

INSIGHTS

POLICY FORUM

CHEMICAL REGULATION

Policy reforms to update chemical safety testing

TSCA reform empowers EPA to use modernized safety testing in the United States

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Toxicological evaluation of chemicals and newly emerging substances, such as engineered nanomaterials, is essential to protect human health and the environment (1). Traditional approaches for chemical safety as-

essment often use high-dose animal studies, human exposure estimates, linear dose extrapolations, and uncertainty factors to determine the circumstances under which human exposure is safe. But in 2016, major bipartisan reform of the antiquated Toxic Substances Control Act (TSCA) in the United States embraced a new paradigm emerging across the globe (2). This

paradigm, relying largely on nonanimal, alternative testing strategies (ATS), uses mechanism-based in vitro assays and in silico predictive tools for testing chemicals at considerably less cost (3). We provide a cautious but hopeful assessment of this intersection of law and science. Although the law generally takes a sensible approach to using ATS for regulatory purposes, commit-



ment by the U.S. Environmental Protection Agency (EPA) and its partner agencies remains the key to successful integration of ATS in TSCA.

The U.S. National Academy of Sciences called for this paradigm shift in 2007, from the conventional descriptive approach of what is observed in animals to one based on an understanding of human cellular re-

A machine secures plastic caps onto bottles of laundry detergent, an example of the many types of consumer and industrial products in need of effective, efficient chemical safety testing.

sponse pathways that, when triggered by a chemical, could initiate key biological events that lead to adverse outcomes at the individual or population level (4). The EPA and other federal agencies have supported research in this area but have not systematically adopted the new paradigm in regulatory decision-making (3).

The new paradigm involves several iterative components (see sidebar), and can inform four types of regulatory decisions: screening to identify chemicals and nanomaterials for more extensive testing and evaluation; ranking or prioritization for further action; qualitative or quantitative risk assessment in support of risk management; and comparative evaluation of the hazards and risks of different substances in support of safer design (4).

TECHNOLOGICAL CHALLENGES

Although ATS approaches offer many potential advantages (e.g., limitation of animal use, speed, mechanistic basis, and high-volume data generation), a key challenge is ensuring that in vitro testing accurately reflects in vivo outcomes in humans. To be useful for regulatory purposes, adverse outcome pathways (AOPs) should faithfully capture the molecular triggering and key events in the actual in vivo disease outcome, because cells do not exhibit the biological complexity of an intact organism. Another challenge is that several redundant molecular events may lead to the same adverse outcome; this can be mitigated by further pathway discovery, e.g., the use of comprehensive multi-omics platforms and computational analyses that are mainstays of the 21st-century systems toxicology approach. We should understand the uncertainty at each step during the iterative implementation process, and the impact of unwanted false-positive or false-negative screening results. Misdirected testing can be reduced by using benchmark test materials, authenticated cell stocks, reliable primary cell sources, and rigorous protocol development for AOP testing.

There is concern that ATS platforms address acute rather than chronic disease outcomes. It is possible, however, to select AOPs that reflect a critical molecular event in a pathway leading to chronic disease, a practice commonly used in selection of clinical laboratory assays in evidence-based medicine. Finally, ATS has to address in vitro dosimetry ranges, which tend to be on the high side and are often chosen without

knowledge of real-life exposure levels. In vitro assays may also lack the quantitative power to discern between dose-response relations leading to cellular perturbation only (without disease progression) versus attaining a cellular threshold that progresses to disease outcome (5). Some of these concerns can be addressed by dose-response extrapolations, such as expressing the inhaled mass dose (e.g., in mg) of the chemical substance that deposits per unit of the alveolar surface area (e.g., in cm^2) of the lung, compared with the mass dose per unit surface area in a tissue culture dish. The surface area in the human lung can be proportionally adjusted for the surface area in a rodent to make interspecies comparisons. This allows in vitro to in vivo comparisons of surface area dose at the steep part of the dose-response curve, which can be compared with a benchmark material. It is also possible to perform benchmark analysis, in which the in vitro point of departure is calculated for an empirical dose-response relation associated with an adverse outcome in vivo, as shown by the EPA (5).

The role of metabolism in chemical toxicity is not captured by ATS. The toxicity of a chemical is not always related to the chemical itself but could be due to a metabolite, which may depend on the rate of metabolism. Although these drawbacks may not apply to nanomaterials that are often not subjected to metabolism, it is of concern to chemical toxicity where a substance that triggers an AOP in vitro might be incapable of doing so after being subjected to first-pass metabolism in the intact organism. This poses a challenge for the use of dose-response extrapolations for chemical substances. Even though there are no ready solutions, the emergence of organs-on-a-chip technology or three-dimensional tissue culture models may help.

INSTITUTIONAL CHALLENGES

Two leading institutional challenges are organizational inertia and onerous validation procedures. Absent strong leadership, norms embracing innovation, or compelling external influences, regulatory agencies tend to rely on traditional techniques and routines. However, EPA is not monolithic; different organizational units may be more or less prone to inertia. Development and diffusion of innovative methods and technologies are central to the EPA Offices of Research and Development (ORD) and Science Coordination and Policy (OSCP). Both have been at the forefront of advances in ATS (6). In contrast, offices charged with regulation of chemicals may move more cautiously, as they reflect substantial investments in existing resources and exper-

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tise, as well as concern regarding legal and institutional constraints on their actions. Methods developed and facilitated by the research arm of EPA and its partners must be smoothly and expeditiously translated to the regulatory arm.

Generally speaking, traditional validation processes—as applied to in vitro toxicity assays—have been onerous in terms of the costs, resources, and time involved and potentially slow adoption of valuable testing methods. The standards for validation placed upon alternative in vitro testing typically exceed those required for in vivo toxicological analysis (7). Moreover, in assessing relevance, conventional validation processes use existing animal tests as the reference against which to measure the in vitro assay by asking whether the method can predict the outcome of the animal examination. This is problematic because many in vivo safety methods have not been adequately validated themselves and are of a descriptive nature, which is at odds with the mechanistic focus of the new paradigm (8). There is reason for optimism, however. Numerous efforts are under way in the United States and internationally to develop new approaches for validation of ATS and the evaluation of AOPs (5, 9). International harmonization of test guidelines—such as under the Organisation for Economic Co-operation and Development's (OECD's) Mutual Acceptance of Data program—plays a key role in the development and validation of ATS (10). OECD guidelines are the main framework for data needs in the TSCA reform bill.

THE ROLE OF LEGAL REFORM

The reformed TSCA includes three provisions explicitly dealing with ATS. The first relates to screening, mandating that EPA consider reasonably available data generated by ATS before requiring testing on vertebrate animals (2). The second directs EPA to encourage and facilitate use of scientifically valid ATS and chemical grouping approaches to reduce or replace testing of vertebrate animals. The Act provides no mandate regarding how this is to be done. The third requires EPA to develop a strategic plan by June 2018 to promote development and implementation of ATS, including computational toxicology, bioinformatics, high-throughput screen-

ing, testing of categories of chemicals, in vitro studies, and systems biological approaches. The strategic plan must include a list of specified alternative test methods or strategies that EPA considers scientifically reliable, relevant, and capable of providing equivalent or better-quality scientific data than vertebrate animal testing (2). The plan must also prioritize and carry out performance assessment, validation, and translational studies for development of scientifically valid test methods and strategies to reduce animal testing (2).

Elements of alternative testing strategies

The new paradigm involves several iterative components, based on an understanding of human cellular response pathways.



Conceptual pathways

The adverse outcome pathway (AOP) is a conceptual construct, linking a molecular initiating event (MIE) at the cellular level to an adverse outcome (e.g., disease) through a series of causally linked key events (5).



Biomolecular events

In vitro testing quantitatively assesses biomolecular triggering events in the MIE and biological mechanisms underpinning the linked key events.



Screening and modeling

High-throughput screening (HTS) and in silico models can reveal correlations of the biomolecular injury to specific chemical or physicochemical properties, as well as the strength of the association to the in vivo adverse outcome.



Integrating evidence

Integrated approaches for testing and assessment rely on existing weight of evidence information, coupled with the generation of new information by AOPs, HTS, and computational modeling (11).



Regulatory applications

These approaches are used iteratively for regulatory purposes, including categorization, hazard and risk assessment, prioritization, and tiered decision analysis (5).

These ATS provisions present challenges. Apart from the obligation to use available ATS for screening, the statute is essentially procedural in nature—compelling EPA to facilitate development of ATS but not obliging the agency to adopt it. The ATS provisions leave in place institutional barriers to the new paradigm, including failure to revise the validation processes, as discussed before. Despite these limitations, two factors bode well for the future of ATS in TSCA implementation. First, various offices within EPA (including ORD, OSCP, and the new chemical review program), and partner entities such as the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods, are already engaged in bringing ATS into the regulatory context (e.g., the Tox21 Program). Second, the Act mandates that EPA prioritize the large number of chemicals now in the marketplace for safety evaluations by specified enforceable deadlines (2). This provides a powerful incentive for the

broader EPA chemical regulatory program to adopt ATS for prioritization and subsequent risk evaluation of chemicals deemed high priority. The agency (and affected regulated companies) will be hard pressed to meet these deadlines using conventional animal testing approaches.

CAPACITY AND CONFIDENCE

Early introduction of successful case studies will advance regulatory adoption by addressing research needs and by providing assurance to cautious regulators and stakeholders of the relevance and utility of ATS methods in place or under development. Examples include work on new chemical substances such as carbon nanotubes and screening of ~10,000 chemicals in the Endocrine Disruptor Screening Program (11, 12). Demonstrated success of a few predictive screening pathways, built on AOPs, will increase enthusiasm for widespread implementation (13). Steady and sustained progress, while identifying and resolving key technological issues, will build technical capacity and institutional confidence rather than trying to achieve immediate across-the-board reform of the regulatory process. This measured approach is reflected in EPA's implementation strategy and the Act (14). To effectively regulate thousands of chemicals already in commerce and new ones to come, EPA will

have to take advantage of ATS approaches. The Act supports that goal, but it is up to EPA to devote resources and attention to bring ATS into mainstream regulation. ■

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