by Roger Clemens

Let's Give Toxicology **the Attention It Deserves**

The explosion of nutritional supplements, novel foods, cannabinoids, botanicals, bioactives, and nanoactives has increased the need for more efficient and accurate characterization and food safety screening and assessment. Moreover, food toxicology is an increasingly important consideration as the food supply chain is becoming more multinational in origin, and any contamination or toxic manifestation, whether natural or synthetic, may cause serious, widespread adverse health effects.

The possible health issues and potential problems are reflected almost daily in the media. Major misunderstandings and confusion raised by these reports are generally due to lack of basic knowledge about toxicology among consumers and even health professionals.

Ever increasing doses of vitamins, hormone precursors, and other micronutrients under the commercial rubric of nutritional supplements have raised serious questions. At doses above the Recommended Daily Allowance and below the tolerable upper intake limit (UL), if established, the molecular pathways are in a dynamic balance that favors homeostasis. As the dose increases beyond the UL, the balance favors pathways leading to potential toxicity and significant adverse events. Just consider hypervitaminosis A from consuming polar bear liver (Rodahl and Moore 1943). This situation, and the imperatives to reduce both toxicity testing costs and the number of animals used, have been recognized over the past decade as drivers for change.

In 2008, the National Institute of Environmental Health Sciences/National Toxicology Program, the U.S. Environmental Protection Agency's National Center for Computational Toxicology (NCCT), and the National Human Genome Research Institute/National Institutes of Health Chemical Genomics Center entered into an agreement on "high throughput screening, toxicity pathway profiling, and biological interpretation of findings." Two years later, the U.S. Food and Drug Administration joined the collaboration, which is known informally as Tox21 (Tice et al. 2013). Using a robotic screening system housed at NCCT, researchers have tested over 10,000 environmental chemicals (known as the Tox21 10K library) for their potential to disrupt biological pathways, which may result in toxicity.

Tox21 data have been cited by the European Chemicals Agency, California's Environmental Protection Agency, Minnesota's Department of Health, the World Health Organization, and the International Agency for Research on Cancer, all in regard to evaluating potential substances of concern for endocrine-disrupting chemicals, pesticide assessments, and potential carcinogenesis.

As timely and ambitious as the Tox21 initiative has been, it remains in its infancy and as yet represents an exciting but very incomplete proof of concept. Significant limitations include those of *in vitro* assays; the failure to recognize isoforms of toxicologically relevant compounds and their differential effects; and the failure to appreciate the mediating effects of particular alleles in the metabolic pathway of various innate food components, environmentally generated substances, and even pharmaceutical agents, some of which are developed and delivered to reduce the initiation or progression of cancer.

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Emerging analytical techniques and applications to detect substances, such as food allergens and novel food ingredients, must be adapted and applied in greater detail and with a comprehensive and evolving strategy. Areas of focus should include natural toxins in food plants and animals; cancer modulating substances; microbial toxins in foods (algal, fungal, and bacterial); and all groups of contaminants (i.e., pesticides), persistent organic pollutants, metals, packaging materials, hormones (even those innate to plants), and animal drug residues. We are reminded that at least 99% of all toxic substances are natural and are innate to virtually every food that we consume (Ames et al. 1990).

The way forward may be an augmentation of the strategy aimed at enhancing the resolution and scope of Tox21 and exploring the adaptability of real-time chemical sensor, digital imaging, and other assays and technologies to toxicity testing. The domain of food toxicology deserves more aggressive and comprehensive energies, including efforts directed to consumer education and certain increased proactive funding. Politics and emotion have clouded our public health priorities. More than $100 million has recently been allocated to a National Institutes of Health "big data" project known as "All of Us," even when existing well-conceived databases exist and are arguably underutilized. Imagine the real clinical and public health impact if funds of similar magnitude were to be directed to bench toxicology. In addition, the prospect of creative collaboration between federal regulatory agencies, scientific organizations, academic institutions, and the food industry is not without precedent and should be revisited in this context. **FT**

References cited are available via hyperlinks in the digital version of this column.

***Roger Clemens**, DrPH, CFS, Contributing Editor • Adjunct Professor, Univ. of Southern California's School of Pharmacy, Los Angeles, Calif. • clemens@usc.edu*