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Commentary

Are we in the dark ages of environmental toxicology?

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ABSTRACT

Environmental toxicity is judged to be in a "dark ages" period due to longstanding limitations in the implementation of the simple conceptual model that is the basis of current aquatic toxicity testing protocols. Fortunately, the environmental regulatory revolution of the last half-century is not substantially compromised as development of past regulatory guidance was designed to deal with limited amounts of relatively poor quality toxicity data. However, as regulatory objectives have substantially increased in breadth and depth, aquatic toxicity data derived with old testing methods are no longer adequate. In the near-term explicit model description and routine assumption validation should be mandatory. Updated testing methods could provide some improvements in toxicological data quality. A thorough reevaluation of toxicity testing objectives and methods resulting in substantially revised standard testing methods, plus a comprehensive scheme for classification of modes/mechanisms of toxic action, should be the long-term objective.

1. Introduction

After a number of attempts to resolve a thorny ecotoxicological problem a colleague, frustrated by theoretical and practical limitations in toxicity test interpretation due to the lack of detailed test information, commented that our predicament "... seems to say we are still in the dark ages!" Perhaps we are; the label may seem extreme, but it may not be inappropriate. The general concept of "dark ages" implies a period of intellectual stagnation after a period of substantial successful development. A few standardized beliefs and approaches have become dogmatic and competing theories and practices are marginalized. Challenges to accepted doctrine are near heresy at worst and unnecessary at best. This is anathema to the traditional scientific approach where the merit of theories and models is judged by their ability to explain experimental observations. The question is: does this label apply to environmental toxicology?

2. Models in toxicity testing

A salient example for addressing the "dark ages" question is the experimental collection of toxicity information. For about 100 years toxicity data have been generated with testing methods based on a simple conceptual model: adverse effects of a given nature that can be observed in exposed organisms (e.g., mortality) are correlated with a series of concentrations of test substance in an exposure medium (air, water, soil/sediment, or diet) and subsequently reported in terms of an estimated exposure medium concentration (e.g., g L^{-1} or mol L^{-1}) associated with a standard magnitude of effect response (e.g., 50% mortality: LC_{50}). In this scheme the exposure-media-based dose metric is in reality a surrogate. The true toxicologically effective concentration/dose is the unknown amount of substance at unknown site(s) of toxic action usually thought to be somewhere in the bodies of the exposed organisms. Although aquatic LC_{50}s are a common dose metric of this type, virtually all environmental toxicity tests, short-term and long-term, lethal and non-lethal, are based on this simple conceptual model.

As George Box noted "...all models are approximations. Essentially, all models are wrong, but some are useful. However, the approximate nature of the model must always be borne in mind..." (Box and Draper, 1987). Although wrong, as is any model according to Box, the approach using exposure-based concentration/dose surrogates has been useful in the revolution in regulatory environmental protection that occurred over the last 50–60 years. However, circumstances change and, as they say in financial matters, past success is not a reliable predictor of future performance. The diagnostic test for rejecting the toxicological "dark ages" classification is two-fold. Firstly, is the conceptual model employed in environmental toxicology properly implemented in commonly employed testing protocols? Secondly, is the conceptual model, and standard testing protocols based on it, periodically reevaluated and updated by appropriate professional and/or regulatory agencies to maintain usefulness in dealing with changing theoretical and practical challenges?

High-quality LC_{50} testing data were used to examine whether this standard aquatic testing method adequately addresses the

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assumptions and limitations of its model-based underpinnings (McCarty, 2012). In short, it does not, in terms of either quality assurance or quality control (QA/QC). The need to routinely validate model assumptions has been well-known for decades. John Sprague in his classic aquatic toxicology review (Sprague, 1969), noted that a key requirement is determination and reporting of an incipient, threshold, or steady-state exposure dose. This is a time-independent toxicity estimate obtained when aquatic organisms are exposed to constant water concentrations of test substance for a sufficient duration such that steady-state between exposure and organism concentrations is likely. However, major aquatic toxicity testing guidance documents typically do not require even this fundamental model validation step. It is the equivalent of statisticians not bothering to check for distribution normality before making claims of statistical significance based on parametric analysis. As well, inadequate (or absent) validation of assumptions fails the minimum requirements under any best practices guidance for environmental modeling. Thus, it is safe to conclude that the exposure-based dose surrogate model for toxicity testing has neither been adequately translated into operational testing protocols nor, despite periodic revisions in toxicity testing guidance documents, has there been substantive reevaluation of recommended test data methods for utility and applicability since Sprague (1969).

3. The regulatory challenge

Although the current toxicity testing model has failed the tests of proper conduct and periodic reevaluation, suggesting we are in a ecotoxicological "dark ages", it should not be construed that existing regulatory guidance is useless or invalid. Data obtained with current protocols were a major component of successful advances in environmental protection. However, older regulatory frameworks were designed to work with limited amounts of exposure-based toxicity data containing substantial uncertainties by using policy-based safety or application factors, often of the order of 10, 100, or 1000 times. The resultant objectives provided simple direction for improving environmental quality, especially as false negatives/positives and cost–benefit analysis were rarely considered in the regulation development process.

However, current regulatory challenges have become sophisticated and daunting:

- larger numbers of chemicals, often with complex chemistry and/or toxicology, and sometimes without adequate analytical methods for expected environmental concentrations, are being considered while, despite increasing regulatory scope and thoroughness, the public expects quick action;
- more organisms and response endpoints, including species sensitivity distributions, are being used in the evaluation process;
- groups of "similar" chemicals are being considered for risk ranking and risk reduction;
- the toxicity of mixtures is becoming more of a regulatory concern;
- modes/mechanisms of toxic action, and previously ignored toxicity modifying factors, especially metabolic biodegradation/biotransformation, are increasing in importance;
- pressures to rely on precautionary approaches must be balanced against the costs and impacts of regulatory action based on false positives and misclassifications in risk evaluations;
- comparisons between toxicity information and biomonitoring data are of increasing interest;
- societal expectations on reducing animal usage, as well as curbing the financial burden of regulatory testing, continues to increase.

The lack of substantive advances in toxicity test design, conduct, and interpretation are limiting progress in meeting these newer challenges. Some of the difficulties in applying old toxicity approaches and data to newer problems are illustrated in a recent paper. The objective was to identify a reliable body residue dataset of organic chemicals causing acute baseline neutral narcosis toxicity in small aquatic organisms (McCarty et al., 2013). Narcosis, studied for over 100 years, is a low toxicity mode/mechanism of action of organic chemicals that is expressed when more specific modes/mechanisms are not. Critical body residues (CBR) are simply the next level of dose surrogate. The whole-body chemical concentration, measured or calculated, is used as the dose metric rather than exposure media concentrations. In terms of the conceptual model it parses the media-based exposure dose/concentration into its components, the bioconcentration factor and the CBR.

Using the Environmental Residue Effects Database (ERED, 2010), and data quality evaluation criteria, an initial working subset of 2267 records for 183 organic chemicals produced a final narcosis set of 161 records for 29 organic chemicals. The range of acute narcosis wet weight CBR data for small aquatic organisms was ~760× with ranges of ~5× to ~330× for individual chemicals with varying sample sizes. Experimental variability issues such as different species, poor body lipid information, inter-/intralaboratory variation, etc. are likely contributing factors. However, experimental work by Peter Landrum and collegues that included some information on PAH metabolic breakdown and/or metabolites (see McCarty et al., 2013) allows an alternative explanation to at least partially illuminate this toxicological darkness.

In some tests with PAHs the specific mode of toxic action of phototoxicity was identified and those data were excluded in the quality evaluation process. However, for fluoranthene, when the putative narcotic ($N = 37$) and the rejected known phototoxic data ($N = 18$) were compared it was found that the latter covered almost all of the final narcosis data range. Thus, fluoranthene appears to cause toxicity by narcosis, yet, when sufficient amounts of UV-light are present, some proportion of the chemical is photo-activated and phototoxicity contributes to the adverse effects. This means that the assumption that there was only one mode of action (narcosis) producing the observed adverse effects is violated. It also means that, without detailed UV spectra information for all PAH toxicity tests, along with observations on the nature and extent of phototoxicity and/or active phototoxic agent concentrations, it is not possible to consistently and reliably separate narcosis-induced mortality from phototoxicity-induced mortality.

The wide, skewed distribution of acute CBRs for fluoranthene that confounds reliable narcosis toxicity evaluation, can also be seen with some other chemicals. This suggests that phototoxicity and/or some other modes/mechanisms of specific toxic action may contribute to the data variability reported. Much of the skew may be due to a combination (i.e., a mixture) of narcotic and specific-toxicity effects. Most importantly, this is an example of where it is not possible to reliably determine mode of toxic action, even for simple baseline narcosis, with results obtained with current toxicity testing methods.

Phototoxicity in aquatic systems has been well-established for 25 years (Giesy et al., 2013), so both the necessity and opportunity to revise standard testing methods to address this confounding issue have been known for a long time. However, in current exposure-based toxicity testing, no residues or evidence of substantial toxicological activation and/or metabolic degradation of the parent chemical is required and few or no observations that might aid in mode/mechanisms of action identification are reported. Thus, sufficient information for validating model assumptions is typically unavailable, let alone for considering alternative toxicological interpretation. Only thorough experimental designs that carefully