A Memorial: Gilman Veith

Our colleague and good friend Gilman Veith died August 18th after a long battle with pancreatic cancer. Over his more than 40 year career Gil provided outstanding vision and inspirational leadership at both national and international levels. His efforts have been truly transformational, impacting a number of key areas in environmental chemistry, toxicology, and risk assessment in a manner that will continue to influence these fields far into the future.

Gil received his PhD in 1970 in Water Chemistry from the University of Wisconsin, where he subsequently spent two years as an Assistant Professor, with a research emphasis on measurement of PCBs in the Great Lakes. His pioneering work in what, at that time was one of the highest profile issues in the environmental field, led to Gil being recruited in 1972 to join the new US Environmental Protection Agency (EPA) lab in Duluth, MN. Gil worked in multiple capacities at EPA, notably serving as the Director of the Duluth facility from 1987-1995, and as the Associate Director for Ecology for the multi-division, National Health and Environmental Effects Research Laboratory (based in RTP, NC) from 1995-2002. After a brief period as a Senior Scientist Gil retired from EPA in 2003; however, this segment of his life was a retirement in name only. He subsequently accepted a Science Advisor position with the Organisation for Economic Cooperation and Development (OECD; which included living for extended periods of time in Paris), and founded the International QSAR Foundation.

Although Gil was involved in many different facets of research in environmental toxicology and chemistry, he is probably best known for his innovative efforts in the application of quantitative structure-activity relationships (QSARs) to assessing chemical risks. In 1976, a key piece of legislation relative to EPA regulatory efforts, the Toxic Substances Control Act (TSCA) was passed. One of the practical consequences of this legislation was that EPA confronted the need to assess potential risks of "new chemicals" for which little or no empirical data existed. Gil's original vision was to develop a 20 year research program, initially addressing critical agency needs created by the implementation of TSCA, and later for attacking more complex problems related to environmental fate and toxicity of chemicals. In developing the program, Gil envisioned not only providing new models and estimation techniques but also making these tools accessible to risk-assessors at their desktop. A critical step to accomplishing this goal was his work on the development of SMILES notation which allowed a computer to interpret a structure including 3D representations, but also provided an means for users to input chemical structure information. Gil took a multidisciplinary approach, leading a research team with experience and knowledge in chemistry, physiology, toxicokinetics and modeling. Significantly, this effort included not only EPA scientists from Duluth but, through various contracts and cooperative agreements, scientific leaders throughout the world. In 1992, at the "bridging the gap" international QSAR Conference in Duluth, a fruitful collaboration started with the European Chemicals Bureau, and many of his ideas reached the risk assessment guidance documents of the OECD and the EU. This was but one example of Gil's ability to mobilize and inspire large, diverse, international groups of scientists and regulators to tackle extraordinarily complex problems.

Gil's efforts with this program focused on the development and validation of mechanistically-rigorous QSAR models that could translate molecular structure into key properties controlling chemical fate and

potential effects. These included models for basic physico-chemical properties such as boiling point, vapor pressure, heat of vaporization, dissociation constants, water solubility, molecular surface area, molar volume, and the octanol-water partition coefficient (Kow). The latter property proved to be particularly critical to providing an interface between molecular structure and biological effects. Gil's pioneering work and resultant publications relating Kow to bioconcentration and acute narcotic toxicity of chemicals to aquatic organisms are among the most highly cited in the field, and have provided the foundation for QSAR-based tools that are widely used for regulation/risk assessment throughout the world by national and international organizations such as the EPA, EU,and OECD.

Gil also was involved in research focused on modeling various reactive mechanisms of toxicity. Under his leadership, the MED-Duluth fathead minnow acute and chronic toxicity databases were developed, testing over 600 chemicals. Gil's recognition (along with others in the field) that chemicals were separating into distinct potency groupings by toxicological mode of action, in contrast to traditional "chemical classes" defined in textbooks, resulted in a whole new way of looking at chemical similarity. Attempts to distinguish modes of action have led to development of (1) the fathead joint toxic action database based on whole organism responses, (2) the definition of fish acute toxicity syndromes based on whole organism cardiovascular-physiology, (3) the utilization of behavioral observations in defining modes of action, and (4) more recent attempts to sort out reactive toxicity mechanisms using biochemistry and cell morphology. These data were subsequently used to identify toxicophores associated with acute modes of toxic action and have led, and continue to lead, to the development of mechanistically-based QSARs. These associated studies from various toxicological disciplines have in common, thanks to Gil, a systematic approach to understanding mechanisms of action and toxic potency across "chemical structure space", all giving support to a definition of "chemical similarity" based on biological/toxicological action, concepts perhaps familiar in fields such as pharmacology, but new to audiences in environmental toxicology and the regulatory community. His systematic approach to attempting to understand all aspects of chemical toxicology also extend to inspiring current efforts to collate metabolism information for building predictive tools to simulate metabolism.

Gil's innovative contributions and dedicated input to the field continued (and, perhaps, even expanded) after leaving EPA. While at OECD he laid the foundation for the QSAR Application Toolbox so that there could be a freely available one-stop shop for predictive toxicology tools and databases for use by risk assessors, industry, non-governmental organizations, professors, students and the general public alike. He saw the importance of making toxicological information available to the broadest audience and maximizing its use through chemical categories and read-across, saving on animals and resources for testing. He constantly challenged models to be transparent (identifying known components but also articulating the uncertainties) and useful (assessed for how well they provide information specific to where it is needed). Gil organized multiple McKim Conferences to systematically identify what we know about chronic adverse effects and identify what we need to work on. His belief was that if you took apart the pieces and laid out what you did know and what you needed to know you then just needed to get to work on tackling the unknowns. Thus the conceptual approach encompassed in what we now call adverse outcome (or toxicity) pathways (AOPs) was envisioned by Gil and implemented in research and application well before we all started using the vocabulary. One of his last major efforts was focused on

what he viewed as the remaining technological challenge, to integrate QSAR models and biological response models. He put much time and effort into the design and development of Effectopedia, another tool he leaves as a part of his legacy that, as we populate it, will provide a comprehensive online encyclopedia of AOPs that will facilitate more transparent and efficient research and risk assessment.

Gil's vision and research career have been recognized through a number of awards both from EPA and professional societies, including the International QSAR Award in 1998 and Henry J. Heimlich, M.D. Award for Innovative Medicine in 2010. Although awards are one way to measure the success of one's career, we think Gil mostly appreciated the respect and interactions he had with his colleagues. Many of these researchers were mentored by Gil who believed in and encouraged the professional development of young scientists throughout his career; many who now author this memorial.

Gil's insights and vision of the future were always ahead of the rest of us. Once we thought we had grasped the challenge at hand and climbed to the peak, he revealed the next view of the future - typically a multi-dimensional hyperspace of chemistry, biology, landscape ecology and socio-economics. Equally remarkable was his ability to lead by inclusion and cooperation and by creating a collective commitment of service – allowing us to recognize, through his lens of humor and a lot of empathy, that the research and scientific advances we strived to achieve would make a difference in protecting human health, the environment, and a sustainable future. Before we would know it the ideas that seemed a bit "out there" matured and were reflected and shared, and the thrill and excitement of taking on the next challenge was intoxicating. His wisdom, leadership, and compassion for solid science will be missed, but the opportunities his intellect created will live on for decades. Gil was and is the inspiration of the idea that people working together can make a difference and create beyond what any of us could ever have imagined or might have dared to try.

Contributors to this piece include Gil's colleagues and friends from multiple EPA labs and offices in Duluth, RTP and Washington, DC, University of Minnesota (including the Natural Resources Research Institute), University of Tennessee, Utah State University, University of Toronto Scarborough ,Trent University, PETA, the European Commission, the OECD Secretariat in Paris, the University of Utrecht and KWR Watercycle Research Institute in Nieuwegein (the Netherlands), DuPont Haskell Global Centers, and participants from countries including Bulgaria, Canada, the Netherlands, Spain, and United Kingdom.