phases can act as cauldrons for complex interactions and transformation of water pollutants. Interfacial phenomena are in-

sufficiently understood with respect to the removal or storage of xenobiotics as well as the creation of new pollutants. Complex and poorly understood interface processes pose numerous questions. As an example, consider the low levels of dissolved antibiotics in environmental waters. Levels monitored in the dissolved aqueous environment, which usually are orders of magnitude below those required to select for antibiotic resistance, may be irrelevant if interface phenomena can serve to bring together much higher concentrations at solid surfaces where biofilms develop. Could microenvironments and niches (such as interfaces occupied by biofilms) serve to maximize exposure concentrations as well as resistance-gene selection and horizontal gene transfer (the movement of genes from one organism to another)? Upstream sewage trunk lines are one example and biosolids (e.g., treated sewage sludge disposed to land) are another where this could occur (Daughton, 2002). The water-air interface, where monomolecular films of lipophilic and amphiphilic pollutants (also called amphipathic or amphiphatic; containing structural features that are attracted to both lipid and water) can concentrate, add yet further complexity and a host of other questions.

### Reassessing Exposure and Chemical Diaspora

**Holistic Exposure Assessment.** The exposure environment to which environmental toxicologists traditionally have focused their attention is limited to the “conventional” pollutants that compose the various lists of regulated pollutants. Many of these are the “high production volume” industrial chemicals (and manufacturing by-products) and those substances specifically designed to kill pests. It is important to note, however, that these chemicals comprise but a very small portion of the numbers of distinct xenobiotics

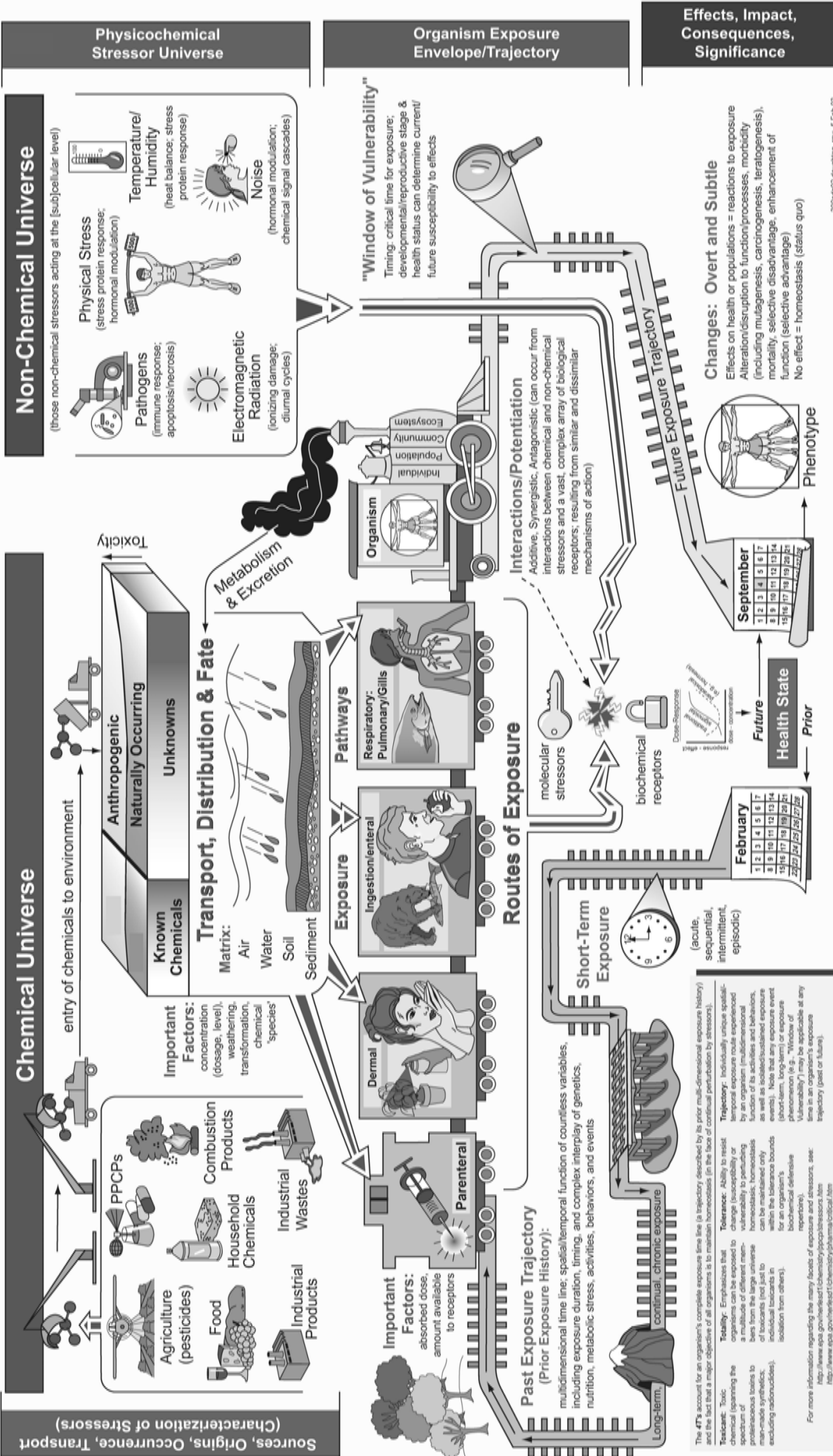
from the universe to which organisms can and do experience exposure. As we have seen, the chemicals composing these high-profile categories are not representative of the full spectrum of known chemical stressors or the multitudes of transformation products. The multifactorial complexity faced by risk assessment includes the exposure frequency and timing, exposure duration, exposure complexity or “totality” (cumulative and aggregate exposure, synergism, and other multiple-stressor interactions), prior exposure history (the foundation for determining exposure “trajectory”), or other factors including delayed-onset toxicity or cross-generational effects. Given these limitations, it is important that progress be made toward more holistic assessments that account for the wide range of potential environmental pollutants and to pinpoint those pollutant scenarios with highest health-effects potential.

**The 4Ts and Homeostasis—the Poison Is Made by More Than Just Its Dose.** Rarely is any organism exposed to but a single chemical stressor at any time, in isolation from all others. Development of a real-world understanding of exposure involves organisms continually interacting with mixtures of multiple or multitudes of stressors, the composition of which continually can vary through time in terms of the specific chemical constituents and their absolute and relative concentrations. A further complication is that stressors for many organisms include not just chemicals (the subject of this article), but also physical (e.g., thermal), psychological (e.g., fear), and biological (e.g., pathogenic) agents. All of these stressors can interact in complex, unforeseen ways, sometimes greatly synergizing each other. The chemical sea to which an organism is exposed washes against critical windows of vulnerability (e.g., developmental stages or diurnal physiological phases). The poison is made not just with the dose, but also with its duration and timing.

Longer exposure durations can drive down the dose needed for the same effects. Completely different types of biological effects can occur at different exposure concentrations. Such a multitude of variables and possible interactions poses complex challenges for predicting the trajectory of exposure outcomes for an organism. These factors are part of the overall consideration of the “4Ts” of exposure, a shorthand term that captures the complete context of an organism’s cumulative exposure to chemical stressors. The “4Ts” describe “toxicant totality tolerance trajectory” and account for an organism’s complete exposure time line (a trajectory traced in part by prior multidimensional exposure history) and the fact that a major objective of all organisms is to maintain homeostasis in the face of continual perturbation by stressors. Homeostasis can be maintained only within the tolerance bounds for the organism’s regulatory and biochemical defensive repertoire. Therefore, the paradigm of the 4Ts sets the stage for the overall true risk as reflected by the sum total of exposure to all toxicants (anthropogenic and naturally occurring) throughout the historical multidimensional space and trajectory of all other exposure variables. A key aspect to this concept is the critical state as determined by the 4Ts—that state at which an additional single exposure event can result in an irreversible adverse effect, one that pushes the organism beyond its ability to maintain homeostasis. A cartoon illustration of the 4Ts is shown in Figure 2 (page 16), with more information available (Daughton, comp.). Potency, dose, timing, duration, and numerous other variables all must be known to fully assess risk. Any single one of these parameters is insufficient.

**Stressor Interactions Confounding Anticipated Toxicity.** As one of many examples of the importance of the 4Ts, the complexity surrounding the numerous factors involved with exposure, and

# Biological Systems and Stressors "Toxicant Totality Tolerance Trajectory" - 4T's



The 4T's account for an organism's complete exposure time line (a trajectory, described by its prior multi-dimensional exposure history) and the fact that a major objective of all organisms is to maintain homeostasis (in the face of continual perturbation by stressors).

**Toxicity:** Toxic chemical (spanning the spectrum of pathogenesis to man-made synthetic, including radionuclides).

**Tolerance:** Ability to resist change (susceptibility or vulnerability) to perturbation by an organism (multi-dimensional function of its activities and behaviors, as well as its homeostasis, homeostasis can be maintained only within the tolerance bounds of individual toxicants in isolation from others).

**Trajectory:** Individuals within a species can be exposed to a multitude of different men-homoeostasis, homeostasis can be maintained only within the tolerance bounds of individual toxicants in isolation from others).

**Tolerance:** Ability to resist change (susceptibility or vulnerability) to perturbation by an organism (multi-dimensional function of its activities and behaviors, as well as its homeostasis, homeostasis can be maintained only within the tolerance bounds of individual toxicants in isolation from others).

**Vulnerability:** "Window of Vulnerability" may be applicable at any time in an organism's exposure trajectory (past or future).

For more information regarding the many facets of exposure and stressors, see: <http://www.epa.gov/nerfescd/chemistry/ppcp/stressors.htm>

the unanticipated ways in which even vastly dissimilar stressors can interact, consider two recent examples dealing with amphibians, which have been undergoing worldwide population declines. The first reports the greatly enhanced toxicity of the carbamate pesticide, carbaryl, toward amphibians when experiencing predatory stress. Carbaryl concentrations from short-term acute exposure that ordinarily would not adversely affect growth or survival can prove lethal when the exposure period is increased or when the exposure occurs in the presence of predatory stress (Relyea, 2003). The end effect is as if the concentration of the chemical stressor were magnified many fold by the increased exposure time or by the non-chemical stressor (in this case, a predator cue). The second reports the greatly enhanced stressor action of normally benign concentrations (the levels of toxicants often occurring in the environment) of the fungicide fenpropimorph to tadpoles when they are developing in the presence of a predator (Teplitsky et al., 2005). The combined action of a predatory stress cue (such as merely sensing the presence of a predator) and the low-level fungicide resulted in delayed and smaller maturation that could adversely impact the fitness of the population. A multitude of non-chemical factors profoundly can affect the outcome of exposure to chemical stressors. With humans, for example, interactive exposure to certain chemicals together with noise can synergistically degrade hearing (ototoxicity; e.g., see Fechter and Pouyatos 2005). Interactions among disparate stressor groups, as opposed to effects mediated solely by one group such as chemicals, is an under-investigated area of research. Interactions between stressors can be extraordinarily complex and lead to completely unanticipated outcomes. Because of the complexity, rarely can these factors be accounted for in conventional ecotoxicity testing protocols relied

upon by regulatory assessments and which usually focus on acute toxicity and on one stressor at a time.

***Epidemiology and Post Hoc Ergo Propter Hoc—It's All in the Timing.***

A natural consequence of developing a systems-level understanding of exposure and effects would be the minimization of confusion resulting from inferring causal relationships between observed adverse effects and exposure to particular chemical stressors that happen to co-occur with the effect. Correlating exposure (to particular chemical stressors) with an observed effect can result in concluding that an exposure causes an effect simply because of a temporal connection—"after this, therefore because of this" (post hoc ergo propter hoc). Conclusions regarding causality must take into consideration the 4Ts rather than just coincidental connections. Formulating actual cause-effect relationships can be a very complex, long-term undertaking (e.g., DDT and eggshell thinning).

***Subtle Shifts Leading to Overt Change—A New Paradigm?*** Acute toxicity, carcinogenesis, teratogenicity, and direct endocrine disruption are several of the highly visible toxicological endpoints that historically have attracted the most concern. The hypothesis has been raised, however, involving the significance of less overt toxicological endpoints, such as immunodisruption, neurobehavioral change, protein misfolding diseases, and other subtle effects (Daughton and Ternes, 1999). Could immediate biological actions on non-target species be imperceptible but nonetheless lead to adverse impacts as a result of continual accretion over long periods? Could subtle effects accumulate so slowly (perhaps seeming to be part of natural variation) that major outward change cannot be ascribed to the original cause? Could latent damage accumulate, only surfacing later in life? Effects that are sufficiently subtle that they are undetectable or unnoticed present a challenge

to risk assessment. These types of effects include very subtle shifts in behavior or intelligence that pass through generations. On the other side of the coin are questions regarding what constitutes the norm. For example, care must be exercised in determining if malformations and sex trait characteristics commonly observed in aquatic organisms are "abnormal" (possibly resulting from chemical stressors) or whether they are simply part of a natural and normal distribution among populations.

***"What Is Normal? What Is Natural?"*** In the context of post hoc ergo propter hoc, a major phenomenon that leads to the conclusion that chemical pollutants lead to adverse environmental effects is the extent, frequency, and prevalence of seemingly abnormal characteristics in aquatic organisms, such as skewed sex ratios and developmental "malformations." These "abnormalities," for example, frequently are cited as evidence of exposure to endocrine modulators (e.g., the synthetic estrogen, ethynylestradiol, in treated sewage). It is critical to consider, however, that the baseline occurrence of these characteristics in pristine "wild" populations often is unknown and therefore causalities cannot justifiably be inferred.

***Exactly Where, How, and When We Search Dictates What We'll Find.***

Analogous to the problems with target-analysis, it is hard to find causes for which we are not looking. It can be equally hard to observe effects not looked for, especially subtle ones. This problem is evident particularly when considering the overlooked ability of certain toxicants to elicit adverse outcomes far after exposure has ceased and thereby escape the formulation of causal connections. Such delayed-onset toxicity almost never is considered in epidemiological studies simply because of the daunting challenge, for example with cancer clusters. Irreversible delayed-onset toxicity can mani-

fest itself weeks, months, or years after exposure in the form of carcinogenicity (aflatoxins, asbestos), teratogenicity (e.g., thalidomide), hepatotoxicity (e.g., pyrrolizidine alkaloids), or neurotoxicity (e.g., organophosphorus nerve agents). Such prolonged latency between exposure and onset of effects not only makes establishment of causality extremely difficult, it can lead to formulation of erroneous associations with chemical stressors that by happenstance are present during the onset of the symptoms. Delayed-onset toxicants also could play major roles in acts of sabotage.

***Beyond the DNA-RNA-Protein Dogma—Inherited Effects Without Genetic Change.*** Beyond the central dogma of DNA governing the phenotype of an organism (via translation to RNA and transcription of RNA to protein), an aspect that steadily has been attracting more attention is “epigenetics,” which comprises a number of processes that regulate transgenerational effects. These heritable changes in gene function can be passed across multiple generations without any alteration to the genetic code. This is accomplished by activation or inactivation of genes by chemical modification of chromatin by processes such as methylation of the DNA (e.g., the so-called, non-RNA-coding “junk” DNA), acetylation of the proteinaceous histones, and RNA interference. These processes can be modulated or interfered with by various xenobiotics. A recent example of the relevance of epigenetics to environmental exposure is the work of Anway et al. (2005), who reported that exposure of pregnant rats to the pesticides methoxychlor or vinclozolin led to male offspring with reduced fertility. This heritable change was passed through four generations after the original exposure to the mother.

***“No-Observed-Effect Level”—You Get What You Want, Not Necessarily What You Need.*** A standard measure

in toxicology is the NOEL (No-Observed-Effect Level) and its variants, such as the NOAEL (no-observed-adverse-effect level). The NOEL is a stressor’s maximum dose that fails to elicit a detectable change under defined conditions of exposure. The NOEL is used in calculating other widely used toxicity measures, such as the “acute/chronic ratio” (ACR; where chemicals having significant chronic toxicity, as measured by the lower levels imparting effects, compared with acute toxicity, have higher ratios). The NOEL, however, can easily mislead as it only can be calculated for known effects endpoints that are pre-determined. Effects endpoints that we are not aware of or that are so subtle they elude detection can possibly lower NOEL values. In reality, the lowest NOEL cannot be determined until all the salient toxicological endpoints are understood.

***The Alchemy of Somethin’ from Nothin’—When a Little Might Be a Lot, or When Less Is More.*** There are growing questions regarding the pervasiveness, significance, and ramifications of exposure to “low” levels of chemical stressors (so-called “micropollutants”). There are many unknowns and controversies regarding such exposures. Of course, “low” is a relative term, one usually deriving its meaning as being “lower” than previously studied or documented. For analytical chemists today (and sometimes toxicologists), “low” often refers to concentrations at or below the parts-per-billion or nanomolar ranges. These concentrations are orders of magnitude below those that could be studied just two decades ago. There are also questions, however, regarding the innate toxicity of a chemical (e.g., under laboratory conditions) versus its ability or potential to actually elicit toxicity in the real world. Regardless, certain chemicals (e.g., ethynylestradiol) do have the ability to impart effects at concentrations of one part-per-trillion

and lower. Effects even can occur at concentrations well below NOELs.

As advances in treatment technology continually lower the concentrations of chemical residues in treated waters, and as analytical chemists reduce the detectable levels further, the toxicological significance of ultra-low-dose exposure needs to be better understood. Concern is heightened for those organisms (such as in aquatic environments) that suffer continual, multigenerational exposure to complex mixtures of low-level toxicants. The toxicology of most xenobiotics is poorly understood at low levels. Particularly needed is to elucidate the significance of low-level effects in the range where so-called “paradoxical” dose responses are prevalent, where the non-conventional U- or J-shaped nature of dose-response curves becomes evident. An example is hormesis (e.g., see BELLE, 2004), a dose-response phenomenon where noninhibitory effects occur below previously established NOELs. Despite hormesis being proposed as a justification for permitting or justifying low-dose exposures (e.g., because one of its common outcomes is growth stimulation), it is important to remember that: (i) any effect (regardless of its anthropocentric interpretation) that perturbs homeostasis has the potential to ultimately result in an adverse outcome and (ii) real-life exposures are to multiple stressors, some of which can share the same mechanism (or mode) of action, thereby effectively having a combined concentration higher than the hormetic level for a single stressor in isolation from all others. These limitations, and others, have now been formally articulated by Thayer et al. (2005).

***Symptoms from Nowhere—the Nocebo.*** An additional way in which effects can manifest from human exposure to seemingly minuscule concentrations of pollutants is via the so-called nocebo response (Daughton, 2004). The nocebo effect (the opposite

of the placebo effect) is a real, physiologically adverse outcome caused simply by the suggestion or belief that something (such as a chemical) is harmful, regardless of any inherent toxicity. The nocebo effect could play a key role in the manifestation of adverse health consequences from exposure even to non-toxic trace levels of contaminants—simply by the power of suggestion. Public education and a better understanding of how risk is perceived and how it best be communicated are important particularly for minimizing the incidence of the so-called nocebo response.

**Same Chemicals, Different Outcomes.** The nocebo effect presents a fascinating juxtaposition against the adage “familiarity breeds boredom.” The way in which risk is perceived can lead to ironic and even contradictory outcomes, pointing to a need for major improvement in the way risk is communicated. One paradox in risk perception relates to the relatively high concentrations and types of a plethora of chemicals formulated in personal care products that are applied directly to the skin or in the mouth, versus the concentrations of some of these very same chemicals that might be found in drinking water but at many orders of magnitude lower concentrations than in commercial products. The high concentrations of various chemicals in personal care products routinely are deemed by the user to be risk-free but not the very same chemicals, in minute concentrations, in drinking water.

Another example involves the occurrence of minuscule traces of drugs in certain drinking waters, which can foster the formation of negative mental and emotional images for the consumer, regardless of the water’s overall purity, as a result of the fact that the origin of these drugs often derives solely from human excretion (Daughton, 2004). A better understanding is needed of the origins of the chasm existing between the communi-

cation of actual hazard/risk and how the risk actually is perceived. This will prove especially important with the growing need to reuse water or to recycle it for drinking.

**A Special Concern Regarding Low-Dose Effects—TILT.** One specific issue regarding low-level human exposure specifically concerns toxic effects from exposures that on prior occasions proved benign. Controversy surrounds the significance of exposure to minute quantities of xenobiotics, whether from food, drink, skin, or air. Exposure by

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*New sources of pollutants include not just chemicals newly introduced to commerce but also new ways to produce and use them, which in turn create new opportunities for their entry into the environment.*

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special subpopulations or during critical windows of vulnerability (e.g., fetal development) has been reported (but not without controversy) to lead to toxicant-induced loss of tolerance (TILT) (or “multiple chemical sensitivity”) (Winder, 2002). In TILT, an initial exposure (perhaps to a larger quantity) purportedly promotes hypersensitivity. Subsequent exposures to levels far below those previously tolerated then trigger symptoms. An obvious question is whether an ecological version of TILT exists, where effects levels can be driven downward by prior exposure—where NOELs be-

come dynamic thresholds that are a function of prior exposure history.

**Like-Minded Chemicals of Similar Persuasions—Too Much of Nothin.’**

Another way in which a little can mean a lot can be illustrated simply by the scenario of simultaneous exposure to multiple chemicals at low concentrations. A special case where low concentrations of chemicals could prove significant is by exposure to multiple stressors, each perhaps at a concentration below which an effect could occur, but which share the same mechanism or mode of action. The overall, combined concentrations of all those chemicals with the same mechanisms of action could very well exceed a toxicity threshold. This poses very difficult regulatory challenges, whether these like-mechanism chemicals originate from the same industry or from different industries. Traditional toxicity testing could show that no single chemical may have any effect at the level it occurs in the environment. In this way, risk could be consistently underestimated. As the numbers of different types of chemicals increases in the environment, the potential for this scenario increases.

**Merging onto a “Toxicity Apportionment” Regulatory Freeway from the Dead-end Chemical-by-Chemical Road?**

The continual introduction of new chemicals to commerce casts doubts as to whether a chemical-by-chemical approach to regulation of water pollutants will continue to be sustainable on a comprehensive scientific footing (Daughton, 2003a; Daughton and Ternes, 1999). Many emerging pollutants, such as PPCPs, have totally new mechanisms of action (MOAs), most have multiple MOAs, and the actual MOAs rarely are even understood fully. With respect to the “exposure universe,” and in a manner analogous to source apportionment, consideration could be devoted to developing the capability of “toxicity apportionment.” The objective would



be to assign toxicity an integrative measure of the total numbers and quantities of stressors present, without the need to know their actual identities in advance. The ultimate objective would be to close the exposure envelope around all chemical-exposure constituents—both naturally occurring and anthropogenic. This alternative approach could consider basing water monitoring programs on assays designed around evolutionarily conserved biochemical features and MOAs rather than on individual chemical entities. The ultimate question is whether the initial target of regulation might be the potential for actual biological effects instead of chemicals themselves. This approach could be a better way to automatically account for a multitude of stressors sharing a common MOA (cumulative exposure), stressors newly introduced to commerce, and pollutants not yet identified.

***Environmental Stewardship versus Pollution Postponement, Pollutant Musical Chairs, and Pollutant Alchemy.*** Since purposeful, direct discharge of chemicals to the environment is inherently undesirable, many ways to reduce these emissions have been developed. These include numerous physical removal technologies (ranging from simple filtration and sedimentation to reverse osmosis for wastewaters), volume reduction (e.g., evaporation), or storage (e.g., landfills). All of these physical approaches essentially eliminate discharge today in exchange for risking potential discharge at a later date (“pollution postponement”). They simply transfer pollutants from one place to another, delaying the way and time by which they can gain entry to the environment. Even destructive processes (e.g., oxidation and combustion, including incineration) sometimes serve to transform existing pollutants into new chemicals (“pollutant alchemy”), a form of pollutant musical chairs. The most significant demarcation among classes of chemicals that

pollute the environment is that between inorganic and organic chemicals. In contrast to the latter (even for DDT, halogenated dioxins/furans, PCBs), which have limited life expectancies, the former often have indefinite life expectancies (e.g., elemental lead) or simply transform into related species until they are “recycled” in the environment back to the parent forms (e.g., various forms of mercury and arsenic). Although pollution postponement and pollutant alchemy might sometimes be the best way to delay the entry of these chemicals to the environment, pollution prevention and pollution minimization are preferred. For perspective, extensive examples of stewardship approaches for minimizing the entry of PPCPs to the environment have been proposed (Daughton 2003a,b).

#### Peeking at the Future

While it is not possible to predict the future regarding the many dimensions of chemical pollution, several concerns and opportunities, just now emerging, might be useful to consider.

***Early Warning—Monitoring for Emerging Contaminants and Homeland Security.*** New sources of pollutants include not just chemicals newly introduced to commerce but also new ways to produce and use them, which in turn create new opportunities for their entry into the environment. Several examples include: (i) commercial introduction of new drugs (including potent illicit designer drugs) with MOAs never before encountered by biological systems, (ii) transgenic production of therapeutants and vaccines by genetically altered plants (especially edible crops), also known as plant-made pharmaceuticals (PMPs), by “molecular farming” or “biopharming,” (iii) newly invented nanomaterials and their ill-defined products that could result from natural weathering processes, (iv) the advent of micro-process technology, where

microreactors will eventually prove capable of widespread and dispersed production (on an individually small scale but on a continual basis) of exotic and highly hazardous chemicals with little knowledge or intervention by technical experts, and (v) accelerated access to exotic chemicals by consumers, resulting in myriads of point sources for environmental contamination as a result of the combined contributions from personal actions, activities, and behaviors, as well as the need for disposing of leftover and unwanted materials. With regard to the last point, the quality of source drinking waters depends in part on the diffuse impacts of the collective activities of multitudes of individuals—from each of whom minuscule (and seemingly insignificant) contributions combine to yield detectable levels of certain pollutants that otherwise have little origin from industrial activities. In addition to these sources are the unknowns associated with sabotage of our environment with exotic chemicals (including those designed for military use) by terrorists.

Given the potential for new pollutants to enter the environment, it would be most useful to know about their presence as soon as possible. An ultimate objective of any program designed to deal with emerging pollutants should be to create a mechanism for identifying their presence in the environment as early as possible—well before becoming pervasive. A mechanism for the real-time detection of new pollutants in water is important, not just for protecting the environment and public health from the effects of inadvertent pollution. It also would help in protecting water supplies from chemical sabotage, a concern for homeland security. The sheer number of potential new contaminants clearly would pose insurmountable obstacles for conventional target-based monitoring approaches. A straightforward way to sidestep this limitation would be to design an early warning system around

the simple approach of detecting compositional “change”—where any perturbation in a sample’s normal chemical “fingerprint” (distribution pattern of types and quantities of solutes) would trigger an immediate in-depth chemical analysis to determine the cause (identify the chemicals responsible for the change). Such an approach circumvents the many inherent limitations of target-based monitoring. The timely elucidation of newly emerging (or previously unrecognized) pollutants also is critical to uncovering trends in geographic pollutant distribution, prevalence, and loads. Having available long-term change-detection data could greatly assist epidemiological studies, especially those involving cancer clusters, which long have been a bane of toxicologists. Another approach is to leverage the involvement of amateur observers to report unusual phenomena in nature that possibly are the result of chemical stressors; one such proposal was noted by the Royal Commission on Environmental Pollution (2003).

***Inadequate and Decaying Water Infrastructure.*** In the absence of effective proactive pollution prevention schemes, reactive pollution control is required. Domestic wastewaters are a major emerging source of pollution (from the combined activities of multitudes of individuals). Conventional municipal sewage treatment facilities never were designed to remove exotic anthropogenic chemicals with structures and mechanisms of biological degradative/transformation systems. Indeed, the ubiquitous, albeit low level, presence of PPCPs in treated sewage effluent reflects this limitation. Even if existing waste treatment and water treatment facilities functioned according to original specifications, the types and quantities of xenobiotics in treated water could continue to rise, partly as a result of the introduction of new chemicals to the marketplace and partly because the nation’s water in-

frastructure requires considerable investment for repair and upgrading. An additional infrastructure need is to reduce the occurrence of unpermitted straight-piping, septic systems, and privies, which serve to maximize the release of xenobiotics to the environment (to both surface waters and groundwaters) via raw sewage.

***Toward a Holistic Solution.*** The growing number and sources of chemicals with the potential to enter the environment via wastewater is challenging our ability to treat these wastes. Actions to reduce any of the associated variables contributing to this vulnerability would be prudent. The major vulnerability for humans results from the nature of the water cycle, where the historic practice of treating domestic wastewaters for discharge to surface waters can result in contamination of source waters destined for drinking (whether surface or ground). The major requirement has been the design of water systems having sufficient spatial and temporal hydraulic “disconnect” so as to “erase” from the consumer’s mind any memory of the original source of the water (Daughton, 2004). The continually diminishing supplies of high-quality freshwater, however, is increasing pressure to actively recycle and reuse waters, even from human waste. This will lead to ever-shortening spatial and temporal hydraulic connectivity between the point of wastewater discharge and the point of use for drinking (the recycle loops will continually shrink). The ultimate rendition of this is the so-called “toilet-to-tap” approach. While this approach has been vilified by many (primarily as a result of the way in which risk is perceived), if properly implemented it could solve many problems faced by areas facing water shortages.

***Decentralized Water Re-Use.*** Less than one percent of all the world’s freshwater resources are readily accessible, representing less than 0.01 percent of all the world’s water (see Fig-

ure 1 in Shiklomanov 1999). The growing shortage of freshwater could drive a transition from centralized municipal water treatment and distribution to truly distributed water reuse—where wastewater is both treated and reused close to its origin, eventually directly on site. Such distributed water reuse systems pose unique challenges regarding public acceptance and effective communication of risk (see Daughton, 2004). However, they also offer fundamental advantages regarding independence and the inherent design advantage of ultimate security from large-scale sabotage. Another advantage of recycling water generated directly from the point of original use (as opposed to collective water from centralized domestic, municipal, and industrial generators) is that the universe of microcontaminants that need to be removed is vastly reduced and the types and number of chemicals that the consumer will discard to sewerage would be reduced as a result of personal incentive (Daughton, 2004).

***“Futuring” and the Precautionary Principle.*** The traditional list-based, chemical-by-chemical approach must wait for emerging pollutants to establish an environmental presence before action can be taken. Regardless of how timely this approach can become, it is at best a reactive one. The fact that corrective reactions can be required long after chemicals achieve environmental footholds leads to discussions of the controversies surrounding the precautionary principle (see links at Daughton, comp. 2005d). An early rendition of the precautionary principle as codified in law would be the European Commission’s proposed new European Chemicals Agency and regulatory framework for chemicals—REACH (Registration, Evaluation and Authorisation of Chemicals) (EC, comp. 2005). A new paradigm, however, would adopt a proactive approach where future concerns are anticipated, long before any preventive or remedi-

ation measures would have major economic, health or environmental ramifications. To minimize the emergence of unanticipated concerns, more resources need to be invested in truly anticipatory research programs and in the process of “futuring,” which are all required for making progress toward sustainability.

**An Emerging Societal Realization—Chemicals as “Weeds.”** Just as weeds are plants growing where they are neither desired, wanted, nor needed, an alternative definition of pollutants or contaminants is out-of-place chemicals. This is true particularly for those chemicals that achieve unexpected footholds in surprising places. Examples include pharmaceutical and illicit drug residues in drinking water sources (Daughton 2004). Given that the vast majority of chemicals or their complex mixtures occurring in the environment cannot conclusively be linked with adverse ecological or human health effects, regulators are hard-pressed to justify any actions. Despite the canyons of absence of data and mountains of data of absence, the public often is averse to the occurrence of even trace residues of certain pollutants in water, food, or air. The actual concentrations of these contaminants, regardless of how minuscule, often are irrelevant in society’s “quest for zero.” Missing in the risk communication process is the failure to realize that zero often is sought not necessarily because of any perceived risk from particular exposure levels, but rather simply because these chemicals do not belong where they occur. They are chemical weeds. Using the weed analogy might lead to a new paradigm where focus could be diverted away from basing regulation on toxicological hazard and risk (and the associated measures that span numerous magnitudes of abstruse jargon—from parts-per-million to yocto-molar) and instead toward active management of chemicals simply as weeds. Perhaps all that

is needed is to implement economically sustainable measures designed to minimize the introduction of all chemicals to the environment. Of special interest would be those originating from consumer use and which therefore pervade the environment. Progress is possible using a balanced repertoire of comprehensive pollution prevention and source reduction measures and waste treatment technologies, coupled with ongoing environmental monitoring to gauge whether these measures are effective at maintaining these chemical weeds at whatever levels society deems acceptable.

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