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Commentary

Strengthening the foundation of next generation risk assessment

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ABSTRACT

In a recent draft report, *Next Generation Risk Assessment: Incorporation of Recent Advances in Molecular, Computational, and Systems Biology*, the US Environmental Protection Agency presents valuable contributions to understanding the roles that evolving toxicity testing methods and associated interpretative techniques can play in assessing the risks associated with chemical exposures. However, the evaluations presented in the NexGen report would benefit from more thorough consideration of several essential components of a critical review of toxicity data, *e.g.*, data quality, data relevance, and the extent to which the test endpoints reflect adverse effects. Such considerations are necessary to ensure that the NexGen report evaluations – and the resulting conclusions and recommendations – are grounded in scientifically sound, representative data reviews. We illustrate these concerns with a critique of the report's prototype ozone evaluation. Although substantial additional research is needed before new toxicity data types can be used reliably in rigorous risk assessment applications, they clearly offer exciting opportunities for advancing toxicological science and risk assessment. By explicitly identifying limitations still to be addressed and providing stronger guideposts for future research needs, the NexGen report could serve an influential role in achieving the promise of these new research approaches.

1. Introduction

In its recent external review draft report, *Next Generation Risk Assessment: Incorporation of Recent Advances in Molecular, Computational, and Systems Biology* (US EPA, 2013a; hereinafter referred to as the NexGen report), the US Environmental Protection Agency (US EPA) presents valuable contributions to understanding the roles that evolving toxicity testing methods and associated interpretative techniques can play in assessing the risks associated with chemical exposures. In particular, drawing upon the expertise of individuals addressing chemical exposures and risks in a variety of settings, the prototype[1] analyses documented in the NexGen report offer useful – and needed – opportunities for synthesizing and reflecting on currently available new data types within specific applications. As recognized in the NexGen report, these analyses provide contexts for exploring how results from new study types can contribute to chemical risk evaluations (*e.g.*, proof-of-concept and value-of-information assessments), limitations in currently available data and interpretative techniques (*e.g.*, decision considerations for data applications), and directions for future research that will most effectively fill identified data gaps and enhance the usefulness of new data types.

While the prototype and other analyses presented in the NexGen report amply illustrate the promise of new toxicity test systems, they also reflect the many challenges yet to be surmounted before such data can be widely and reliably incorporated into risk assessment decisions, even for data-rich chemicals (such as those studied in the Tier 3 prototypes). In particular, as observed in the report, "logistical and methodological challenges in interpreting and using newer data and methods in risk assessment... remain significant" [p. xii]. Still, there are a number of ways that the usefulness and scientific foundation of the report should be enhanced. For example, as an initial step to strengthen the overall context for understanding the risk assessment implications of the prototype analyses, the report should discuss the key risk assessment paradigm changes reflected in and implied by the new testing methodologies. In addition, the evaluations presented should more thoroughly address essential key factors that underlie critical review of toxicity information [including weight-of-evidence (WoE) evaluations], such as data relevance, endpoint adversity, and data quality. Moreover, the scientific soundness of the NexGen analyses should be improved by better documentation of the processes used to compile the literature reviewed in the prototypes and conduct the analyses based on that literature. Finally, the NexGen report

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[1] The NexGen report presents analyses for three Tiers of prototypes, defined as: "Tier 3—major scope decision-making (considerable data indicating high hazard or widespread exposures); Tier 2—limited decision-making (limited exposure potential or limited hazard potential or data); and Tier 1—prioritization and screening (very little or no traditional data for chemicals known to be in commerce)" [p. x].

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should provide a clearer, more specific roadmap for guiding future research.

Below, we discuss ways in which the NexGen analyses could be enhanced to refine their usefulness for guiding future research and risk assessment applications. These issues are first discussed more generally and then illustrated in detail using examples from the ozone case study. We conclude with a summary of recommendations for strengthening the NexGen report, as well as future research efforts.

2. Risk assessment paradigm context for NexGen evaluations

Although the NexGen report provides some context for the risk assessment evaluations considered in the report (*e.g.*, in Section 2 *Preparation for Prototype Development*), it would benefit from stronger grounding in the underlying changes in risk assessment paradigms that are inherent in the acceptance and application of new data and methodologies. Such considerations would highlight the importance of the critical toxicity data review elements discussed here in Section 3 and would provide a valuable foundation for considering and prioritizing data gaps and future research needs.

As recognized in the NexGen report and reviewed in Rhomberg (2010) and National Research Council (NRC, 2007), evolving risk assessment methodologies and underlying developments in toxicity testing approaches present numerous opportunities to enhance our understanding of chemical toxicity. Chief among the potential advantages offered by new toxicity testing approaches and new data types are the ability to conduct testing that is less expensive, less time consuming, and less resource intensive than traditional toxicity testing. In particular, new approaches present the potential to reduce or replace animal studies for risk assessment purposes (as discussed in Scholz et al., 2013). Moreover, because of the "high-throughput" and low cost of many of the new tests, it is practical to examine many more test conditions (*e.g.*, to test more dose levels to better evaluate dose–response relationships; to test lower, more environmentally relevant doses where test systems are often more sensitive than traditional methods; to use model systems that are most relevant to human health; to test different patterns of exposure over time; to test effects of combinations of agents; or to evaluate interindividual variability). Because of such features, new toxicity testing approaches offer the possibility of evaluating more chemicals more efficiently, and conducting chemical screening on a greater scale. New toxicity testing techniques also offer the potential to enhance our scientific understanding of chemical-specific modes of action (MoAs)[2] and to transfer such insights to a broader spectrum of chemicals.

The evolution of toxicity testing techniques – and the changes in perspective regarding MoAs and other indicators of toxicity that accompany new data – also requires consideration of changes to standard risk assessment paradigms that accompany such data. Most notably, as discussed in Rhomberg (2009), the current risk assessment paradigm primarily works from observations of apical responses (*e.g.*, adverse effects observed in traditional animal or epidemiological studies) to explore underlying mechanisms of toxicity. By contrast, the risk assessment paradigm inherent to the new data types reverses this process and begins with studies of underlying mechanistic elements, working from there to evaluate apical effects that could result. To fully comprehend the risk assessment implications of this shift in perspective requires a thorough understanding of the biological control processes reflected in the available data and analyses (*e.g.*, sufficient knowledge regarding how statistical analyses and predictive profiles relate to apical effects of concern in humans).

In particular, interpretation of new data types requires a central focus on what constitutes sufficient perturbation of normal processes to yield adverse apical effects. As reviewed in Rhomberg (2011), connections between process perturbations and apical events can be viewed as a cascade of causative processes, with the outputs of earlier processes constituting the causes of later ones. Such processes are inherently and markedly non-linear; *i.e.*, processes reflecting continuous variation in causal factors are translated into discontinuous change-of-state outcomes. These discrete changes of state and underlying processes can be seen as either a series of interconnected control processes (from a systems-theory viewpoint) or as failure modes of adaptive processes (from a catastrophe-theory viewpoint). Factors to be considered in such evaluations include identification of key events, how sequences of events relate to each other, the persistence or independence of events, and factors leading to dose–response observations (*e.g.*, interindividual variation or event accumulation). Such considerations provide a valuable and necessary perspective for understanding the roles that process perturbations can play in apical effects, defining adverse effects, and evaluating dose–response relationships and their overarching implications.

In considering the implications of the changing risk assessment paradigm for interpretation of new toxicity data, it is also important to maintain a perspective on long- *vs.* short-term uses and goals for such data (*e.g.*, as discussed in Chiu et al., 2013). For example, in the short-term, gene expression changes may be used as markers of toxicity pathways that have been identified previously based on traditional toxicity data. In the future, such data will evolve in their application as investigative tools used to identify potential adverse outcome pathways that have yet to be established. The way in which the data are used, accompanying uncertainties, and dependence of the research on existing knowledge differ between these two uses of the data. Clearly, routine and reliable application of new toxicity data types in settings requiring a high degree of scientific certainty and rigor – and routine acceptance of such applications by the risk assessment community – will require far more extensive analysis of such methods than has yet occurred. However, as the test methodologies and risk assessment applications evolve, the new data types can play other useful roles (*e.g.*, as screening tools, biomarkers, or approaches for diagnoses and characterizing MoAs). They can also provide support to dose–response analyses, interspecies extrapolations, and evaluations of interindividual variability (*e.g.*, Rhomberg, 2010; Burgess-Herbert and Euling, 2013). As discussed below, the NexGen report could help achieve long-term goals for use of these data by more clearly defining such goals and specific research needed to reach them.

3. Recommended enhancements to NexGen report

The evaluations presented in the NexGen report would benefit from more thorough consideration and acknowledgement of certain essential key factors that underlie critical review of toxicity information (including WoE evaluations, as reviewed in Rhomberg et al., 2013), particularly within the prototype evaluations. Factors that merit particular emphasis in the NexGen evaluations include the relevance of the data derived from new toxicity test systems for human health risk assessment, the extent to which the endpoints under consideration reflect adverse effects, and the quality of the data derived from various applications of the new test systems. Such considerations are necessary to ensure that the types of evaluations presented in the NexGen report – and the

[2] Although "mode of action" is the term generally used to describe a mechanistic understanding of the effect of a chemical on human health, the NexGen report states that it instead uses the term "mechanism of action" in accordance with the NRC report, *Science and Decisions: Advancing Risk Assessment* (2009). The term mode of action is used here.