

The Heart of Toxicology: “The Dose Makes the Poison” (EXTENDED ABSTRACT)

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Remarks offered at presentation of the  
IS RTP International Achievement Award  
Washington, DC,  
December 2, 2015

It is indeed a great pleasure and honor to be the recipient of the 2015 International Society of Regulatory Pharmacology and Toxicology International Achievement Award. I have always regarded the IS RTP and its journal Regulatory Toxicology and Pharmacology as representing the tip of the spear of what stands as the heart of toxicology, i.e., demonstrating what it means to truly practice toxicology’s core tenet of “the dose makes the poison” as the primary means for accomplishing science-based risk assessments of environmental chemicals. My award presentation remarks will reflect on a series of revelations from my personal professional journey in recognizing what I believe this tenet stands for.

My journey began with my undergraduate training in Medicinal Chemistry at the University of Michigan, in which I had the good fortune to take a course in Biopharmaceutics taught by John G. Wagner, one of the modern fathers of this dose-oriented science. The key revelation was, to paraphrase Wagner, “If you can’t get the drug to the pharmacologic target through the maze of intervening complex biology, you don’t have a drug”. Little did I realize at this young age how this concept would emerge as so obviously relevant to my future career as a toxicologist. My next revelation developed during my graduate training in the Department of Pharmacology at Michigan State University, in which I had more good fortune to be matched up with a group of young faculty, James Gibson, Jerry Hook and Jay Goodman, who would all go on to be Presidents of the Society of Toxicology. That training began my real journey of translating undergraduate book-learned concepts to appreciation of the value of whole animal experimental science in identifying the central importance of complex biology controlling target-organ dosimetry and ultimate effect outcomes.

My next major career step as a research scientist at the newly created Chemical Industry Institute of Toxicology offered me entirely new revelations about “dose” as a key determinant of environmental chemical toxicity and risk. It was soon apparent that while the opportunity to apply mechanistic data to construct science-informed risk assessments was highly intellectually and professionally satisfying, these efforts were all too often directed at explaining the likely lack of human relevance of animal toxicity observed only under conditions of Maximum Tolerated Doses (MTD) testing that was frequently, and increasingly (due to regulatory and product stewardship exposure-reducing activities beginning in the post-1970’s era), separated by several orders of magnitude from real-world exposures. From those experiences came the recognition that closer attention to “dose” in the design and interpretation of animal bioassays were key elements to resolving this growing and frustrating conundrum. The potential approach to addressing this problem began to be visualized from my ensuing professional work in the pharmaceutical industry, which was well ahead of the chemical industry at the time in emphasizing the

value of comparative internal dosimetry, *e.g.*,  $C_{\max}$  and AUC internal dose parameters, as an effective means for differentiating doses eliciting animal toxicity from those driving pharmacological efficacy.

The opportunity to apply these cumulating career revelations to environmental chemical evaluations came with my next move to the Dow Chemical Company, which through the leadership of Perry Gehring, Phil Watanabe and many others, was rapidly extending the science boundaries revealing how “dose” was core to building science-informed risk assessments. At Dow we demonstrated how proactive collection of toxicokinetic data, collected under conditions under which the toxicity tests were commonly conducted (*e.g.*, diet, drinking water), resulted in refined dose selection strategies that specifically addressed the dose-exposure conundrum presented by continued uncritical conduct of MTD-based toxicity testing. This progress was most clearly exemplified with the successful implementation of the “Kinetically-Derived Maximum Dose” (KMD) concept in which the inflection point for onset of dose-dependent nonlinear toxicokinetics was established as a scientifically-defensible biological basis for limiting top selection in bioassays to less than might otherwise be selected in conventional MTD-based testing. Simply put, the KMD captured analytical biomarkers indicative of biological processes being overwhelmed as reflected by nonlinear changes in toxicokinetics, and were akin to changes in body weight or appearance of pathology used as parallel evidence of the overwhelming of homeostatic processes in conventional MTD determinations. Thus, a pragmatic outcome of the KMD concept was to offer an option for selection of doses having greater relevance to real-world human exposures compared to the conventional MTD approach. The value of the KMD-based dose selection strategy has now been affirmed by its institutionalization into regulatory test guidance recommendations, *e.g.*, OECD.

Applications of toxicokinetic data beyond that solely focused on refined dose selection strategies were soon realized, however, in opportunities for integrating such data within the rapidly emerging 21<sup>st</sup> century toxicity testing paradigm that emphasized *in vitro* high throughput experimentation as alternatives to time- and animal resource-consuming whole animal toxicity testing. Although extensive effort in this new testing paradigm has been directed at establishing phenotypic anchoring of *in vitro* methodology to projection of realistic whole animal responses, it was quickly apparent that access to toxicokinetic data similarly allowed for equally or perhaps even more important “dosimetric anchoring” of *in vitro* test concentrations to blood and/or tissue concentrations resulting in effect and no effect level doses in animal toxicity tests. Thus, dosimetric anchoring represents a logical extension of the KMD concept into meaningful dose selection strategies for 21<sup>st</sup> century *in vitro* toxicity testing, *i.e.*, responses restricted to *in vitro* test concentrations exceeding blood concentrations at the onset of nonlinear toxicokinetics in test animals, or even worse, higher than would be clearly tolerated in test animals, are not likely to be relevant to identification of human hazards or risks.

Beyond the above science-based revelations shaping my perspectives on the applied value of “dose” considerations for improving the science of toxicity testing, it was a revelation from a non-scientist that provided the passion for why a commitment to “dose” science was indeed so very critical in my broader responsibilities as a toxicologist engaged in *public health*. Very *apropos* to being the first keynote lecture delivered at a Society of Toxicology Annual Meeting in 1994, the Pulitzer Prize-winning journalist Jon Franklin reminded toxicologists that in the Age of Enlightenment we toxicologists were the High

Priests holding the key knowledge from which the lay public entrusted to us to shape reasonable science-based policies and actions required for safe use of rapidly expanding technologies increasingly necessary to sustaining a modern society. Franklin astutely warned, however, in direct analogy to Middle Ages abuse of Biblical texts for personal and/or institutional preservation and gain by the High Priests of that era, that toxicologists, as modern day holders of toxicological knowledge, carried the corresponding responsibility to avoid creation of “Poisons of the Mind”. Certainly for me, an in-depth understanding of what constitutes “the dose makes the poison” is at the heart of differentiating a “poison of the mind” from a real-world public health threat.