



**Assessing exposure to multiple chemicals requires an all-inclusive systems perspective.**

## The 4 Ts: Assessing Exposure to Multiple Chemicals

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*please see the chart on page 23*

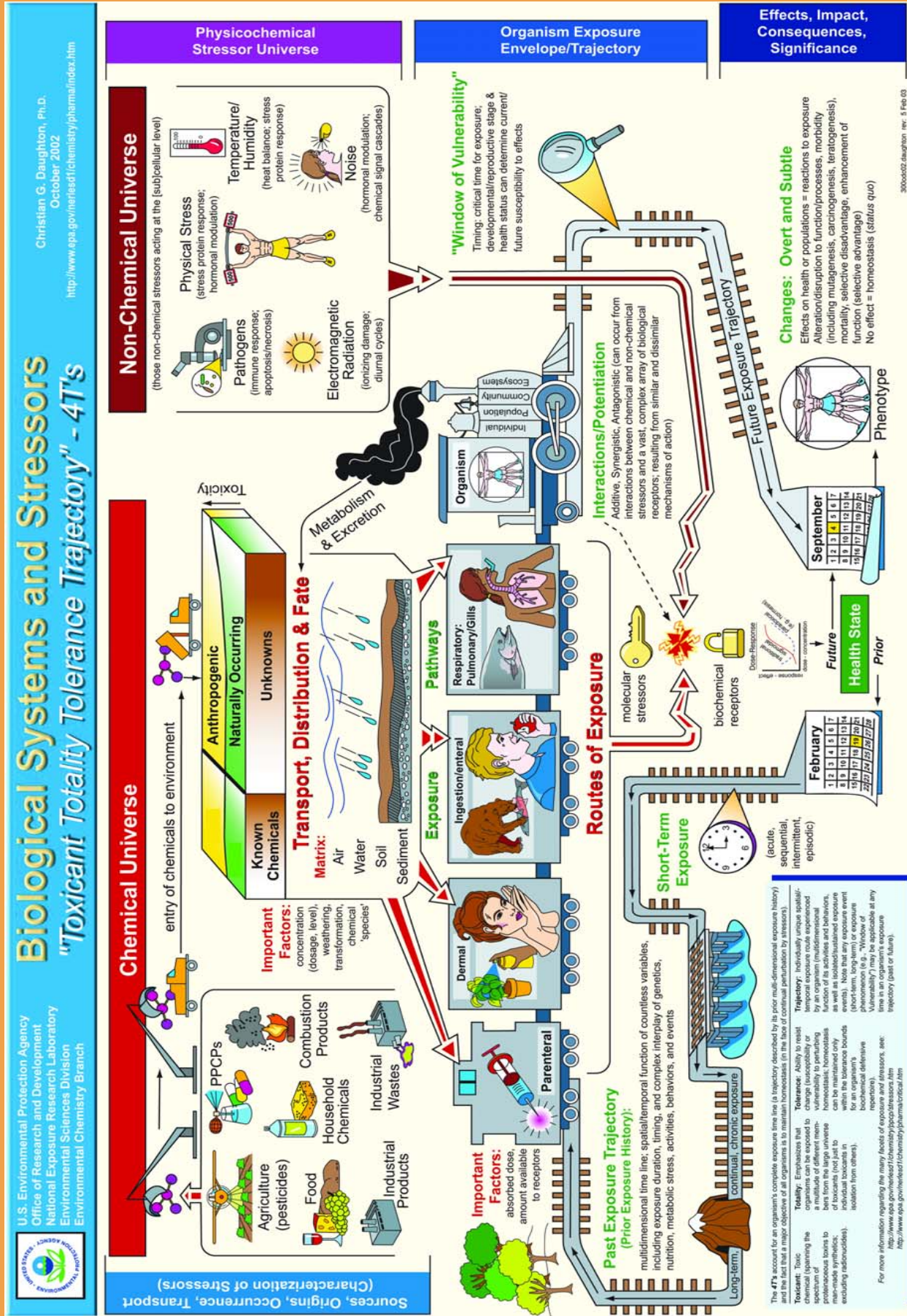
Humans, like most life forms on Earth, are bombarded daily with multiple chemicals. Rarely are we exposed to a single, isolated chemical stressor. In analyzing the effects chemicals have on organisms, toxicologists traditionally have focused on a select number of pollutants regarded as “high volume” chemicals; but these represent only a small sample of the substances most organisms are exposed to on a regular basis. Although this type of research is valid and relevant, investigating the effects of one chemical on organisms or ecological systems may not be the best way to understand the toxic effects of multiple chemicals. Due to the large number of chemicals introduced into the environment in the 20th century, this approach does not account for many biologically transformed metabolites and other naturally occurring toxicants.

Assessing exposure to risk for multiple chemicals requires an all-inclusive systems perspective, and EPA senior scientist Christian Daughton has developed such a model: it outlines a way to conduct a holistic assessment of chemical exposure as it actually occurs in the real world. Dubbed “The 4Ts,” the model’s four primary categories are Toxicant, Totality, Tolerance, and Trajectory.<sup>1</sup> Daughton says, “The paradigm of the 4T’s sets the stage for the overall true risk as reflected by the sum total of exposure of all toxicants (anthropogenic [or created by humans] and naturally occurring) throughout the historical multidimensional space and trajectory of all other exposure variables.”<sup>2</sup>(p15) The categories encompass not only individual offending substances (toxicants), but the entire world of stressors (totality), the vulnerability of an organism (tolerance), and combined history of an organism’s exposure (trajectory) in assessing risk.

### Holistic Exposure Assessment: Toxicant, Totality, Tolerance, Trajectory

In addition to exposure to chemicals, multiple nonchemical stressors—physical, biological, and psychological—effect organisms and react in complex, often synergistic, ways. An individual organism’s vulnerability varies depending upon a variety of condi-

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## Holistic Exposure Assessment

### Toxicants

Naturally occurring and human-made toxicants that enter organisms through respiration, ingestion, dermal exposure, or parenteral (intravenously)

### Totality

All stressors including exposure to chemicals

### Tolerance

Ability to resist change at organismic level—determined by fitness and genetics

### Trajectory

Long term, intermittent, episodic, and acute—past and potential future cumulative exposures to toxins

tions; for humans, our developmental stages are one particularly important variable. For example, gestation and early childhood are more vulnerable stages of the human life cycle. Different toxicant dose concentrations and exposure duration—for example, lower doses for longer periods of exposure—may increase risk during these periods.

The macro-environment continues to accumulate “toxicants”—both naturally occurring and anthropogenic toxic chemicals. Chemicals may enter biological organisms in 4 ways: respiration, ingestion, dermal exposure, or parenteral (direct entry into the organism, e.g. through intravenous injection, such as a vaccine).

Rather than considering a one-time exposure to a single toxicant, it is important to take account for total number of past and present exposures, which occur in temporal patterns along a trajectory—long term, intermittent, episodic, and acute. This gives a more accurate picture of the organism’s exposure by looking at the duration and concentration of individual toxicants as well as all previous toxic exposures. This “totality” may be synergistically enhanced or resisted by nonchemical stressors—such as pathogens, electromagnetic radiation, physical stressors, temperature/humidity, emotional stress and noise—that affect the organism.

An organism’s “tolerance,” which accounts for its ability to resist change at the organismic level, is determined by its general fitness and genetic disposition. Various chemical and nonchemical stressors challenge the individual’s capacity for maintaining homeostasis, i.e., the tendency to return to a healthy physiological equilibrium.

The “trajectory” encompasses not only past cumulative exposures but also future exposure; this is a more accurate picture of overall exposure and resulting risk over time. Key to the 4Ts model is the critical state, which is defined as the “state at which an additional single exposure event can result in irreversible adverse effect, one that pushes the organism beyond its ability to maintain homeostasis.”<sup>2(p15)</sup> In humans, we call this state disease.

The 4Ts model offers a more sophisticated and systemic approach than previously available for addressing the complex distribution and effects of multiple chemical exposure on living organisms. The significance of this model will emerge as toxicologists and physicians begin to utilize this valuable resource.

## REFERENCES

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