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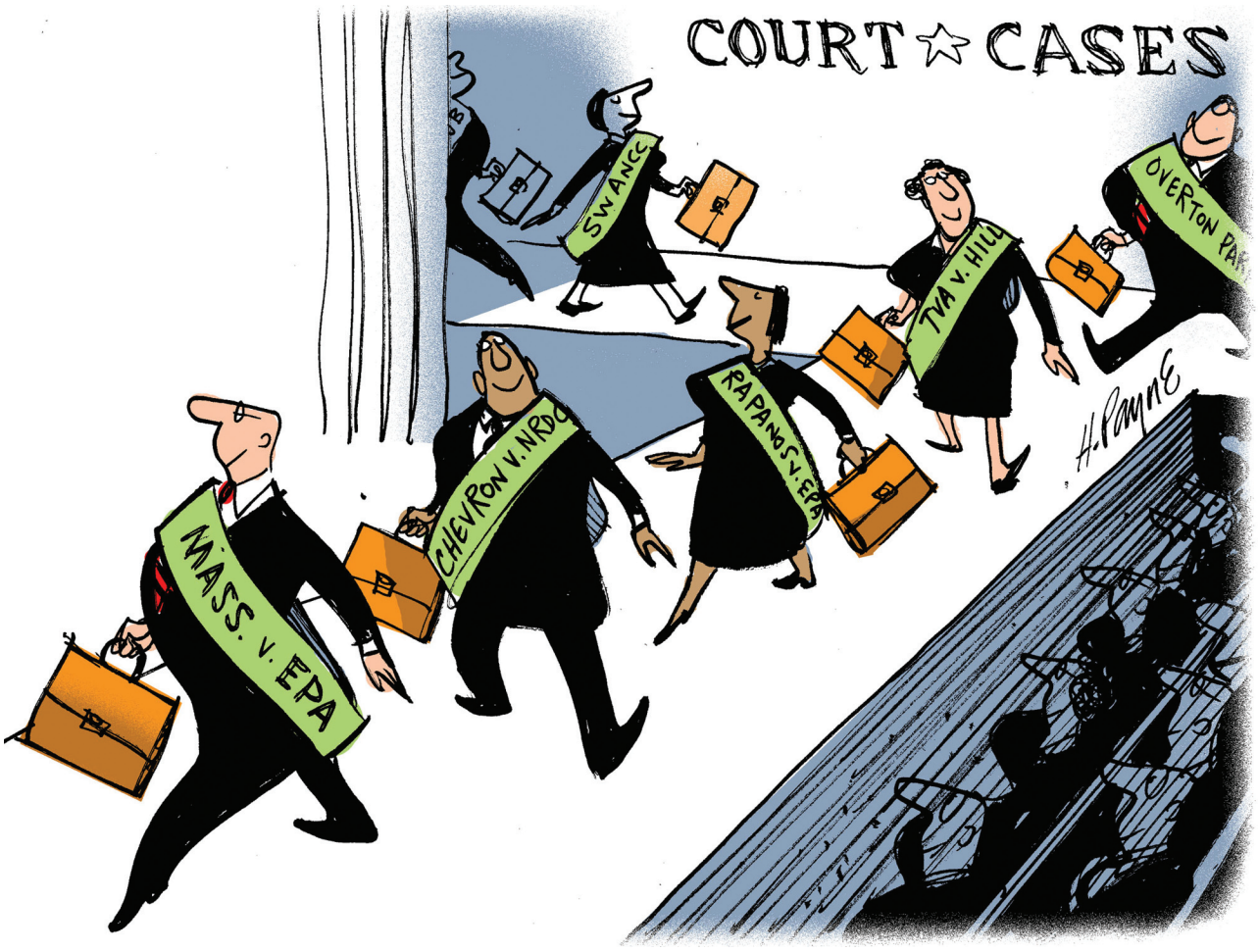

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Revising Regulatory Science

Scientific, technological, and political trends are revolutionizing EPA risk assessment practices. How the agency navigates this challenging, changing landscape will affect not only how we manage chemical hazards but also public health and the overall economy

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Science at EPA has attracted a lot of criticism throughout the lifetime of the agency, seemingly more intense with each passing year. Evaluation and management of risks from hazardous substances have caused concern. Assessment and regulation of chemicals under the Toxic Substances Control Act and other statutes have been limited by slow, resource-intensive, and at times politicized scientific procedures and programs. Testing chemicals for potential human toxicity and utilizing that information in risk assessments have proven cumbersome. The perceived gap between the information EPA needs to adequately manage chemical risks and the information it can obtain through existing programs has led to several legislative proposals, including some to fundamentally revise TSCA.

But things are changing. The White House is building on efforts made during the Bush administration to incorporate revolutionary new toxicity testing science and technology into a refined risk assessment process. Anticipated gains in efficiency and accuracy from these advances, if implemented wisely, could potentially reduce the information gap.

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The Obama administration has also changed course on a number of Bush science policies. It has streamlined the process for chemical assessments under the Integrated Risk Information System. IRIS is an influential (but lately controversial) chemical toxicity database. The Bush administration's procedural revisions had done little to help the database's backlog of assessments. The current White House has also taken measures to "restore science to its rightful place," as President Obama said in his inaugural speech, by reining in the role of the White House Office of Management and Budget in reviewing agency rulemaking, significantly increasing funding for EPA science programs, and promoting transparency and scientific integrity across the federal government.

Though these changes involve a range of aspects of EPA science, they are likely to all act together to make chemical assessments faster, more accurate, and more trusted by the public. While this potential promises great benefits, there is also peril if the changes are rushed or mismanaged. In addition to their direct impacts on the public and the regulated community — impacts which are themselves potentially enormous — all of these changes also shape the ongoing debates regarding America's chemicals management policies. It is important to understand these developments in EPA science in order to put these debates in context.

Developments in Toxicity Testing

Information and models regarding the potential human toxicity of chemicals are important ingredients in decisions regarding chemicals management. Such regulatory decisions can have substantial impacts on companies as well as on public health, so it is no surprise that scientific and political controversies regarding toxicity testing have often been prolonged and intense. However, the basic, decades-old system for obtaining toxicity information has changed only very slowly — until recently.

Currently, toxicity studies generally involve testing large numbers of living animals exposed to relatively high doses of chemical substances. Observed outcomes are extrapolated to humans using uncertainty factors. This "in vivo" approach is criticized as time-consuming, expensive, ethically controversial due to its heavy reliance on test animals, and insufficiently reliable. In vivo testing's inefficiency, moreover, restricts the degree to which it can provide information on the effects of combinations of chemicals or other complexities. EPA also uses structure-activity relationship, or SAR, analyses to estimate the toxicity of some chemicals based on that of structurally similar chemicals, but the reliability of these analyses is limited by their base data sets and existing models.

Yet with the advent of new sciences such as informatics (advanced information management) and genomics (genetic mapping) and the development of new high-throughput testing and data processing techniques, we are poised for a revolution in toxicology. The most influential statement on this revolution is a report from the National Research Council, "Toxicity Testing In The 21st Century: A Vision And A Strategy," which was commissioned by EPA and published in 2007.

The NRC vision would generally replace analysis of ultimate disease endpoints in whole animals with analysis of upstream perturbations in cellular response pathways, or "toxicity pathways." Perturbations in these pathways can lead to mechanisms of action that ultimately cause adverse health effects if they are of sufficient duration and magnitude. The NRC vision therefore initially depends on finding and analyzing a suite of toxicity pathways, using modern techniques such as:

- *functional genomics*, which focuses on understanding the function and regulation of gene sequences and their products;
- *systems biology*, an interdisciplinary field focused on integrative study of complex interactions among parts of biological systems; and
- *bioinformatics*, which applies information technology and advanced computer science to manage and analyze large amounts of biological and molecular data.

The responses of mechanisms within the identified cellular pathways to doses of chemical substances would then be tested via high-throughput, robot-assisted "in vitro" screening assays using cells and even in some cases molecular targets. Whole-animal testing would continue to provide important information, especially until more reliable prediction of in vivo metabolism from in vitro systems can be attained.

This thoroughly revised mechanism-based approach presents a number of advantages. Most notably, the assays could characterize dose-response relationships — which measure specific effects of specific exposures — far more quickly and cost-effectively. This could allow for assessments to better account for complexities, such as interaction effects and susceptible subpopulations, while still meeting budgets and deadlines. Reliability could also increase: the assays could utilize a broader range of doses, and extrapolations across species would present fewer problems.

The innovative vision presents extraordinary practical challenges. Reliance on assays, even for screening, must not outpace scientists' and decisionmakers' understanding of the data they will produce, or the new data could lead to excessively conservative risk assessments. For example, exposure of "naked" cellular targets to chemicals may produce perturbations which in the real world would be modulated by larger metabolic systems. EPA must also be careful to validate its new models, a complex task given the flaws in the existing animal testing models against which the new assays would mainly be measured. The NRC report suggested that implementing its recommended toxicity testing program would require an investment of hundreds of millions of dollars over one to two decades, a level of funding well above even the combined resources of EPA and other science agencies.

Despite the high hurdles, EPA is moving forward with implementing NRC's vision. Its "Strategic Plan for Evaluating the Toxicity of Chemicals," released in March 2009, builds on NRC's recommendations. Implementation will be aided by a number of earlier programs. The "Tox21" memorandum of understanding among EPA, the National Toxicolo-

gy Program, and the National Institutes of Health's Chemical Genomics Center coordinates efforts to develop new test methods in support of the vision. ToxCast, which EPA launched in 2007, combines high-throughput screening and computer modeling to enhance the agency's prioritization of chemicals. EPA is developing sophisticated, trademarked virtual models of the human embryo (v-Embryo) and liver (v-Liver). And outside the agency, the expected avalanche of data from the European Union's Registration, Evaluation, Authorization, and Restriction of Chemical Substances regulations — the famed REACH program — will be an important driver of changes in toxicity testing and chemical risk assessment in the United States.

Improvements in IRIS

The Integrated Risk Information System was established by EPA in 1985 to combine and communicate chemical toxicity data. It allows quick access by EPA, other agencies, and the public to authoritative information on hazard and dose-response data for several hundred chemicals. The information is provided in several forms. For carcinogens, IRIS gives narrative weight-of-the-evidence descriptors (e.g., "likely to be carcinogenic") and numeric unit risks (excess cancer risk from continuous exposure to a standard concentration). For chemicals considered to have other effects, IRIS provides a reference dose or concentration (lifetime daily exposure level likely to be without an appreciable risk). EPA has used IRIS as a basis for many risk assessments and regulatory decisions under TSCA, the Clean Air Act, the Clean Water Act, and other authorities.

However, the IRIS program has amassed a large and growing backlog of unfinished assessments, to the point that the Government Accountability Office considers the program "at serious risk of becoming obsolete." For a variety of reasons, preparation of assessments often takes years, over which time new research may arise leading to yet more delays. For example, the assessment for trichloroethylene was initiated in 1998 and still has not been finished. EPA's ability to update prior assessments is also limited, despite the fact that the average age of most assessments is well over a decade.

Moreover, the Bush administration revised the IRIS process in 2008, adding additional, off-the-record interagency consultations and further delays. The revised process also allowed agencies like the Department of Defense to identify "mission critical" chemicals integral to their operations, and to suspend the assessment process to conduct further study on those chemicals for an additional 18 months or more. Typical assessments would take many years even on schedule. IRIS, and in particular the Bush administration's process revisions, received a great deal of critical attention from Congress, the GAO, and NGOs.

But in May 2009, EPA announced that it was largely overturning the Bush administration's procedural changes and instituting new reforms. Under the new, streamlined IRIS process, all comments must be public and science-based, other agencies cannot delay the process, and final assessments are generally to be issued within approximately 23 months after first assembling the assessment team and beginning data review. The White House also requested a substantial funding and staffing increase for IRIS. Even so, at a congressional hearing in June 2009 entitled "Fixing EPA's Broken Integrated Risk Information System," a GAO spokesman noted some skepticism of the agency's ability to meet its stated timelines.

Risk Assessment Advances

Like IRIS and toxicity testing more generally, the risk assessment process in which these data are used has been criticized as slow and its results as flawed and unrealistic. EPA's choices of default assumptions, such as the multipliers used to apply animal testing data to humans, have been the subjects of bitter battles with industry and NGOs. So have the agency's treatments of uncertainty, variability, and cumulative risks. Efforts to reduce or quantify uncertainty and promote "sound science" have been viewed by some as anti-regulatory, dilatory tactics in an already-lengthy process. The scientific and technological advances in toxicity testing and modeling described earlier also add uncertainty regarding the interpretation and use of these new inputs. The agency therefore requested another set of recommendations from NRC, focusing on EPA's assessments of human health risks from environmental contaminants. The NRC released its report, "Science and Decisions: Advancing Risk Assessment," in December 2008. The report largely agrees with many of the NGOs' criticisms and proposes recommendations that can be broadly grouped into two categories.

The first deals with improving the utility of risk assessments through a greater emphasis on the ultimate risk management options in the initial scoping phase of the assessment. The dominant paradigm has been that risk assessors should be shielded from the specific decisionmaking issues that their analyses will support — risk management. The NRC argues that the prime question should be not

EPA: Stakeholders Laud Agency Announcement

EDITOR'S NOTE: In September, The Environmental Forum *asked the EPA press office whether the agency would be willing to contribute an* ANOTHER VIEW *column to run alongside our feature on the future of toxics regulation. An EPA spokesman declined, declaring that "EPA is not far enough along in the TSCA reform discussions." Eleven days later, on the 28th, the agency issued a press release declaring, "EPA Administrator Jackson Unveils New Administration Framework for Chemical Management Reform in the United States." The agency declined a followup request for comment. Then, on October 1 EPA released the following compilation of comments on the proposal, which we reprint verbatim below.*

Stakeholders and members of Congress are commending an historic announcement by EPA Administrator ***Lisa P. Jackson*** to reform America's chemical management law in order to help protect all Americans. On Tuesday, September 29, Administrator Jackson announced core principles that outline the Obama Administration's goals for legislative reform of the 1976 Toxic Substances Control Act, TSCA. In parallel with this legislative initiative, Administrator Jackson also announced plans for a major effort to strengthen EPA's current chemical management program and increase the pace of the agency's efforts to address chemicals that pose a risk to the public.

The following are statements from stakeholders and members of Congress in response to Administrator Jackson's announcement:

September 29: Statement by U.S. Sen. ***Frank R. Lautenberg*** (D-NJ): "America's system for regulating toxic chemicals is broken. Far too little is known about the hundreds of chemicals that end up in our bodies and EPA has far too little authority to determine their safety. Today's announcement marks a breakthrough for public health and makes clear that President Obama and the EPA understand the problem and will fight for the right solution. I will introduce legislation soon to turn these new principles into law. Americans deserve to know that products they rely on — from household cleaners to personal care products to building materials — are safe and will not harm their families."

September 29: "What a refreshing change," said Dr. ***Arnold Schecter*** of the University of Texas School of Public Health, Dallas, who studies persistent organic pollutants such as the ones the EPA singled out for special review. He has found PBDEs in 100 percent of American mothers' breast milk tested, with some women carrying "orders of magnitude" more than women in Europe, where the compounds have been phased out since 2004. Schecter said stronger federal action on risks from persistent organic compounds was overdue.

September 29: "It's a tremendous step forward," said ***Richard Wiles,*** head of the Environmental Working Group, a Washington-based environmental group. He noted that the George W. Bush administration had opposed any significant changes in the law.

September 29: "The chorus of voices calling for reform of our nation's chemical regulations now includes the Obama administration, health professionals, environmental advocates, the states, and even industry," said Earthjustice President ***Trip Van Noppen.*** "Now we look to Congress to join the fight to protect our children and our environment from dangerous chemicals."

September 29: "It's historic. They're very clear that this is about a new law, new rules of the game. It's not about little tweaks. This is a fundamental overhaul," says ***Richard Wiles,*** senior vice president for policy at the Environmental Working Group in Washington, D.C.

September 29: "We understand that industry has to provide more data and a greater transparency to that data," said ***Cal Dooley,*** president of the American Chemistry Council. "Without a comprehensive approach, the American people will be left with minor adjustments to the current federal regime, and a patchwork of state and federal laws that will not enable a robust chemical management system that can become the gold standard for the world."

September 29: "The Obama administration is in sync with a public demanding safer chemicals and better information they can use to protect their families from toxic chemicals," said ***Andy Igrejas***, National Campaign Director for Safer Chemicals, Healthy Families.

September 30: "There's general agreement that we need to reform this law," says ***Glenn Ruskin*** with the American Chemical Society, representing chemists and chemical engineers. "That's very rare that you find such typically disparate groups agreeing."

September 30: "The system we have now assumes that chemicals are innocent until proven guilty," said ***Jane Houlihan***, senior vice president for research at the Environmental Working Group in Washington, D.C. "These reforms introduced today would flip that."

September 30: "This really gets the ball rolling," said ***Ernie Rosenberg***, President & CEO of The Soap and Detergent Association, which represents the U.S. cleaning products industry. "Cleaning product makers and their suppliers want to ensure that there is public confidence in the system that governs the use and management of the ingredients in our products."

the probability of adverse consequences, but rather the risk reductions associated with possible risk management options (against a baseline of the risks associated with no intervention). Investments in additional information or procedural steps would be based on explicit analysis of their value for decisionmaking objectives to shorten "protracted scientific debate," to use NRC's phrasing. The involvement of risk managers and other stakeholders early in the process, and at set intervals thereafter with time limits, would ensure the assessment's utility to and acceptance by decisionmakers.

The second category of NRC recommendations relates to improving the relevancy and accuracy of the technical analysis:

Uncertainty and Variability. A well-done risk assessment must communicate to decisionmakers the uncertainty and variability behind the estimates, but doing so takes care and time. Moderating the conflict between proponents of highly detailed and quantitative uncertainty analysis and those who view it mainly as a dilatory tactic, the NRC report states that such analysis "is appropriate only to the extent that it is needed to inform specific risk-management decisions." However, it argues that greater attention should be paid to characterizing susceptibility for specific population groups.

Selection and Use of Defaults. Some NGOs have argued for conservative standard assumptions (defaults), such as a 10-fold uncertainty factor to account for risks to children. Industry, meanwhile, has generally promoted the use of chemical-specific rather than default safety factors wherever possible, arguing that data are often sufficient to overcome the need for the most conservative defaults. NRC takes a somewhat conservative stance, saying that EPA needs "clear, general guidance on what level of evidence is needed to justify use of agent-specific data" but that overall, established defaults should be retained. NRC also states that the omission of chemicals lacking data from risk characterization and decisionmaking amounts to an implicit default that should be made explicit.

Thresholds. Under the current system, a threshold (i.e., a dose below which no effects are expected) is assumed for non-cancer endpoints. This has tended to lead to under-emphasis of such risks relative to cancer risks, for which no threshold is assumed. The proposed revision would harmonize the two, redefining the bright-line reference dose or concentration as a description of the percentage of people below a defined risk, with a specific degree of confidence.

Cumulative Risks. The NRC report recommends greater attention to risks from multiple other chemicals, non-chemical stressors, vulnerability, and background risk, focusing on shared adverse health outcomes rather than more narrowly on shared mechanisms of action. Taking into account these complex factors would necessitate a careful delineation of boundaries.

Obviously, implementation of the NRC report's recommendations will be a challenge for EPA. NRC recognized that its recommendations represent "major transformations in [EPA's] culture." Its report has not ended controversies with regard to uncertainty, defaults, thresholds, and cumulative risks, nor will the new risk analysis framework that is emerging be easy to reconcile with the shift to in vitro toxicity testing techniques discussed above. Some of the report's suggestions, particularly for solution-focused risk assessment, have faced some resistance within and outside EPA. Nevertheless, at the time NRC released its report EPA stated that it would "thoroughly" review the recommendations and develop a plan for implementing them. While the details of a plan have not been announced at the time of this writing, EPA has taken a number of other concrete actions, including hosting workshops, discussing the issue within its Science Advisory Board, and working closely with scholarly institutions like the Society for Risk Analysis.

"Scientific Integrity"

Though EPA was analyzing how to improve its uses of toxicity testing and risk assessment well before January 20, condemnation of the Bush administration as "anti-science" was a popular theme among many commentators. Critics pointed to alterations and rejections of certain reports, most famously the agency's first assessment of global warming, and alleged that conservative political ideology played an excessive role in the appointment of individuals to advisory committees overseeing scientific endeavors. In addition, critics charged that the Bush administration favored businesses by demanding "sound science" for regulation while cutting funding for government science programs. Much of the denunciation centered on OMB, whose influence over agency rulemaking increased dramatically during the Bush years. During the 2008 presidential campaign, candidate Obama declared that "we need to end the Bush administration's war on science, where ideology trumps scientific inquiry and politics replaces expert opinion."

The Obama White House has taken measures to reverse or revise some of the policies that fueled the criticisms of the prior administration. President

Obama set goals to "devote more than 3 percent of our GDP to research and development," an unprecedented level, and to focus more on basic research. Toward the goal of government-wide transparency, the White House Office of Science and Technology Policy launched an Open Government Initiative; one part of that initiative is compiling public input for a new directive for federal agencies, while another, the website data.gov, aims to provide free public access to agencies' data and research. In addition, Obama has begun revising the process by which OMB reviews the science-based decisions of administrative agencies. Ten days after taking office, the new administration overturned several Bush-era executive orders that had expanded OMB's power and directed agencies to develop recommendations for a new executive order on federal regulatory review.

In another memorandum issued in March, Obama ordered the White House Office of Science and Technology Policy to devise a set of recommendations for executive agencies "for ensuring the highest level of integrity of the executive branch's involvement with scientific and technological processes." This memorandum outlined principles dealing with procedural rules, peer review, public availability of information, selection of candidates for government positions, and whistleblower protections. At the time of this writing, OSTP has not formally issued recommendations, though it continues its efforts under the Open Government Initiative.

EPA has responded to the scientific integrity memorandum by, among other things, having its Science Policy Council "inventory[] all our guidelines and policies that relate to scientific integrity," including the *Peer Review Handbook*, "to look for gaps and possible areas for improvement." After this inventory, industry perspectives could become more sidelined during peer review, especially at the majority of EPA science advisory committees that currently appoint panels on the basis of interest group representation. GAO has suggested that it is generally more appropriate for EPA to appoint science advisory committee members as special government employees, subject to conflict-of-interest reviews, rather than as representatives of stakeholder interest groups.

Conclusion

The developments and trends highlighted in this brief overview span a wide range of EPA's scientific practices and policies relating to chemical risks, but they are interconnected. The conduct of toxicity studies, the compilation of these studies into IRIS toxicity values, the use of the studies and the values in risk assessments, and the measures for transparency at each step are all at a crossroads, feeling the effects of political dynamics as well as of ever-compounding scientific and technological advances. The challenge for EPA will be to manage these changes to maximize benefits while minimizing upheaval and unintended consequences, all while operating under resource constraints.

The most striking implication is the potential for much faster and less expensive assessment of chemical risks. Mechanism-based in vitro assays and other advanced technologies can speed the acquisition and processing of safety data on chemicals, while procedural reforms to IRIS and risk assessment can speed the use of chemical data in decisionmaking. The changes also target the accuracy and realism of chemical assessments. The emerging focus on path-ways and mechanisms of action, the unified treatment of cancer and non-cancer risks, and the use of more realistic doses could reduce some instances of excessive conservatism in risk assessments. Greater accounting for variability and cumulative risks are said by proponents to make risk assessments more realistic as well, though they could also add in more conservatism. The reforms to transparency and integrity and the increase in science funding will help assure that the full impacts of the potential gains in efficiency and accuracy are felt in the policy realm. In some cases the level of regulatory scrutiny for particular chemicals may be reduced based on updated science, while in others EPA will have a stronger evidentiary basis for regulating more stringently. When EPA does regulate, greater consideration of management options at the outset of risk assessment could broaden the range and creativity of options ultimately considered.

These developments offer something for stakeholders on all sides of the debate over modernizing TSCA, the key statute for regulating most chemicals in the United States. Significantly, EPA has weighed in on the debate with a set of principles for legislation to modernize TSCA. Several of the agency's core principles will be directly impacted by the scientific developments discussed above, particularly using "sound science" as the basis for risk management in the face of uncertainty, obtaining "sufficient" hazard data to support safety determinations, accounting for sensitive subpopulations, and encouraging "safer" products through green chemistry. Stakeholders should consider how best to leverage the changing nature of science at EPA to move their interests forward. •