MODERNIZING U.S. CHEMICALS LAWS: HOW THE APPLICATION OF TWENTY-FIRST CENTURY TOXICOLOGY CAN HELP DRIVE LEGAL REFORM

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There is general agreement among stakeholders that reform for U.S. chemicals laws is long overdue. While the details of this reform have not yet emerged, under almost every scenario now being discussed, massive amounts of new scientific data will be needed. Obtaining this data will require a quantum leap in the amount of toxicity testing being performed. Surprisingly, little discussion in the legal literature has evaluated the extent, nature, and implications of the need for an expanded testing system.

This article explores how toxicity testing reform fits into the broader legal and policy landscape. An ever-accelerating scientific evolution is underway, endorsed by the National Research Council, and new advances are changing the way we approach chemical testing. Faster, cheaper, and more efficient testing

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methods are being put into practice or are on the horizon—methods that rely more on cell lines, robots, and computers than on animals. These twenty-first century approaches will ultimately provide higher-quality results that improve our decision-making about chemicals. But the question remains how best to build this new science into the law and policy framework governing chemicals.

The authors first determine that although current federal laws governing toxic chemicals present no insurmountable barriers to implementing the new toxicological paradigm, regulatory changes will be essential. They then examine toxicity testing reform in the context of ongoing discussions over modernizing the Toxic Substances Control Act—vis-à-vis the push toward international harmonization of chemical regulation driven by the European Union. The authors conclude that while toxicity testing reform can survive under existing legal and institutional mechanisms, building toxicity testing reform into expected TSCA legislative amendments provides the best hope that modern toxicological approaches will take root in U.S. chemical policy and thrive. Also, without active regulatory recognition and support of such approaches, U.S. chemicals law reform is unlikely to succeed.

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INTRODUCTION

In perhaps no other area of environmental policy is the interdependence of science and law as evident—and as crucial—as it is in the field of chemical regulation. As U.S. lawmakers, industry, and environmental groups move increasingly closer to a modernization of the principal U.S. law governing toxic chemicals, a more careful examination of the science underlying regulatory decision-making has become necessary. Many of the animal-based chemical-testing methodologies expected to shoulder this legal reform were developed in the middle of the twentieth century. Toxicology has evolved rapidly since then, and today's scientists are working with a dizzying array of new tools and methodologies—absent certainty about how these modern approaches will be used by regulators and industry in their testing

and decision-making. Ironically, we stand on the verge of producing a twenty-first century legal vehicle powered by a mid-twentieth-century engine—just as the knowledge and technology needed to build a modern scientific engine are within our grasp. As we explain in this article, synchronizing toxics legal reform with scientific advancements in toxicology has suddenly become both a necessity and priority.

The legal backbone of the U.S. federal system that controls the use of chemicals in commerce consists of the Toxic Substances Control Act (TSCA), the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and their implementing regulations. These legal frameworks were enacted, promulgated, or underwent substantial amendments in the 1970s and 1980s. Since that time, their key legislative provisions have remained largely unchanged.[1] As early as 1984, the scientific community recognized that a substantial amount of toxicological information regarding chemicals in commerce was unavailable and could not be generated under the U.S. federal system as implemented.[2] This "toxics data gap" has only widened since that time. Under the existing U.S. legal and policy framework for ensuring chemical safety, a mere fraction of the 80,000 or so chemicals to which we are all potentially exposed has been adequately tested.[3] Public awareness of the health risks associated with the failure to regulate substances such as asbestos, or, more recently, BPA, has increased. As a result, the persistent drumbeat for reform of U.S. chemical

[1] *See* Brett H. Oberst, Lynn N. Hang & Lindsay K. Larris, *Obama and EPA Take on TSCA Reform*, 40 ENVTL. L. REP. NEWS & ANALYSIS 10123, 10123 (2010).

[2] *See, e.g.*, STEERING COMM. ON IDENTIFICATION OF TOXIC & POTENTIALLY TOXIC CHEMS. FOR CONSIDERATION BY THE NAT'L TOXICOLOGY PROGRAM, NAT'L RESEARCH COUNCIL OF THE NAT'L ACADEMIES, TOXICITY TESTING: STRATEGIES TO DETERMINE NEEDS AND PRIORITIES 195-96 (1984) [hereinafter NRC STRATEGIES].

[3] Daniel Krewski, *Without Changes, Testing Will Evolve Slowly*, ENVTL. F., Mar./Apr. 2008, at 50. *See, e.g.*, ENVTL. DEF. FUND, TOXIC IGNORANCE: THE CONTINUING ABSENCE OF BASIC HEALTH TESTING FOR TOP-SELLING CHEMICALS IN THE UNITED STATES 3 (1997) [hereinafter TOXIC IGNORANCE] (concluding that "even the most basic toxicity testing results" are unavailable in the public record for nearly 75% of the top-volume chemicals in commercial use). This does not necessarily mean that we are or will be harmed by these chemicals—rather, it means that we are ignorant of what, if any, adverse effects may result from our exposure to them. *Id.* at 8.

laws grows louder.[4] It has become apparent that a substantial change in our approach to regulating chemicals is needed if regulators and the public are to have access to the data and information they need to make the federal chemical laws work as they were intended.[5]

At the same time that our legal framework governing toxic chemicals has lagged behind the demands being placed on it, the science of toxicology has advanced rapidly, using new tools to ask new questions. An ever-accelerating scientific evolution is underway, and it is reshaping how scientists think about toxicity testing.[6] It is partially founded on a new understanding about cellular molecular mechanisms, and how disease processes progress. It is also based on advancements in technology in toxicology, such as the rise of the "-omics" and related techniques.[7] These advances are changing the way we think about testing chemicals and have led to a new paradigm in the toxicity testing community. Faster, cheaper, and more efficient methods are being put into practice, or are on the horizon—and, most importantly, we expect these methods to provide higher-quality results that would improve our decision-making about chemicals.

The relationship between this evolution in tools for toxicity testing and the broader regulatory environment was documented

[4] *See, e.g.*, Sen. Kirsten Gillibrand, *Keeping Our Children Safe*, HUFFINGTON POST (Aug. 10, 2011), http://www.huffingtonpost.com/rep-kirsten-gillibrand/keeping-our-children-safe_b_923117.html (arguing that "TSCA has failed" and calling for legal reform); *Mothers on a Mission to Bring Awareness to Toxic Chemicals in Common Products,* CBS NEW YORK (Aug. 10, 2011), http://newyork.cbslocal.com/2011/08/10/mothers-on-a-mission-to-bring-awareness-to-toxic-chemicals-in-common-products/ (describing "stroller brigades," consisting of mothers campaigning for toxics reform).

[5] *See, e.g.*, Kevin M. Crofton, *The Need for a Paradigm Shift in Toxicology*, ENVTL. F., Mar./Apr. 2008, at 48 (EPA neurotoxicologist noting lack of hazard information on thousands of compounds and lack of understanding of the biological bases of human diseases).

[6] *See, e.g.*, Francis S. Collins, George M. Gray & John R. Bucher, *Transforming Environmental Health Protection*, 319 SCIENCE 906, 906 (2008) (discussing coordinated activities by several agencies).

[7] *See* Thomas Hartung, *Evidence-Based Toxicology—The Toolbox of Validation for the 21st Century?*, 27 ALTEX 253, 253–61 (2010) (discussing advances in technology including "-omics"). The term "-omics" includes a suite of technologies including genomics, proteomics, metabolomics, and others. Generally speaking, these are techniques that study cell signaling, gene expression, and protein changes and their potential role in disease progression. *See* NRC VISION, *infra* note 8, at 102, 107, 144.

and explained in a groundbreaking 2007 report by the National Research Council (NRC) of the National Academy of Sciences. In *Toxicity Testing in the 21st Century: A Vision and a Strategy* (NRC Vision), the NRC proposed a new paradigm for how chemicals should be tested for toxicity and what regulators should do with the resulting test data.[8] The NRC cited ongoing breakthroughs in scientific research and recommended a transformative approach to toxicity testing that it believes should, over time, replace the status quo. Over the span of two to three decades, the NRC report envisions the emergence of a system of toxicity testing that depends primarily on the use of high-speed, automated experiments[9] on cell lines to evaluate perturbations in "toxicity pathways" that underlie the progression toward disease.[10] The resulting data will lead to better predictions than are currently possible about how chemical exposures are linked to adverse effects in humans.[11] The NRC Vision argues that this system, once fully implemented, will produce test results that are more scientifically robust and better suited to public health and environmental decision-making. The NRC anticipates "improved

[8] COMM. ON TOXICITY TESTING AND ASSESSMENT OF ENVTL. AGENTS, NAT'L RESEARCH COUNCIL OF THE NAT'L ACADEMIES, TOXICITY TESTING IN THE 21ST CENTURY: A VISION AND A STRATEGY (2007) [hereinafter NRC VISION]. The Committee's work was undertaken at the request of the U.S. Environmental Protection Agency, and the final report followed a 2006 interim report. The NRC Vision identifies various challenges faced by the existing system, including "evaluating various life stages, numerous health outcomes, and large numbers of untested chemicals." *Id.* at 3.

[9] Often described as "high-throughput assays." *E.g.*, *id.* at 7.

[10] The vision articulated by the NRC consists of five overall components: chemical characterization (component A), toxicity testing (component B), dose-response and extrapolation modeling (component C), population-based and human exposure data (component D), and risk contexts (component E). *See id.* at 50, 56–97. The toxicity testing component, which is the heart of the new approach, involves toxicity-pathway testing, complemented by targeted whole-animal testing. *Id*. A detailed scientific critique of the NRC Vision, its recommendations, and the evidence it cites is beyond the scope of this article.

[11] Confidence in the future envisioned by the NRC is growing. At a 2011 congressional briefing hosted by one of the authors of this article, Representative Jim Moran (D-Va.), who chairs the Congressional Animal Protection Caucus, said, "It has been shown that the technology is such today that animal testing is outdated." By way of example, the Congressman argued that computational and high-throughput testing would be more effective than current methodologies at testing for the cumulative effects of small, trace exposures to multiple chemicals. Jeremy P. Jacobs, *Expert Calls for End to Animal Testing of Toxics*, ENV'T & ENERGY DAILY (Sept. 14, 2011), http://www.eenews.net/EEDaily/2011/09/14.

risk-based regulatory decisions and possibly greater public confidence in and acceptance of the decisions."[12] As added benefits, toxicity testing under this new paradigm would take place more quickly, less expensively, and with the sacrifice of vastly fewer animals.[13] The European Union is already well along this path, guided by broadening scientific horizons and, at least in part, by opportunities to advance new technologies in toxicity testing.[14]

The NRC Vision holds great promise for closing the toxics information gap and moving the U.S. federal chemicals system closer to the goals of the laws that underlie it. But at the end of the day, the NRC Vision is not self-implementing. Even the high levels of enthusiasm and commitment evident today will not, without more, ensure that decision-makers actually rely on the results of the new science in assessing chemical risk. It is clear that if this new paradigm is to become viable and succeed in the United States, it must take root in the legal, regulatory, and institutional framework governing chemical regulation. The NRC Committee appears to presume that much of the recommended paradigm shift can be implemented under existing law—while recognizing the likely need for at least some changes in regulatory policy, and perhaps even the law.[15]

This article posits that the many ongoing, evolutionary changes in toxicology provide fuel for a regulatory revolution that can and will fundamentally change the way in which we evaluate chemical hazards for chemicals in commerce. It is not an

[12] NRC VISION, *supra* note 8, at 2. *See also* Thomas Hartung & Mary McBride, *Food for Thought. . .on Mapping the Human Toxome*, 28 ALTEX 83, 91 (Feb. 2011) ("In contrast to the currently used phenomenological 'black box' animal testing, pathways of toxicity . . . will be identified in human *in vitro* systems to provide more relevant, accurate, and mechanistic information for the assessment of human toxicological risk.").

[13] NRC VISION, *supra* note 8, at 120. However, the NRC does contemplate the need for an investment of "moderately large funding" to undertake the necessary large-scale, long-term research program needed to support the Vision. *Id.* at 158.

[14] Megan Schwarzman & Michael Wilson, *New Science for Chemicals Policy,* 326 SCIENCE 1065, 1065–66 (2009).

[15] In this regard, Chapter 6 of the NRC Vision anticipates the need for new policies "to support and reward effective use of new testing concepts and methods," as well as new policies to encourage the use of data generated with the new testing paradigm in chemical assessments by the agencies." NRC VISION, *supra* note 8, at 170. But the NRC Vision itself does not provide a roadmap explaining precisely *which* regulatory and legal forms are necessary or how they should be designed and implemented.

overstatement to say that the future of chemical regulation in the United States is inextricably linked to the underlying changes in the science of toxicology as applied to toxicity testing. This hypothesis raises central questions about chemical toxics law reform. Can the current system of laws afford the new science all the room it needs not only to take hold, but also to flourish? Or does this rapid evolution in toxicology require a change in existing federal laws? And, regardless, if legal reform is on the way for other reasons, must the new science necessarily be incorporated? And perhaps most importantly, can legal reform of chemicals regulation succeed *without* twenty-first century toxicology?

The threshold legal question is whether the NRC's proposed paradigmatic shift from primarily animal-based testing of chemical toxicity to primarily cell-based testing of chemical toxicity can be implemented under the laws currently on the books.[16] As Part I of this article will explain, the answer to that question is an unequivocal "yes." Part I examines the federal laws that together provide the principal legal basis for chemical regulation. The Toxic Substances Control Act (TSCA), administered by the U.S. Environmental Protection Agency (EPA), establishes the statutory framework for regulating industrial chemicals. Pesticides are governed by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), together with part of the Federal Food, Drug, and Cosmetic Act (FFDCA) pertaining to limits on the amount of pesticide residue that may remain on food. Accordingly, Part I explores whether implementation of the NRC Vision is consistent with the requirements of TSCA, FIFRA, and related portions of the FFDCA.[17]

Assuming that the Vision *can* be implemented under current law, as we conclude, the question remains whether any future reform to the chemicals laws (many of which are under discussion)

[16] The NRC Vision essentially poses this question by observing that "[l]awmakers will need to determine whether the regulatory statutes that form the basis of [human exposure guidelines for environmental agents judged to have toxic potential] need to be modified to reflect the greater reliance on indicators of toxicity-pathway perturbations than on overt health outcomes." NRC VISION, *supra* note 8, at 180.

[17] Although full implementation of the NRC Vision in the United States may also require further analysis of other federal laws—including those, for example, governing the regulation of pharmaceuticals—TSCA and FIFRA provide the appropriate legal starting point for a discussion of how the NRC Vision fits into the existing regulatory framework for industrial chemical regulation.

should nevertheless be used to help drive implementation of the Vision. In Part II, the article considers by way of example the role of two federal bills, the Safe Chemicals Act of 2011 and the Endocrine Disruptor Screening Enhancement Act of 2011, which, if enacted, would substantially change federal chemicals policy. The article also analyzes the relevance of international efforts to harmonize chemical regulation. The focus of our analysis is on whether the NRC Vision could be implemented if these bills became law—and whether these harmonized guidelines are consistent with the implementation of the Vision. Finally, Part III introduces the process of validation of new tests pursuant to the existing Interagency Coordinating Committee on the Validation of Alternative Methods of 2000 (ICCVAM). ICCVAM was established under federal legislation that, while intended to aid in the validation of alternative testing methodologies, has, unfortunately, operated more as an impediment to progress in validating new *in vitro* approaches in the United States.

The article reaches several conclusions. First, successful implementation of the NRC Vision does not require Congress to enact new environmental laws governing industrial chemicals and pesticides. Implementation, however, will require significant changes in EPA policy, regulations, guidelines, and programs. This is because the prevailing regulatory framework established over many years by EPA under the major toxics laws is premised on obtaining key data primarily and preferentially from whole-animal toxicology. Accommodation for and encouragement of new tools and techniques will be absolutely necessary and overcoming institutional inertia will be critical.

Even if, as we conclude, toxicity testing reform *can* be implemented administratively under existing law, we cannot ignore the fact that TSCA may soon be subject to a once-in-a-generation legal overhaul. Oddly, the public debate over TSCA reform has rarely touched upon the corresponding imperative of toxicity testing reform.[18] Pending bills, together with broader

[18] Why this is so is not entirely clear. One possible explanation lies in the complexity of the science, which can seem impenetrable to the scientific layperson. It is not readily susceptible to crisp public messaging. Another possibility is that proponents of TSCA reform worry that toxicity testing reform could be marshaled by opponents of reform as an obstacle to obtaining new legislation. (This article argues that the two aims can and should go hand in hand.) Yet another possibility is that proponents of TSCA reform see the

pressures to harmonize chemical testing methodologies for international industry, do create additional drivers for chemical testing reform. But more is almost certainly needed: the legislation working its way through Congress, intended to improve U.S. chemicals policy and decision-making, does not, as currently written, fully implement the NRC Vision. And the existing federal interagency mechanism for the acceptance and validation of alternative testing models has fallen short. Legislative reform represents a rare opportunity to drive implementation of toxicity testing reform, just as modernization of chemical testing methodologies can help ensure the success of an amended TSCA.

Finally, any meaningful legislative reform of TSCA will bring with it a vast new demand for chemical testing and toxicological data.[19] The backlog of untested substances is daunting, and it is clear that the present-day toxicological paradigm cannot meet this need. This means that the long-term viability of TSCA reform may well depend on the successful implementation of twenty-first century toxicology.

I. IMPLEMENTING THE NRC VISION UNDER CURRENT LAW: TSCA, FIFRA, AND RELATED PORTIONS OF THE FFDCA

This Part examines the prevailing legal framework governing toxic chemicals to assess opportunities for and obstacles to implementing toxicity testing reform under current law. A review of the relevant statutory provisions, legislative history, regulations, and policies makes clear that the NRC Vision *can* be implemented under current legislation—though administrative changes are necessary. Whether this is the *best* way forward is another question, which we address in the balance of the article.

We begin our analysis with TSCA and then turn to the relevant pesticide laws.

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emerging science of toxicity-pathways testing as insufficiently proven to yet play a starring role in toxics regulation.

[19] *See, e.g.*, Press Release, Lautenberg Press Office, Sen. Lautenberg Introduces "Safe Chemicals Act of 2011" (Apr. 14, 2011), *available at* http://lautenberg.senate.gov/newsroom/record.cfm?id=332785& ("The new legislation will give EPA more power to regulate the use of dangerous chemicals and require manufacturers to submit information proving the safety of *every chemical in production and any new chemical seeking to enter the market*.") (emphasis added).

A. *TSCA*

The Toxic Substances Control Act (TSCA) is the principal U.S. law governing industrial chemicals.[20] Enacted in 1976 and made effective in 1977, TSCA establishes a legal framework that charges the EPA Administrator with identifying potentially toxic chemicals and regulating their usage.[21] The stated aim of TSCA is to ensure the regulation of chemicals that present "an unreasonable risk of injury to health or the environment."[22] The statute mandates that the Administrator "shall consider the environmental, economic, and social impact of any action" taken by EPA under the Act.[23] TSCA's core regulatory provisions have never been amended.[24]

TSCA divides the universe of chemicals into "existing" chemicals and "new" chemicals. Existing chemicals (i.e., chemicals that were in commerce prior to the enactment of TSCA) may remain in use unless EPA makes an affirmative showing that

[20] Toxic Substances Control Act (TSCA), §§ 2-412, 15 U.S.C. §§ 2601-2692 (2006). TSCA regulates "chemical substances" and manmade "mixtures" of chemical substances. *See* TSCA § 6(a), 15 U.S.C. § 2605(a) (scope of regulation); TSCA § 3(2), 15 U.S.C. § 2602(2) (definition of "chemical substance"); TSCA § 3(8), 15 U.S.C. § 2602(8) (definition of "mixture"). For simplicity, this article uses the word "chemical" as a shorthand for "chemical substance or mixture" as that phrase appears throughout the statute. Also, the term "chemical substances" for purposes of TSCA does *not* include pesticides, which are regulated primarily under the federal laws discussed later in this article. *See infra* Part I.B.

[21] TSCA § 2(c), 15 U.S.C. § 2601(c) (EPA Administrator to carry out requirements of TSCA). For a helpful overview of TSCA's requirements, see LINDA-JO SCHIEROW, CONG. RESEARCH SERV., RL31905, THE TOXIC SUBSTANCES CONTROL ACT (TSCA): A SUMMARY OF THE ACT AND ITS MAJOR REQUIREMENTS (2010).

[22] *E.g.*, TSCA § 6(a), 15 U.S.C. § 2605(a) (scope of regulation of hazardous chemical substances and mixtures). Under Section 6 of TSCA, EPA is authorized to restrict or ban chemicals on a showing that they present an unreasonable risk of injury to health or the environment. Courts, however, have interpreted EPA's power in this regard very narrowly. *E.g.*, Corrosion Proof Fittings v. EPA, 947 F.2d 1201 (5th Cir. 1991) (landmark case rejecting EPA attempt to ban asbestos through a TSCA Section 6 rule).

[23] TSCA § 2(c), 15 U.S.C. § 2601(c).

[24] These core provisions are contained in Subchapter I of TSCA. TSCA has, however, been amended to add new titles on asbestos (TSCA Subchapter II, added in 1986); radon (TSCA Subchapter III, 1988); lead (TSCA Subchapter IV, 1992); and school environments (TSCA Subchapter V, 2007). For more on recent proposals to amend TSCA, see *infra* Part II.A.

they pose a hazard.[25] The law essentially presumes the safety of existing chemicals. Given that more than 60,000 chemicals were grandfathered in as "existing" under TSCA, it is significant that the statute places the burden on EPA to demonstrate that any of these chemicals poses a hazard if the agency wants to regulate its use. By contrast, when a manufacturer intends to introduce a "new" chemical or undertake a significant new use of an existing chemical, it must at least come forward with any existing data that could assist EPA in assessing the chemical's potential adverse effects on health or the environment.[26]

EPA maintains the TSCA Chemical Substance Inventory: a list of about 84,000 chemicals that are in commerce in the United States.[27] EPA also maintains what is known as the Master Testing List (MTL), which the agency uses to set chemical testing priorities under TSCA in coordination with the needs of other federal agencies.[28]

As we explain below, nothing in TSCA erects a statutory barrier to implementing the NRC Vision under current law—though substantial changes by EPA at the regulatory level would be needed. Our analysis of obstacles and opportunities under TSCA takes into account the statute's text and legislative history, as well as how EPA has expressly and impliedly articulated its policy approach to toxicity testing though regulations, guidelines, interagency relationships, and other means.

1. *Key TSCA Provisions Concerning Chemical Data and Testing*

TSCA establishes a federal policy that adequate data "should"

[25] *See* TSCA §§ 6–7, 15 U.S.C. §§ 2605–2606 (regulation of existing chemicals and imminently hazardous substances).

[26] TSCA § 5, 15 U.S.C. § 2604, (regulation of new chemicals via Pre-Manufacture Notice (PMN) process and regulation of significant new uses). For a short overview of EPA's different treatment of existing versus new chemicals, see *Is a Filing Necessary for My Chemical?*, U.S. ENVTL. PROT. AGENCY (Apr. 15, 2011), http://www.epa.gov/oppt/newchems/pubs/whofiles.htm.

[27] *TSCA Chemical Substance Inventory*, U.S. ENVTL. PROT. AGENCY (Mar. 15, 2012), http://www.epa.gov/opptintr/existingchemicals/pubs/tscainventory/index.html. For more on the TSCA Inventory, see SCHIEROW, *supra* note 21, at 3 (noting the universe of chemicals—including those that could be synthesized and those that have yet to be identified—has been characterized as "unimaginably immense").

[28] For more on the Master Testing List, see *Master Testing List—Introduction*, U.S. ENVTL. PROT. AGENCY (Feb. 3, 2012), http://www.epa.gov/oppt/chemtest/pubs/mtlintro.html.

be developed on the effect of chemicals on health and the environment—and that data development "should" be the responsibility of those who manufacture and process chemicals.[29] Section 5 of TSCA regulates industry submission of existing data to EPA in connection with the proposed introduction of new chemicals or significant new uses of existing chemicals.[30] Generally, the testing of existing chemicals is governed by the test rule requirements contained in TSCA Section 4.

a. *Test Rules*

Under Section 4 of TSCA, EPA must, by rule, require the chemical industry to test a chemical for its environmental or health effects if EPA makes either what is known as a *hazard finding* or an *exposure finding*.[31] EPA must make a hazard finding with respect to a chemical if:

- the chemical poses an unreasonable risk of injury to health or the environment;
- there are insufficient data about the chemical to predict its health or environmental effects; *and*
- testing is necessary to develop data on these effects.[32]

EPA must make an exposure finding if:

- the chemical will be produced in substantial quantities, *and either*
  - it may enter the environment in substantial quantities, *or*
  - there may be substantial human exposure to the chemical;
- there are insufficient data about the chemical to predict its health or environmental effects; *and*
- testing is necessary to develop data on these effects.[33]

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[29] TSCA § 2(b)(1), 15 U.S.C. § 2601(b)(1).

[30] TSCA § 5(b), (d), 15 U.S.C. § 2604(b), (d).

[31] TSCA § 4(a)(1), 15 U.S.C. § 2603(a)(1)(A)–(B). *See also TSCA Chemical Testing Policy*, U.S. ENVTL. PROT. AGENCY (Apr. 27, 2011), http://www.epa.gov/opptintr/chemtest/pubs/sct4main.html. Although TSCA provides authority to guide EPA in the issuance of formal test rules, the Agency, as a practical matter, opts whenever possible to work with industry by way of enforceable consent agreements (ECAs) and Voluntary Testing Agreements (VTAs) that avoid using the more cumbersome and expensive rulemaking mechanism of Section 4. *See infra* Part I. A.3.a.

[32] TSCA § 4(a)(1)(A), 15 U.S.C. § 2603(a)(1)(A).

[33] TSCA § 4(a)(1)(B), 15 U.S.C. § 2603(a)(1)(B). Even in the absence of an EPA finding for a particular chemical, a chemical manufacturer can petition EPA to prescribe standards for test data for the chemical. TSCA § 4(g), 15 U.S.C. §

When EPA makes either of these findings for a chemical, the agency must then promulgate a rule requiring that testing be conducted on the chemical "to develop data with respect to the health and environmental effects for which there is an insufficiency of data and experience," and that are relevant to a determination by EPA that the chemical "does or does not present an unreasonable risk of injury to health or the environment."[34]

An EPA testing requirement rule under TSCA Section 4 must contain, among other things, "standards for the development of test data" for the chemical.[35] TSCA defines "standards" in this context to mean a prescription of the relevant health and environmental effects for which the chemical is to be tested; the information related to toxicity, persistence, and other chemical characteristics for which data is to be developed and analyzed; and, as needed to assure that the data are reliable and adequate, the manner in which the data must be developed, specification of any test protocol or methodology, and "such other requirements" as are necessary.[36]

TSCA further directs EPA in the design of a testing requirement rule by setting forth factors for the agency to consider in formulating these standards[37] and identifying relevant health and environmental effects, chemical characteristics, and methodologies.[38] A careful reading of these provisions confirms that Section 4 of TSCA poses no obstacle to implementation of the NRC Vision; in fact, certain aspects of the Section 4 regime reinforce and support the NRC Vision approach.

First, and most importantly, EPA enjoys broad discretion in determining the health and environmental effects for which testing standards may be set. These effects "include carcinogenesis, mutagenesis, teratogenesis, behavioral disorders, cumulative or synergistic effects, *and any other effect which may present an unreasonable risk of injury to health or the environment*."[39] The Administrator's discretion, anchored in broad "any other effect"

2603(g).

[34] TSCA § 4(a), 15 U.S.C. § 2603(a). An EPA rule under this Section requiring that a chemical be tested expressly preempts any similar state testing requirement for the chemical. TSCA § 18(a)(2)(A), 15 U.S.C. § 2617(a)(2)(A).

[35] TSCA § 4(b)(1)(B), 15 U.S.C. § 2603(b)(1)(B).

[36] TSCA § 3(12), 15 U.S.C. § 2602(12).

[37] TSCA § 4(b)(1), 15 U.S.C. § 2603(b)(1).

[38] TSCA § 4(b)(2)(A), 15 U.S.C. § 2603(b)(2)(A).

[39] *Id.* (emphasis added).

language, would appear to allow for mechanism-based testing of substances designed to reveal whether a particular toxicity pathway is perturbed by the substance in such a way as to signal likely adverse effects in humans or the environment.[40]

Second, in determining the chemical characteristics for which such testing standards may be set, EPA again has great flexibility. Characteristics for which EPA may prescribe standards "include persistence, acute toxicity, subacute toxicity, chronic toxicity, *and any other characteristic which may present such a risk*."[41] A chemical's potential to perturb a toxicity pathway would seem to meet the common-sense definition of a "characteristic" of that chemical.

It is significant that TSCA grants to EPA expansive discretion in identifying both the injurious health and environmental outcomes for which to be tested as well as the chemical characteristics for which standards may be set. The NRC Vision is premised on the idea that biologic perturbations identified in key toxicity pathways through *in vitro* testing can be correlated to adverse health outcomes in humans.[42] Under Section 4 of TSCA, EPA has flexibility to set standards for the development of test data that take into account a broad swath of chemical characteristics and potential effects.

Third, TSCA lays out the kinds of methodologies that EPA may prescribe in its standards. These methodologies "include epidemiologic studies, serial or hierarchical tests, *in vitro* tests, and whole animal tests."[43] Here, then, is an express statutory reference to the potential use of *in vitro* testing methodologies, made in clear juxtaposition to *in vivo* testing. On its face, TSCA allows EPA to rely on non-animal tests. And again, the core of the NRC Vision is

[40] Traditionally, toxicity testing is geared to an "apical endpoint"—i.e., an observable outcome from an animal test that served an indicator of toxicity. Such endpoints might be growth defects, developmental issues, tumor formation, mortality, carcinogenicity, or disease progression. Apical endpoint tests evaluate the end result of exposure but do not necessarily provide detailed information about the mechanism by which the response occurred. The NRC Vision approach looks, instead, to the underlying mechanistic effects of the substance being tested.

[41] TSCA § 4(b)(2)(A), 15 U.S.C. § 2603(b)(2)(A) (emphasis added).

[42] *See* NRC VISION, *supra* note 8, at 11–12, 90.

[43] TSCA § 4(b)(2)(A), 15 U.S.C. § 2603(b)(2)(A) (emphasis added). This provision also contains a caveat, not relevant to the present analysis, concerning epidemiologic studies of employees.

a testing paradigm that pairs high-throughput toxicity-pathway assays with, as needed, targeted animal tests.[44]

Additionally, it is worth noting that in fixing the standards for a testing requirement rule, TSCA dictates that EPA include in its considerations both the relative costs of various test protocols and methodologies and the availability of the facility and personnel needed to perform the testing.[45] Finally, TSCA's mandate to EPA to consider testing costs and resource availability aligns with one of the stated goals of the NRC Vision, which is to shift to a system of toxicity testing that protects human health while, whenever possible, simultaneously conserving resources—including dollars, time, and animal usage.[46] This explicit congressional concern with the cost of testing resurfaces in Section 30 of TSCA, which requires that EPA include in its required annual reporting under the statute both a list of the tests required under Section 4 and an estimate of the costs incurred by those who had to perform the tests.[47] Obviously, public health and environmental concerns cannot and should not be dictated solely by factors of cost and availability of appropriate staff or testing facilities. Given that EPA must consider such factors by law, however, it is significant that, over time, the kinds of pathway-based approaches envisioned by the NRC will be substantially less expensive to administer than prevailing animal-based testing methodologies.

Section 4 of TSCA also covers other issues pertaining to chemical testing, including who is required to conduct tests and submit data to EPA;[48] the circumstances under which exemptions will be granted;[49] how EPA is to prioritize chemicals for purposes of issuing testing requirement rules;[50] the duration of testing requirement rules;[51] and steps EPA must take upon receiving the required test data.[52]

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[44] The NRC acknowledges that, for the foreseeable future, targeted animal testing will be a necessary part of any *in vitro* strategy as a means of assessing likely metabolites. *See* NRC VISION, *supra* note 8, at 8 (discussing the reduction of animal testing).

[45] TSCA § 4(b)(1), 15 U.S.C. § 2603(b)(1).

[46] NRC VISION, *supra* note 8, at 4.

[47] TSCA § 30, 15 U.S.C. § 2629.

[48] TSCA § 4(b)(3), 15 U.S.C. § 2603(b)(3).

[49] TSCA § 4(c), 15 U.S.C. § 2603(c).

[50] TSCA § 4(e), 15 U.S.C. § 2603(e).

[51] TSCA § 4(b)(4), 15 U.S.C. § 2603(b)(4).

[52] *E.g.*, TSCA § 4(d), (f), 15 U.S.C. § 2603(d), (f).

Overall, the TSCA Section 4 test-rule provisions present no obstacle to implementation of the NRC Vision. To the contrary, Section 4's explicit identification of *in vitro* tests, viewed in tandem with the broad discretion lodged in the EPA Administrator to set testing standards and methodologies, present a clear path for implementation. Moreover, the benefit of any cost savings in testing that will ultimately emerge from implementation of the NRC Vision over the longer term aligns with the TSCA mandate that EPA consider costs and resource availability.[53]

All of the inherent weaknesses in Section 4 of TSCA regarding *when* EPA may issue a test rule (i.e., EPA must first make either a hazard finding or an exposure finding), however, constrain EPA's power to require *any* type of testing—pursuant to the NRC Vision or otherwise. Despite the flexibility that Section 4 of TSCA seems to afford to EPA in shaping testing approaches, the provision has been the target of blistering criticism over the years. This is not only because, as noted above, TSCA places a heavy burden on EPA to determine the safety of "existing" chemicals. It is also because of the relatively high bar set by TSCA's requirement that EPA make a hazard finding or exposure finding before it can require testing. One former EPA Assistant Administrator testified, "It's almost as if . . . we have to, first, prove that chemicals are risky before we can have the testing done to show whether or not the chemicals are risky."[54] The testing provisions have been characterized as creating "a Catch-22: [EPA] must already *have* data in order to show that it *needs* data."[55] It is this core feature of TSCA that has driven persistent modern calls for reform of the law.[56]

[53] Of course, in the near term, more likely the opposite could be true: building up the necessary research and development base to support implementation of the NRC Vision will be expensive. Moreover, industry will in some instances run the risk that, despite having performed certain *in vitro* tests, regulators continue to demand the results of classic animal toxicity tests. This reality could, in the near-to-mid term, result in duplicative testing and its attendant costs. These appear to be inevitable costs of migrating from a long-accepted system to a new paradigm.

[54] *See* SCHIEROW, *supra* note 21, at 14 (citing 1994 testimony of Lynn Goldman before a Senate subcommittee).

[55] TOXIC IGNORANCE, *supra* note 3, at 26.

[56] *See, e.g.*, Lisa P. Jackson, Adm'r, U.S. Envtl. Prot. Agency, Remarks to the Commonwealth Club of San Francisco (Sept. 29, 2009), *available at* http://yosemite.epa.gov/opa/admpress.nsf/8d49f7ad4bbcf4ef852573590040b7f6/fc4e2a8c05343b3285257640007081c5!OpenDocument; Council on Envtl.

b. *Health and Safety Studies*

Under Section 8(d) of TSCA, EPA must promulgate rules requiring the chemical industry to submit to EPA lists of existing health and safety studies that the industry has conducted or of which it is otherwise aware.[57] TSCA defines a "health and safety study" as "any study of any effect" of a chemical "on health or the environment or on both, including underlying data and epidemiological studies, studies of occupational exposure to a [chemical], toxicological, clinical, and ecological studies of a [chemical], and any test performed pursuant to [TSCA]."[58]

TSCA broadly defines the kinds of existing studies and data that industry is required to make available to EPA in carrying out its statutory mandate. EPA's discretion under this provision is not limited by whether the testing was obtained through *in vitro* or *in vivo* methods. Although this data provision presents no obstacle to implementation of the NRC Vision, it does not appear to present any particular opportunities, given the focus on *existing* studies and information.

c. *Developing the Necessary Research and Test Methods*

The NRC recognized that implementing its vision would be a long-term enterprise and expected that two decades or more could be required to make the transition to the cell-based, proactive testing system it outlined.[59] In addition, it said that a paradigm shift in toxicity testing would require new applied and basic research.[60] This would in turn demand extensive development and refinement

Health, Amer. Acad. of Pediatrics, *Policy Statement—Chemical-Management Policy: Prioritizing Children's Health*, 127 PEDIATRICS 953 (2011); SAFER CHEMICALS, HEALTHY FAMILIES COALITION, http://www.saferchemicals.org/ (last visited June 27, 2012); *Protecting People From Unsafe Chemicals*, NAT. RESOURCES DEF. COUNCIL, http://www.nrdc.org/health/toxics.asp (last visited June 27, 2012); *Chemicals Policy Reform*, ENVTL. DEF. FUND, http://www.edf.org/page.cfm?tagID=12814 (last visited June 27, 2012); *Kid-Safe Chemicals*, ENVTL. WORKING GROUP, http://www.ewg.org/kid-safe-chemicals-act-blog/ (last visited June 27, 2012). *See also, e.g.*, AMER. CHEMISTRY COUNCIL, 10 PRINCIPLES FOR MODERNIZING TSCA, *available at* http://www.americanchemistry.com/Policy/Chemical-Safety/TSCA/10-Principles-for-Modernizing-TSCA.pdf. *See also* discussion *infra* Part II.A.

[57] TSCA § 8(d), 15 U.S.C. § 2607(d).

[58] TSCA § 3(6), 15 U.S.C. § 2602(6).

[59] NRC VISION, *supra* note 8, at 122.

[60] *Id.* at 120.

of existing *in vitro* test methods and approaches, as well as the creation and validation of new techniques.[61]

TCSA grants EPA substantial authority over the types of research and coordination activities that would presumably be necessary to implement the NRC Vision. As an initial matter, Section 10 of TSCA provides that EPA "shall . . . conduct such research, development, and monitoring as is necessary to carry out the purposes of [TSCA]."[62]

More specifically with respect to research, Section 10 requires EPA to:

- coordinate research directed toward the development of "rapid, reliable, and economical screening techniques" for harmful effects of chemicals;[63]
- establish research programs "to develop the fundamental scientific basis" of these screening techniques, the bounds of their reliability, and opportunities for their improvement;[64] and
- establish and coordinate a system for exchange of chemical research and development results among all levels of government (federal, state, and local), including "a system to facilitate and promote the development of standard data format and analysis and consistent testing procedures."[65]

The NRC envisioned the need for a coordinated and transformative research program—one involving a "long-term, large-scale concerted effort"—to bring the new paradigm to fruition.[66] TSCA Section 10 provides clear authority for EPA to establish research programs to assist the agency in satisfying the statute's mandates, authority that could be deployed by EPA in service of implementing the NRC Vision.

Similarly, Section 27 of TSCA authorizes EPA to support projects for the development and evaluation of "inexpensive and efficient methods" for determining and evaluating the environmental and health effects of chemicals as well as their toxicity, persistence, and other relevant characteristics.[67]

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[61] *Id.* at 81–82.
[62] TSCA § 10(a), 15 U.S.C. § 2609(a).
[63] TSCA § 10(c), 15 U.S.C. § 2609(c).
[64] TSCA § 10(e), 15 U.S.C. § 2609(e).
[65] TSCA § 10(g), 15 U.S.C. § 2609(g).
[66] NRC VISION, *supra* note 8, at 155.
[67] TSCA § 27(a), 15 U.S.C. § 2626(a). This support is to be provided through

Furthermore, EPA is required to "consider" methods developed under this Section in prescribing standards for the development of test data under TSCA Section 4.[68] Thus, to the extent that new *in vitro* approaches and methodologies are developed pursuant to Section 27, EPA must take them into account in any standards rulemaking for chemicals under Section 4. Additionally, TSCA requires that the methods developed through the Section 27 vehicle be "inexpensive and efficient"—a requirement that dovetails with the NRC Vision approach of moving in the direction of cost-effective, high-throughput, mechanized methodologies where the science allows.

TSCA Section 27, then, gives EPA a tool for building and sustaining a research agenda that could be foundational in implementing the NRC Vision.[69] Ultimately, a wealth of new information must be developed and broadly shared.

This issue of full and fair access to the chemical data generated through the next toxicity testing paradigm is an important one. All such data should be placed in a publicly available database for easy access via the internet. While TSCA does not bar disclosure of health and safety studies or underlying data, the statute does provide for the protection of trade secrets and other "confidential business information" (CBI).[70] Historically, TCSA has been dogged by assertions that confidentiality claims are overused.[71] It remains to be seen whether TSCA's confidential business information protections and industry practice respecting confidentiality claims could slow or even hinder implementation of

grants and contracts to public and non-profit private entities. *Id.*

[68] *Id.*

[69] Of course, the question of whether EPA has the legal authority to undertake the relevant research agenda—it clearly does under TSCA Sections 10 and 27—is very different from the question of whether sufficient funding exists to support the agenda, or key parts of it. This issue is front and center at a time of highly constrained federal budgets—especially for EPA. *See, e.g.*, *2011 Budget Deal Would Slash EPA Budget 16 Percent*, REUTERS (Apr. 12, 2011), http://www.reuters.com/article/2011/04/12/us-usa-budget-epa-idUSTRE73B7NZ20110412.

[70] TSCA § 14(c), 15 U.S.C. § 2613(b).

[71] *See, e.g.*, TOXIC IGNORANCE, *supra* note 3, at 49 n.61 (referencing claims under TSCA that "underlying data" is confidential); *see also* LOWELL CTR. FOR SUSTAINABLE PROD., THE PROMISE AND LIMITS OF THE UNITED STATES TOXIC SUBSTANCES CONTROL ACT 4 (2003) (discussing industry reluctance to provide risk information and the "excessive use of confidential business information claims").

the NRC Vision by allowing industry to erect barriers to the high level of cooperation and data sharing that is needed to ensure the development of the proposed new testing paradigm.

In any event, changes in CBI practice already appear to be underway at EPA. In 2010, the agency instituted a policy to review confidentiality claims for chemical identities and data in health and safety studies submitted under TSCA.[72] More recently, EPA's list of regulatory actions initiated for February 2011 indicated that the agency is considering a rulemaking addressing the assertion of CBI claims under TSCA. According to this list:

> EPA is considering establishing regulations relating to claims for confidential business information (CBI) submitted under the Toxic Substances Control Act (TSCA) that would require the periodic reassertion and resubstantiation of such claims. Confidentiality claims which are not reasserted and resubstantiated would expire. EPA expects this action would increase transparency and availability of public health and environmental effects information on chemicals in commerce.[73]

This apparent trend toward a more rigorous treatment by EPA of CBI claims, coupled with the typically non-confidential nature of the data generated by *in vitro* testing, suggests that the CBI concern may not be a significant one with respect to implementation of the NRC Vision.

2. *Legislative History of TSCA*

The extent to which TSCA can support robust implementation of the NRC Vision is informed by not only the text of the law, but also a review of TSCA's legislative history. That is, what can we learn from reviewing the contemporary evidence of what legislators said they were doing and intended to accomplish when they enacted TSCA thirty-five years ago? In certain situations, U.S. courts can take into account legislative history when ruling on challenges to how a federal agency like EPA interprets and administers a law.[74] Relevant aspects of TSCA's legislative history

[72] *See* Claims of Confidentiality of Certain Chemical Identities Contained in Health and Safety Studies and Data from Health and Safety Studies Submitted Under the Toxic Substances Control Act, 75 Fed. Reg. 29754 (May 27, 2010).

[73] *See* CBI: Reassertion and Resubstantiation of Confidentiality Claims Submitted Under TSCA, 75 Fed. Reg. 29754 (proposed Jan. 21, 2010) (to be codified at 40 C.F.R § 2).

[74] *See* Chevron v. Natural Res. Def. Council, 467 U.S. 837 (1984).

reveal a series of themes that speak to the contemporary question of whether TSCA can support a modernized system of toxicity testing.

One theme is that for Congress in the 1970s, testing on animals was, not surprisingly, viewed as an accepted way of doing business that was expected to continue. For example, Representative Harley Staggers explained that "[t]he validity of applying animal test results to man is now firmly based upon empirical evidence and thus such results provide an invaluable tool for predicting human health effects."[75] Nevertheless, nothing in the legislative history of TSCA indicates that Congress believed that animal testing would forever remain the sole, or even primary, means of generating test data under the statute.

A second theme evident in TSCA's legislative history is that innovation in testing methodologies was expected in response to scientific advancements. Rep. Staggers explained: "[M]ajor methodological advances are occurring with respect to improving testing and monitoring methods for assessing the long-term effects of a chemical . . . . Analytical methods have improved as well."[76]

Congress appeared to understand at the time of TSCA's passage that, as a result of future scientific breakthroughs, the need for animal data would fade. Congress, however, was unwilling to bind EPA's hands with respect to the types of tests or testing that would be required under the law:

> The Committee considered and rejected an amendment [to TSCA Section 4(b)] which would have instructed the Administrator to give preference to tests which do not involve the use of animals if other tests provide an adequate and accurate means for ascertaining the effect of a chemical substance or mixture on health or the environment. The Committee determined not to so limit the Administrator's discretion since protection of human health demands that the

[75] H.R. REP. NO. 94-1341, at 5–6 (1976). *Accord First Session on S.776 to Regulate Commerce and Protect Human Health and the Environment by Requiring Testing and Necessary Use Restrictions on Certain Chemical Substances, and for Other Purposes Before the Subcomm. on Env't of the S. Comm. on Commerce*, 94th Cong. 236 (1975) (statement of Dr. Frank Rauscher, Director, National Cancer Institute) ("In the absence of clinical, epidemiologic or similar evidence of direct carcinogenic effect in man, laboratory animal studies constitute the classic and definitive procedure for determination of possible human carcinogenic hazards attributable to chemicals.").

[76] H.R. REP. NO. 94-1341, at 5–6 (1976).

> Administrator not be denied the best, most reliable data possible. *However the Committee does not intend that the Administrator needlessly require whole animal tests. The Administrator should consider alternative test methods. With the development of reliable non-animal tests for predicting the long-term effects of chemicals on health, the need for animal test data to determine if a substance or mixture causes or significantly contributes to an unreasonable risk will diminish.*[77]

Certain aspects of TSCA's legislative history further suggest that Congress believed EPA could use its TSCA authority to advance the field of toxicity testing, consistent with the NRC Vision. Representative Andrew Maguire, who proposed the amendment containing what is now TSCA Section 27, said:

> [W]hich tests, from among available test methods, might be ordered by the Administrator under [TSCA Section 4] authority[?] Recent developments in the field of toxicological testing have centered on the emergence of low-cost, short-term bacteriological and mammalian cell tests for mutagenicity. These tests show great potential for cutting down on the cost to all companies of testing their products to show what degree of hazard, if any, may be posed by their products . . . . My amendment [TSCA Section 27] authorizes [EPA and Health, Education, and Welfare] to conduct and make grants and contracts for continued research into the field of low-cost and efficient test methodologies.[78]

In support of his position, Rep. Maguire presented a letter from the Assistant Secretary for Health:

> We share your view that establishing the reliability of rapid bioassay tests is very likely to have a far-reaching impact on future regulatory decisions. . . . [W]ithin the Department the NIEHS [National Institute of Environmental Health Science] and the National Cancer Institute (NCI) are conducting and supporting most of the research and development in this area. . . . [The Department of Labor and the Department of Health favor] developing short term tests and establishing their acceptability as prescreens and possible alternatives . . . .[79]

A third relevant theme to emerge from TSCA's legislative

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[77] *Id.* at 19 (emphasis added).

[78] 122 CONG. REC. H27161 (daily ed. Oct. 11, 1976) (statement of Rep. Maguire).

[79] *Id.*

history, already made explicit in the passages cited above, is that the EPA Administrator enjoys broad discretion in establishing testing and data requirements under TSCA. It is noteworthy—and to many, perhaps, even surprising—that as early as the mid-1970s, a House floor debate on TSCA included lively exchanges on the question of whether the EPA Administrator should be *required* to consider and use non-animal alternative testing methods when they proved sufficiently accurate and adequate. As noted above, a proposed House amendment to this effect was rejected—ultimately, it appears, because legislators believed it could have potentially limited the Administrator's discretion. The back-and-forth between Congressmen on this point is instructive, and it demonstrates that the issue of pursuing alternatives to animal testing is far from new.[80]

[80] Representative Richard Ottinger proposed the following amendment to TSCA Section 4(b): "In prescribing tests, the Administrator, in his discretion shall give preference to available tests which do not involve the use of animals if such tests provide an adequate and accurate means for ascertaining the effect of a chemical substance or mixture on humans and the environment. *Id.* at 27163. The stated purpose was "to require the Administrator to consider alternative testing methods and direct him to use them when, in his discretion, he finds they are adequate and accurate" and to "minimize the pain and suffering administered to laboratory animals." *Id* .

Rep. Ottinger quotes Nobel-laureate biologist Dr. Renato Dulbecco, from *Science* Magazine, April 26, 1977, saying, "Identification by conventional (animal) tests is difficult because they are costly and laborious, but they can now be replaced by the bacterial tests for promutagens." *Id.* at 27177. Representative G. William Whitehurst rose in support of this amendment, saying, "[W]e probably cannot eliminate the use of animals altogether [but] I believe that we have a responsibility to limit the pain and suffering of animals used in laboratory experiments to the maximum feasible extent." *Id.*

Opposing the amendment was Representative Bob Eckhardt:

> [T]he Administrator usually does not come into the game early enough to determine what kind of tests are to be used, whether they are on animals or not on animals, because the Administrator ordinarily merely requires testing. He does not determine the precise nature of the tests in most instances. He only prescribes the tests to be applied to the extent necessary to assure that such data are reliable and adequate, the manner in which such data are to be developed, the specification of any test protocol or methodology to be employed in the development of such data, and such other requirements as are necessary to provide such assurance. . . . Ordinarily, the choice of use of tests is with the person producing the chemical.

Id. at 27178.

Rep. Ottinger countered that TSCA does in fact specify that the Administrator shall approve methodologies, that those methodologies include "whole animal tests," and, because EPA can recommend their use, the Administrator's

Taken as a whole, the legislative history of TSCA supports the idea that Congress was concerned about a long-term reliance on animal-based toxicology. It recognized that moving away from an animal-centered testing paradigm was possible, and perhaps desirable. As early as the 1970s, legislators understood that with the march of science and the development of new methodologies, toxicology would evolve. While Congress ultimately chose not to adopt a "technology-forcing" requirement mandating the adoption of non-animal testing, it spent time discussing whether this approach was desirable. Ultimately, Congress decided to provide flexibility to EPA so that the agency could choose the best science. Seen in this light, the NRC Vision is a result of a scientific evolution that is now bumping up against a longstanding regulatory system—and underlying regulatory inertia—that may slow and constrict the acceptance of the new toxicity testing methods.

3. *The Regulatory Framework for Toxicity Testing under TSCA*

Unlike TSCA itself, EPA's regulatory framework for toxicity testing under the statute reveals some barriers to implementing the NRC Vision. These can, however, be overcome at the agency level. Policy changes now underway are already creating new

recommendation as to such methodology should be tempered by Rep. Ottinger's amendment. *Id.* After a brief quarrel over the wisdom of this provision, Rep. Eckhardt asks, "Who is to determine whether other experimentation is adequate? Is it going to be the court, or is it going to be a scientist?" *Id.* Representative Edward Koch's reply: "It seems to me the amendment is very carefully drawn so as to allow that discretion to the Administrator, who certainly should know whether or not there are adequate substitutes." *Id.* He later adds:

> I repeat I am not an antivivisectionist. I am simply saying that there is a role here for lay persons and an opportunity for people to be interested in what is taking place in this field, and where we can explore any of these basic problems with non animal substitutes . . . then we should. Where it is not possible, and if the project is scientifically worthwhile—and I am not the one to suggest which projects are worthwhile; I am going to leave that to the Administrator—then obviously it should proceed.

Id. at 27179.

Concerns were then raised about the litigation the proposed amendment could trigger. *Id.* A further modification was offered to emphasize that the preference was to be given by the Administrator in his "sole" discretion. *Id.* However, further concerns arose as to whether any such language would sacrifice some discretion of the Administrator, or favor some animal lives over statistical human lives. The amendment, as modified, was rejected. *Id.* at 27180.

opportunities for implementation.

a. *EPA's Regulations*

EPA regulates toxicity testing under TSCA by way of a set of regulations that have undergone a notice-and-comment rulemaking process.[81] Relying primarily on its authority under Section 4 of TSCA,[82] EPA has issued the following categories of regulations to govern testing:

- Procedures Governing Testing Consent Agreements and Test Rules[83]
- Data Reimbursement[84]
- Good Laboratory Practice Standards[85]
- Provisional Test Guidelines[86]
- Chemical Fate Testing Guidelines[87]
- Environmental Effects Testing Guidelines[88]
- Health Effects Testing Guidelines[89]
- Identification of Specific Chemical Substance and Mixture Testing Requirements[90]

Although Section 4 is the key provision in TSCA concerning toxicity testing approaches, EPA's regulations convey the Agency's intent to accomplish testing through the use of enforceable consent decrees (rather than a TSCA Section 4 rulemaking) where a consensus exists "among EPA, affected manufacturers and/or processors, and interested members of the

[81] These rules are codified at 40 C.F.R. parts 790–799. They are available at *TSCA Section 4 Test Rules*, U.S. ENVTL. PROT. AGENCY, http://www.epa.gov/opptintr/chemtest/pubs/790_799.html (last visited Oct. 11, 2012).

[82] *See supra* Part I.A.1.a.

[83] 40 C.F.R. § 790 (2012).

[84] 40 C.F.R. § 791 (2012). This part was also enacted under EPA's authority under TSCA § 8, 15 U.S.C § 2607.

[85] 40 C.F.R.§ 792 (2012). Many of the provisions in this part detail how laboratory test animals are to be housed and maintained.

[86] 40 C.F.R. § 795 (2012). This part sets forth provisional guidelines on chemical fate, environmental effects, and health effects. All five of the health effects rules involve animal experimentation.

[87] 40 C.F.R. § 796 (2012). The regulations contained in this part cover tests involving physical and chemical properties, transport processes, and transformation processes.

[88] 40 C.F.R. § 797 (2012). The regulations contained in this part reflect EPA's aquatic testing guidelines and involve non-mammalian testing.

[89] 40 C.F.R. § 798 (2012).

[90] 40 C.F.R. § 799 (2012). This part was also enacted under EPA's authority under TSCA §§ 12, 26, 15 U.S.C §§ 2611, 2625.

public concerning the need for and scope of testing."[91]

While a handful of EPA regulations do provide for *in vitro* or non-mammalian approaches, EPA's regulatory framework as it pertains to toxicity testing is built on the more traditional animal-testing paradigm.[92] For example, EPA's health-effects testing regulations for chemicals cover subchronic exposures,[93] chronic exposures,[94] and specific organ and tissue toxicity.[95] Each of the studies described in these three categories of regulations requires the use of experimental animals.[96] EPA's health-effects testing regulations also cover genetic toxicity[97] and neurotoxicity.[98] Among the twelve studies set forth under the genetic toxicity regulations, six require the use of experimental animals; the remaining six do not, relying instead on insects and *in vitro* methods.[99] All of the neurotoxicity studies require the use of animals.[100]

EPA's regulations for individual chemicals and mixtures contain a set of twelve chemical-specific testing rules, each of which involves animal experimentation.[101] A set of four rules on multi-chemical testing[102] contains a single *in vitro* test.[103] Finally,

[91] 40 C.F.R. § 790.1(c) (2012).

[92] *See, e.g.*, 40 C.F.R. § 721.3 (2012) (defining "acutely toxic effects" for purposes of significant new uses of chemicals in terms of lethal-dose testing on exposed mammalian test animals).

[93] 40 C.F.R. § 798(C) (2012).

[94] 40 C.F.R. § 798(D).

[95] 40 C.F.R. § 798(E).

[96] Pursuant to EPA regulations, test sponsors may, under certain circumstances, request modifications to test standards or schedules. 40 C.F.R. § 790.55 (2012). This provision, however, is directed toward modifications on the order of altering test species, routes of administration, and schedule timelines; it does not appear to be a vehicle for changing test methodologies (e.g., from an *in vivo* test to a set of *in vitro* tests). *See also* 40 C.F.R. § 790.68 (2012) (changes in testing scope, standards, or schedules under consent agreements).

[97] 40 C.F.R. § 798(F).

[98] 40 C.F.R. § 798(G).

[99] *See* 40 C.F.R. §§ 798.5265 (the salmonella typhimurium reverse mutation assay), 798.5275 (sex-linked recessive lethal test in drosophila melanogaster), 798.5300 (detection of gene mutations in somatic cells in culture), 798.5375 (*in vitro* mammalian cytogenetics), 798.5500 (differential growth inhibition of repair proficient and repair deficient bacteria: bacterial DNA damage or repair tests), 798.5955 (heritable translocation test in drosophila malanogaster).

[100] 40 C.F.R. § 798(G).

[101] 40 C.F.R. § 799(B) (2012).

[102] 40 C.F.R. § 799(D).

[103] 40 C.F.R. § 799.5115 (chemical testing requirements for certain chemicals

among a set of twenty-four additional testing rules focusing on health effects, all but three of the rules involve animal experimentation.[104]

It is hardly surprising that EPA's current TSCA regulations are dependent on the longstanding paradigm of whole-animal testing serving as the driver of toxicity testing. Certainly EPA could, through one or more rulemakings, begin to significantly reshape this regulatory framework to accommodate robust implementation of the NRC Vision. For example, EPA could take one or more of the following actions: (1) open a rulemaking pursuant to TSCA Section 4 that expressly identifies how data generated from pathway testing will be used by the agency;[105] (2) carry out a "ground truthing" exercise by running animal tests and *in vitro* tests side by side; or (3) convene a group of legal and policy scholars to strengthen and continue the policy implementation that was outlined in the NRC Vision report.[106]

b. *EPA Policy*

The nuances of a federal agency's policy with respect to any issue can be discerned in a variety of ways. Aside from EPA's formally promulgated TSCA regulations, there are other indicators of the agency's position (and intentions) with respect to toxicity testing and risk assessment and the role for new *in vitro* methodologies and approaches. These indicia include, for example, the testing guidelines the agency has approved, the contents of interagency arrangements into which EPA has entered, and its public statements.[107]

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of interest to the Occupational Safety and Health Administration).

[104] The exceptions appear at 40 C.F.R. §§ 799.9510 (TSCA bacterial reverse mutation test), 799.9530 (TSCA *in vitro* mammalian cell gene mutation test), and 799.9537 (TSCA *in vitro* mammalian chromosome aberration test).

[105] *E.g.*, Bret C. Cohen, *Legal Obstacles Are Bumps, Not Roadblocks*, ENVTL. F., Mar./Apr. 2008, at 48 (arguing that EPA rulemaking under TSCA can help support implementation of NRC Vision).

[106] *E.g.*, E. Donald Elliott, *Needed: A Strategy for Implementing the Vision,* 29 RISK ANALYSIS 482, 482 (2009).

[107] In addition, an analysis of any relevant judicial decisions and the positions taken by EPA in response to petitions and in litigation would be informative. Such a review is outside of the scope of this article. Another means of discerning the contours and nuances of EPA policy here would be to conduct interviews with Agency staff. These activities may be a useful way to build on the existing research. For a relatively recent assessment by EPA of its implementation of toxics laws and programs, see generally OFFICE OF POLLUTION PREVENTION &

Going forward, it will also be important to monitor EPA's treatment of alternatives in the implementation of several large, ongoing chemical programs,[108] as well as other EPA initiatives that draw on the latest advances in toxicology.[109]

TOXICS, U.S. ENVTL. PROT. AGENCY, OVERVIEW: OFFICE OF POLLUTION PREVENTION AND TOXICS LAWS AND PROGRAMS (Mar. 2008), *available at* http://www.epa.gov/oppt/pubs/oppt101-032008.pdf.

[108] Since the 1990s, EPA has launched (and now supports) three large-scale chemical testing programs, each of which relies primarily on traditional whole-animal testing approaches for the development of toxicological data. One is the voluntary High Production Volume (HPV) Chemical Testing Program (http://www.epa.gov/HPV/pubs/general/basicinfo.htm), through which companies are "challenged" to make health and environmental effects data publicly available on chemicals produced or imported in quantities of one million pounds or more, annually. Another is the Endocrine Disruptor Screening Program (EDSP) (http://www.epa.gov/endo/), established by the Food Quality Protection Act of 1996, which calls for the screening of pesticides and other environmental contaminants for their potential to affect the endocrine systems of humans and wildlife. *But see* OFFICE OF INSPECTOR GENERAL, U.S. ENVTL. PROT. AGENCY, EPA'S ENDOCRINE DISRUPTOR SCREENING PROGRAM SHOULD ESTABLISH MANAGEMENT CONTROLS TO ENSURE MORE TIMELY RESULTS, EVALUATION REPORT NO. 11-P-0215 (May 3, 2011) ("Fourteen years after passage of the FQPA and Safe Drinking Water Act amendments, EPA's EDSP has not determined whether any chemical is a potential endocrine disruptor."). Finally, there is the Voluntary Children's Chemical Evaluation Program (VCCEP) (http://www.epa.gov/oppt/vccep/index.html), through which EPA asks companies that manufacture or import chemicals to which children have a high likelihood of exposure to voluntarily provide information on health effects, exposure, risk, and other data needs. Overall, EPA continues to grapple with chemical assessment and decision-making. Even as, for the first time ever, EPA uses its TSCA authority to create a list of "chemicals of concern"—see discussion of EPA "Chemical Actions Plans" at http://www.epa.gov/opptintr/existingchemicals/pubs/ecactionpln.html, and EPA's December 2009 press release on "Chemicals of Concern" at http://yosemite.epa.gov/opa/admpress.nsf/a543211f64e4d199852573590040444 2/2852c60dc0f65c688525769c0068b219!OpenDocument—this effort has encountered obstacles. *See, e.g.*, Maria Hegstad, *EPA Rethinks Chemical Action Plans to Bolster TSCA Regulatory Actions*, INSIDE EPA, Apr. 1, 2011, at 1 (EPA officials are "struggling to obtain adequate data from their chemical action plans to make precedent-setting regulatory decisions under [TSCA], prompting plans for new risk assessments to justify chemical management efforts and the possible slowing of development of new plans . . .").

[109] For example, EPA's ToxCast Program, launched in 2007, is "building computational models to forecast the potential human toxicity of chemicals." *ToxCast: Screening Chemicals to Predict Toxicity Faster and Better*, U.S. ENVTL. PROT. AGENCY, http://www.epa.gov/ncct/toxcast/ (last visited Oct. 12, 2012). ToxCast is an initiative of EPA's National Center for Computational Toxicology (NCCT), housed in EPA's Office of Research and Development (ORD) and located in Research Triangle Park, North Carolina. *See also* Richard Judson et al., *Analysis of Eight Oil Spill Dispersants Using Rapid, In Vitro Tests*

i. *Harmonized Testing Guidelines*

A key indicator of EPA policy on toxicity testing is the Series 870 Health Effects Test Guidelines issued by EPA's Office of Chemical Safety and Pollution Prevention (OCSPP).[110] EPA developed these guidelines to be used to satisfy the data and information requirements of *both* TSCA and FIFRA, and they have been harmonized with guidelines published by the Organization for Economic Cooperation and Development (OECD).[111]

The testing methodologies set forth in the Series 870 guidelines primarily reflect traditional mammalian approaches to toxicity testing. Although some of the guidelines do contain *in vitro* methodologies,[112] these appear to be the exception to the general rule. It is at this level of detail (i.e., the level of EPA-approved toxicity testing methodologies) that the policy underlying the NRC Vision must take hold, eventually replacing many existing animal-based tests with methodologies that focus instead on toxicity pathways.

ii. *Tox 21*

In 2008, EPA's Office of Research and Development (ORD) entered into a Memorandum of Understanding (MoU) with the National Institute of Environmental Health Sciences/National Toxicology Program (NTP) and the National Human Genome Research Institute (NHGRI)/NIH Chemical Genomics Center.[113] In

for Endocrine and Other Biological Activity, 44 ENVTL. SCI. & TECH. 5979, 5979–85 (2010); Jeremy Jacobs, *EPA Grants Contracts for Toxicity Testing*, E&E NEWS PM (Aug. 4, 2011), http://www.eenews.net/eenewspm/2011/08/04/9 (noting EPA's award of contracts under ToxCast to four companies for screening up to 10,000 chemicals for toxic effects).

[110] *See OCSPP Harmonized Test Guidelines, Series 870–Health Effects Tests Guidelines*, U.S. ENVTL. PROT. AGENCY (June 26, 2012), http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm. Note that this EPA office was previously known as the Office of Prevention, Pesticides and Toxic Substances.

[111] OECD GUIDELINES FOR THE TESTING OF CHEMICALS (2011), *available at* http://www.oecd-ilibrary.org/content/package/chem_guide_pkg-en.

[112] *See, e.g.*, *Id.* at Guideline 870.5300 (*in vitro* mammalian cell gene mutation test), Guideline 870.5375 (*in vitro* mammalian chromosome aberration test). Additionally, the guidelines do typically reflect EPA's stated intent to reduce the use of animals in toxicity testing. *E.g.*, *Id.* at Guideline 870.1100(d) (acute toxicity testing—background).

[113] Tripartite Memorandum of Understanding on High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings, between

2010, the Food and Drug Administration (FDA) formally joined this collaboration,[114] which is known as "Tox 21."[115]

Starting from the premise that "[t]he convergence of science, technology, regulatory need, and public opinion has produced an historic opportunity to transform toxicology and risk assessment into more accurate, rapid, and cost-effective sciences," the parties to Tox 21 explain their joint purpose as follows:

> to guide the construction and governance of a detailed research strategy to make the NRC Committee's vision a reality. [The] MoU builds on a number of separate and joint efforts among our organizations that are very much aligned with the NRC Committee's vision. Building on the strengths of the individual organizations is intended to facilitate the advancements necessary to move toxicology to a more predictive science based on the most relevant and meaningful tools of modern molecular biology and chemistry.[116]

Tox 21 holds substantial promise for the development of valuable, high-speed testing tools and methodologies.[117] An important factor in the implementation and ultimate success of Tox 21 (at least with respect to TSCA and FIFRA) may be the extent to which EPA's Office of Chemical Safety and Pollution Prevention becomes vested in the success of these MoUs—which were

Nat'l Inst. of Envtl. Health Scis., Nat'l Human Genome Research Inst. & U.S. Envtl. Prot. Agency Office of Research & Dev. (entered into on Feb. 14, 2008), *available at* http://www.niehs.nih.gov/news/assets/docs_f_o/high_throughput_screening_memorandum_of%20understanding_508.pdf.

[114] Memorandum of Understanding on High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings, between Nat'l Inst. of Envtl. Health Scis., Nat'l Human Genome Research Inst., U.S. Envtl. Prot. Agency Office of Research & Dev. & U.S. Food & Drug Admin. (announced on July 19, 2010), *available at* http://www.epa.gov/ncct/download_files/tox21/MOU_EPA-NTP-NCGC-FDA-Without-Signature-Page.pdf.

[115] *See Tox 21 Computational Toxicology Research Program*, U.S. ENVTL. PROT. AGENCY, http://www.epa.gov/ncct/Tox21/ (last visited June 27, 2012).

[116] *Memorandum of Understanding*, *supra* note 114, at 3. *See also* Francis S. Collins et al., *Transforming Environmental Health Protection*, 319 SCIENCE 906 (2008) (expressing joint view of representatives of EPA, NHGRI, and the NTP [in the authors' individual capacities] that these entities "are promoting the evolution of toxicology from a predominantly observational science at the level of disease-specific models *in vivo* to a predominantly predictive science focused on broad inclusion of target-specific, mechanism-based, biological observations *in vitro*").

[117] *See, e.g.*, Jeremy Jacobs, *Agencies hope robot can speed toxics evaluations, end animal testing*, NRDC GREENWIRE (May 12, 2011), http://www.eenews.net/Greenwire/2011/05/12/archive/4.

entered into by the EPA ORD. Full implementation of the NRC Vision will require not only robust interagency collaboration, but also close coordination between these two EPA offices. In other words, the scientific advances in toxicity testing that emerge from the Tox 21 program must be translated into tools that regulators use in making decisions. While this culture of translation is emerging,[118] it bears close scrutiny and nurturing in order that the NRC Vision moves expeditiously toward full implementation.

iii. *Public Statements by EPA*

EPA's current Administrator, Lisa Jackson, has been an advocate for reforming EPA's approach to regulating chemicals. In September 2009 she unveiled six principles for reauthorizing TSCA.[119] These principles are:

1. Chemicals Should Be Reviewed Against Safety Standards That Are Based on Sound Science and Reflect Risk-based Criteria Protective of Human Health and the Environment.
2. Manufacturers Should Provide EPA With the Necessary Information to Conclude That New and Existing Chemicals Are Safe and Do Not Endanger Public Health or the Environment.
3. Risk Management Decisions Should Take into Account Sensitive Subpopulations, Cost, Availability of Substitutes and Other Relevant Considerations.
4. Manufacturers and EPA Should Assess and Act on Priority Chemicals, Both Existing and New, in a Timely Manner.
5. Green Chemistry Should Be Encouraged and Provisions Assuring Transparency and Public Access to Information Should Be Strengthened.
6. EPA Should Be Given a Sustained Source of Funding for Implementation.[120]

These principles neither specifically embrace the role of alternatives to animal testing nor discuss the NRC Vision. Nevertheless, it seems clear that implementation of the NRC

[118] *Id*. *See also, e.g.*, Schwarzman & Wilson, *supra* note 14; Judson et al., *supra* note 109.

[119] *See* Press Release, U.S. Envtl. Prot. Agency, EPA Administrator Jackson Unveils New Administration Framework For Chemical Management Reform in the United States (Sept. 9, 2009), *available at* http://yosemite.epa.gov/opa/admpress.nsf/bd4379a92ceceeac8525735900400c27/d07993fdcf801c2285257640005d27a6!OpenDocument.

[120] *Id*.

Vision is consistent with these principles and their general approach to TSCA reauthorization. The NRC Vision advocates proactive, cost-effective decision-making based on the best science and scientific techniques.[121] In addition, the high-throughput *in vitro* tests advocated by the NRC Vision are well-suited to prioritization and tiered decision-making regimes.[122] The new testing technologies called for by the NRC Vision also qualify as "green chemistry," as that term is used by EPA in explaining these principles.[123]

At a 2010 symposium on toxicity testing reform convened by the authors, EPA then-Assistant Administrator for the Office of Chemical Safety and Pollution Prevention Steve Owens gave a keynote talk in which he stressed the agency's support for implementation of the reforms promoted by the NRC Vision.[124] Owens emphasized EPA's six principles of reform and stressed the need for solid science and accepted methods as well as having a scientific rationale that is "clear and transparent." He added,

> "[W]e also must be clear that we are absolutely committed to moving away from the traditional approaches for assessing toxicity to the new era of testing that utilizes more heavily high-throughput assays and computational methods . . . . We are committed to doing that . . . . Let me assure you that we are in this for the long haul and that we'll be right there with you as we all move forward to bring toxicity testing into the twenty-first century."[125]

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[121] *See* NRC VISION, *supra* note 8, at 23–25 (discussing risk assessment).

[122] *See* David M. Reif et al., *Endocrine Profiling and Prioritization of Environmental Chemicals Using ToxCast Data*, 118 ENVTL. HEALTH PERSP. 1714 (2010).

[123] Press Release, *supra* note 119 ("The goal of these [green chemistry] efforts should be to increase the design, manufacture, and use of lower risk, more energy efficient and sustainable chemical products and processes.").

[124] *See* Flyer for Symposium at the National Press Club in Washington, D.C., Chemical Toxicity Testing: The Future of Chemical Toxicity Testing in the U.S.: Creating a Roadmap to Implement the NRC's Vision and Strategy (Jun. 21, 2010), *available at* http://toxtestingdc.files.wordpress.com/2010/03/eli-ad.pdf.

[125] *Toxicity Testing: Symposium on Toxicity Testing, Realizing the National Research Council's Vision and Strategy*, ENVTL. F. Sept./Oct. 2010, at 55. For audio of Assistant Administrator Owens' talk, see Steve Owens, Assistant Adm'r, U.S. Envtl. Prot. Agency Office of Chem. Safety & Pollution Prevention, Keynote Address at Environmental Law Institute Conference, The Future of Chemical Toxicity in the US: Creating a Roadmap to Implement the NRC's Vision and Strategy (June 21, 2010), *available at* http://www.eli.org/audio/06.21.10dc/6.21.10.IntroductoryRemarks.mp3. For his prepared remarks, see

B. *FIFRA and the FFDCA (as Related to Pesticide Residues)*

Although TSCA establishes the principal legal framework under which industrial chemicals are regulated (and toxicity testing for those chemicals occurs), pesticides are treated separately and come within the purview of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).[126] Enacted in its modern form in 1972, FIFRA establishes the legal framework for pesticide regulation in the United States and, like TSCA, is administered by EPA.[127] The agency's authority under FIFRA is guided by what is essentially a balancing standard: the congressional mandate to prevent "unreasonable adverse effects on the environment" while taking into account the economic, social, and environmental costs and benefits of the use of any pesticide.[128] This standard is recited throughout the statute.[129]

Pesticides are further regulated under the Federal Food, Drug, and Cosmetic Act (FFDCA),[130] the relevant portions of which authorize EPA to issue regulations setting a tolerance, or limit, for the amount of pesticide chemical residue that may remain in or on food.[131] FIFRA and the FFDCA as they exist in their current form are the result of a major congressional overhaul of the pesticide laws by way of the Food Quality Protection Act of 1996 (FQPA).[132]

Steve Owens, Assistant Adm'r, U.S. Envtl. Prot. Agency, Office of Chem. Safety & Pollution Prevention, Keynote Address at Environmental Law Institute Conference, The Future of Chemical Toxicity in the US: Creating a Roadmap to Implement the NRC's Vision and Strategy (June 21, 2010), *available at* http://epa.gov/ocspp/pdfs/steveowens.eliconference.june212010.pdf.

[126] Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), 7 U.S.C. §§ 136–136y (2006).

[127] FIFRA § 25, 7 U.S.C. § 136w.

[128] "The term 'unreasonable adverse effects on the environment' means (1) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under [FFDCA § 408]." FIFRA § 2(bb), 7 U.S.C. § 136(bb).

[129] *E.g.*, FIFRA § 3(a), 7 U.S.C. § 136a(a) ("To the extent necessary to prevent unreasonable adverse effects on the environment, the Administrator may by regulation limit the distribution, sale, or use in any State of any pesticide that is not registered under [FIFRA] . . . .").

[130] Federal Food, Drug, and Cosmetic Act (FFDCA), 21 U.S.C. §§ 301–399d (2006).

[131] FFDCA § 408(b)(1), 21 U.S.C. § 346a(b)(1).

[132] Food Quality Protection Act of 1996, Pub. L. No. 104-170, 110 Stat. 1489

Unlike TSCA, FIFRA places the burden to demonstrate a chemical's safety on the manufacturer rather than on EPA.[133]

Existing pesticide laws present both potential opportunities and obstacles for implementing the NRC Vision, given their texts, legislative histories, and EPA's policy approach to toxicity testing for pesticides though regulations, guidelines, and other means. Certainly, neither FIFRA nor the FFDCA stands as a barrier to implementing the NRC Vision under current law.

1. *Key FIFRA & FFDCA Provisions Concerning Chemical Data and Testing*

Neither FIFRA nor the FFDCA contains provisions on chemical data and testing that approach the level of detail seen in TSCA Section 4.[134] Rather, each of the pesticide laws contains various, more modest provisions.

a. *FIFRA Provisions*

i. *Submission of Data and Studies*

EPA's primary regulatory tool under FIFRA is the authority to register a pesticide.[135] It is illegal to sell or distribute unregistered pesticides.[136] FIFRA requires EPA to register a pesticide if, among other things, it will perform its intended function and may be used without unreasonable adverse effects on the environment.[137]

The FIFRA registration procedure includes a data submission requirement.[138] The statute places the details of this process almost entirely within the discretion of the EPA Administrator, who "shall publish guidelines specifying the kinds of information which will

(1996). Prior to passage of the FQPA, FIFRA underwent significant amendment in 1975, 1978, 1988, 1990, and 1991. *See generally* ELIZABETH C. BROWN ET AL., PESTICIDE REGULATION DESKBOOK 10–11 (2001) (discussing legislative origins of FIFRA).

[133] *See* FIFRA § 3(c), 7 U.S.C. § 136a(c) (procedure for registration of pesticides).

[134] TSCA § 4, 15 U.S.C. § 2603. *See* discussion of TSCA Section 4 at *supra* Part I.A.3.a and accompanying notes.

[135] FIFRA § 3, 7 U.S.C. § 136a (registration of pesticides).

[136] FIFRA § 3(a), 7 U.S.C. § 136a(a).

[137] FIFRA § 3(c)(5)(C)-(D), 7 U.S.C. § 136a(c)(5)(C)-(D).

[138] FIFRA § 3(c)(2), 7 U.S.C. § 136a(c)(2).

be required to support the registration of a pesticide and shall revise such guidelines from time to time."[139] EPA may request of an applicant for registration "a full description of the tests made and the results thereof upon which the claims [regarding the pesticide] are based, or alternatively a citation to data that appear in the public literature or that previously had been submitted to the Administrator . . . ."[140] EPA may also, at any time, request the submission of additional data to maintain an existing registration of a pesticide.[141] This is known as a "data call-in."[142] And where other federal or state regulatory authorities also request data, EPA is required, to the extent practicable, to "coordinate data requirements, test protocols, timetables, and standards of review and reduce burdens and redundancy caused to the registrant by multiple requirements on the registrant."[143]

EPA also has the ability to initiate a public interim administrative review process with respect to a pesticide based on "a validated test or other significant evidence raising prudent concerns of unreasonable adverse risk to man or to the environment."[144]

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[139] FIFRA § 3(c)(2)(A), 7 U.S.C. § 136a(c)(2)(A). The statute does provide some basic guidance to the Administrator in establishing standards for data requirements for the registration of "minor use" pesticides—those for which total domestic crop production falls below a certain acreage threshold or whose uses provide insufficient economic incentive for a registrant to satisfy registration requirements. FIFRA § 2(*ll*), 7 U.S.C. § 136(*ll*) (definition of minor use). With respect to such minor uses, EPA must make the standards for data requirements "commensurate with the anticipated extent of use, pattern of use, the public health and agricultural need for such minor use, and the level and degree of potential beneficial or adverse effects on man and the environment. . . . In the development of these standards, the Administrator shall consider the economic factors of potential national volume of use, extent of distribution, and the impact of the cost of meeting the requirements on the incentives for any potential registrant to undertake the development of the required data." FIFRA § 3(c)(2)(A), 7 U.S.C. § 136a(c)(2)(A).

[140] FIFRA § 3(c)(1)(F), 7 U.S.C. § 136a(c)(1)(F). Additionally, EPA is authorized to issue an experimental use permit for a pesticide. If the pesticide contains a chemical that has not been included in a previously-registered pesticide, EPA may require that studies be conducted to detect whether the use of the pesticide under the permit may cause unreasonable adverse effects on the environment. FIFRA § 5(d), 7 U.S.C. § 136c(d).

[141] FIFRA § 3(c)(2)(B), 7 U.S.C. § 136a(c)(2)(B).

[142] *See* BROWN ET AL., *supra* note 132, at 32 (discussing data call-ins).

[143] FIFRA § 3(c)(2)(B)(viii)(I), 7 U.S.C. § 136a(c)(2)(B)(viii)(I).

[144] FIFRA § 3(c)(8), 7 U.S.C. § 136a(c)(8). FIFRA leaves it to EPA to define the terms "validated test" and "other significant evidence."

Amendments to FIFRA in 1988 established a process of re-registration for certain earlier-registered pesticides, with the aim of ensuring that they had been reviewed in light of then-current data and safety standards.[145] Among other requirements, FIFRA requires applicants for re-registration of a pesticide to submit summaries of previously-submitted studies concerning active ingredients, as well as a reformat of the data from each study summarized insofar as it concerns information about "chronic dosing, oncogenicity, reproductive effects, mutagenicity, neurotoxicity, teratogenicity, or residue chemistry of the active ingredient . . . ."[146]

EPA must ensure that there are no "outstanding data requirements" with respect to a pesticide.[147] Under FIFRA, an outstanding data requirement is a requirement for "any study, information, or data" that is necessary for EPA to make a determination as to pesticide registration, if the study, information, or data has either not been submitted or is determined by EPA to be invalid, incomplete, or inadequate.[148] In making this determination, EPA "shall examine, at a minimum, relevant protocols, documentation of the conduct and analysis of the study, and the results of the study to determine whether the study and the results of the study fulfill the data requirement for which the study was submitted . . . ."[149]

FIFRA provisions addressing data requirements present no barriers to implementation of the NRC Vision. Indeed, the flexibility that FIFRA affords to EPA and the authority that EPA possesses to call for additional data can facilitate implementation.

ii. *Developing the Necessary Research*

FIFRA requires EPA to undertake research (on its own, by grant, or by contract) to carry out the purposes of the law.[150] Additionally, EPA must undertake, in cooperation with other

[145] FIFRA § 4, 7 U.S.C. § 136a-1 (2006). *See also* BROWN ET AL., *supra* note 132, at 34 (discussing re-registration).

[146] FIFRA § 4(e)(1)(A)–(C), 7 U.S.C. § 136a-1(e)(1)(A)–(C). EPA was further required to issue guidelines to be followed by registrants in summarizing and reformatting studies. FIFRA § 4(e)(4), 7 U.S.C. § 136a-1(e)(4).

[147] FIFRA § 4(a)(1), 7 U.S.C. § 136a-1(a)(1).

[148] FIFRA § 2(ff)(1), 7 U.S.C. § 136(ff)(1).

[149] FIFRA § 2(ff)(2), 7 U.S.C. § 136(ff)(2).

[150] FIFRA § 20(a), 7 U.S.C. § 136r(a).

federal, state, and local agencies, pesticide monitoring activities in air, soil, water, humans, plants, and animals.[151] These legal authorities provide EPA with flexibility as it moves from the current system of toxicity testing to one more like that envisioned by the NRC.

FIFRA further makes significant human capital available to EPA. First, FIFRA establishes a seven-member Scientific Advisory Panel, from which EPA must solicit comments, evaluations, and recommendations "for operating guidelines to improve the effectiveness and quality of scientific analyses made by [EPA]" that lead to EPA decisions under FIFRA.[152] Among other requirements for panel membership, the panel must have multi-disciplinary composition, comprising representation from the disciplines of toxicology, pathology, environmental biology, and related sciences.[153]

The chair of the FIFRA Scientific Advisory Panel (SAP), in consultation with the EPA Administrator, may create "temporary subpanels on specific projects" to assist in the work of the full SAP.[154] A subpanel may be composed of scientists other than members of the full SAP, "as deemed necessary for the purpose of evaluating scientific studies relied upon by the Administrator with respect to proposed action."[155]

Second, with respect to human capital, the Food Quality Protection Act of 1996 added to FIFRA the requirement of a 60-member Science Review Board to assist in the work of the SAP.[156] Third, EPA is required by FIFRA to develop written procedures that "provide for peer review with respect to the design, protocols, and conduct of major scientific studies" conducted under FIFRA.[157]

FIFRA's mandate to EPA to draw upon the advice of a range of experts in the agency's decision-making processes makes available potent scientific expertise as the agency shifts its system

[151] FIFRA § 20(c), 7 U.S.C. § 136r(c).

[152] FIFRA § 25(d)(1), 7 U.S.C. § 136w(d)(1).

[153] *Id.* For more on the work and status of the FIFRA Scientific Advisory Panel, see *Scientific Advisory Panel*, U.S. ENVTL. PROT. AGENCY (Aug. 23, 2012), http://www.epa.gov/scipoly/sap/.

[154] FIFRA § 25(d)(1), 7 U.S.C. § 136w(d)(1).

[155] *Id.*

[156] FIFRA § 25(d)(2), 7 U.S.C. § 136w(d)(2).

[157] FIFRA § 25(e), 7 U.S.C. § 136w(e).

of toxicology testing toward a model that relies increasingly on advanced *in vitro* methodologies. In addition to working with the SAP and the Science Review Board in this regard, EPA could, through a consultation with the chair of the Panel, decide to convene one or more "temporary subpanels" on discrete aspects of the NRC Vision as they pertain to advancing toxicity pathway and other *in vitro* testing methodologies and approaches for pesticide chemicals.

It is equally true, however, that FIFRA's scientific panels could slow implementation of the NRC Vision if either: (1) EPA chooses not to actively engage the membership of the panels on issues pertaining to pathways-based alternatives, or (2) members of these panels are not ultimately supportive of the paradigm shift envisioned by the NRC. EPA could overcome this potential roadblock by appointing to the panels scientists who understand, appreciate, and utilize pathway-based approaches and the NRC Vision.

Information sharing also will be essential to implementation of the Vision under FIFRA, and the statute accommodates public dissemination and availability of most registration data. FIFRA does make an allowance for the protection of trade secrets and other confidential business information, but data and information generated for purposes of pesticide registration—as well as the underlying testing methodologies for pesticide chemicals and their effects—must be made available for disclosure to the public.[158]

b. *FFDCA Provisions (Relating to Pesticide Residues)*

i. *Submission of Data and Studies*

EPA may establish or leave in effect a tolerance for a pesticide chemical residue in or on a food only if it determines that

[158] Under FIFRA:

> All information concerning the objectives, methodology, results, or significance of any test or experiment performed on or with a registered or previously registered pesticide or its separate ingredients, impurities, or degradation products, and any information concerning the effects of such pesticide on any organism or the behavior of such pesticide in the environment, including, but not limited to, data on safety to fish and wildlife, humans and other mammals, plants, animals, and soil, and studies on persistence, translocation and fate in the environment, and metabolism, shall be available for disclosure to the public.

FIFRA § 10(d)(1), 7 U.S.C. § 136h(d)(1).

the tolerance, or pesticide residue limit, is safe—and EPA is required to modify or revoke a tolerance that it determines is not safe.[159] The term "safe" in this context means that EPA "has determined that there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information."[160]

Any person may petition EPA to issue a regulation establishing, modifying, or revoking a tolerance for a particular pesticide residue (or an exemption from a tolerance requirement).[161] A petition to establish a tolerance or exemption "shall be supported by such data and information as are specified in regulations issued by the Administrator," including, among other things:

- "full reports of tests and investigations made with respect to the safety of the pesticide chemical, including full information as to the methods and controls used in conducting those tests and investigations;"
- "full reports of tests and investigations made with respect to the nature and amount of the pesticide chemical residue that is likely to remain in or on the food, including a description of the analytical methods used;"
- any information that EPA may require as to whether "the pesticide chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects;" and
- any other data and information that EPA may by regulation require to support the petition.[162]

The FFDCA leaves to EPA the establishment by regulation of information and data requirements necessary to support a petition to modify or revoke a tolerance (or exemption).[163]

In making determinations with respect to a tolerance, EPA is required to consider the following factors, among others, specified by the FFDCA:

- "the validity, completeness, and reliability of the available

[159] FFDCA § 408(b)(2)(A)(i), 21 U.S.C. § 346a(b)(2)(A)(i).

[160] FFDCA § 408(b)(2)(A)(ii), 21 U.S.C. § 346a(b)(2)(A)(ii).

[161] FFDCA § 408(d)(1), 21 U.S.C. § 346a(d)(1).

[162] FFDCA § 408(d)(2)(A)(iv)–(v), (x), (xiii), 21 U.S.C. § 346a(d)(2)(A)(iv)–(v), (x), (xiii).

[163] FFDCA § 408(d)(2)(B), 21 U.S.C. § 346a(d)(2)(B).

data from studies of the pesticide chemical and pesticide chemical residue;"

- "the nature of any toxic effect shown to be caused by the pesticide chemical or pesticide chemical residue in such studies;"
- "available information concerning the relationship of the results of such studies to human risk;"
- "available information concerning the dietary consumption patterns of consumers (and major identifiable subgroups of consumers);"
- "available information concerning the cumulative effects of such residues and other substances that have a common mechanism of toxicity;"
- "available information concerning the aggregate exposure levels of consumers (and major identifiable subgroups of consumers) to the pesticide chemical residue and to other related substances, including dietary exposure under the tolerance and all other tolerances in effect for the pesticide chemical residue, and exposure from other non-occupational sources;"
- "available information concerning the variability of the sensitivities of major identifiable subgroups of consumers;"
- "such information as the Administrator may require on whether the pesticide chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effects;" and
- "safety factors which in the opinion of experts qualified by scientific training and experience to evaluate the safety of food additives are generally recognized as appropriate for the use of animal experimentation data."[164]

EPA is required to pay particular attention to information concerning the effects of exposure on infants and children.[165] In setting a tolerance, EPA is further allowed to take into account available data and information on both anticipated and actual (measured) residue levels of a pesticide level in or on food.[166] Similarly, under certain circumstances, EPA may, in assessing chronic dietary risk, consider available data and information on "the percent of food actually treated with the pesticide

[164] FFDCA § 408(b)(2)(D)(i)–(ix), 21 U.S.C. § 346a(b)(2)(D)(i)–(ix).
[165] FFDCA § 408(b)(2)(C), 21 U.S.C. § 346a(b)(2)(C).
[166] FFDCA § 408(b)(2)(E)(i), 21 U.S.C. § 346a(b)(2)(E)(i).

chemical."[167]

The FFDCA, as amended by the Food Quality Protection Act of 1996, grants EPA the power to take into account substantial, real-world exposure data. This wide range of factors established by the FFDCA for consideration in tolerance-setting aligns with the NRC Vision and its risk contexts component.[168]

If EPA determines that additional information or data are reasonably necessary to support the continuation of a tolerance or an exemption from a tolerance, the FFDCA gives EPA several options. These include issuing a notice requiring the pesticide registration holder to submit the data under Section 3 of FIFRA or issuing a new testing requirement rule under Section 4 of TSCA.[169]

In sum, the key provisions in U.S. federal law governing tolerances for pesticide residues in food present no hurdles to implementation of the NRC Vision. Indeed, the relevant provisions of the FFDCA are consistent with both the Vision's aims and its focus on human toxicology.

ii. *Developing the Necessary Research*

The Food Quality Protection Act of 1996 amended the FFDCA to require EPA to establish a new screening program for estrogenic substances.[170] Using "appropriate validated test systems and other scientifically relevant information," EPA is required to determine "whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen" or other endocrine effects.[171]

In implementing this program, EPA is required to provide for the testing of all pesticide chemicals, and may also provide for the testing of other substances that "may have an effect that is cumulative to an effect of a pesticide chemical," if a substantial population may be exposed.[172] EPA may order the appropriate party (e.g., a pesticide registrant, manufacturer, or importer) to conduct the required testing and provide the resulting information

[167] FFDCA § 408(b)(2)(F), 21 U.S.C. § 346a(b)(2)(F).

[168] *See* NRC VISION, *supra* note 8, at 49.

[169] FFDCA § 408(f), 21 U.S.C. § 346a(f).

[170] FFDCA § 408(p), 21 U.S.C. § 346a(p).

[171] FFDCA § 408(p)(1), 21 U.S.C. § 346a(p)(1). *See also Endocrine Disruptor Screening Program*, U.S. ENVTL. PROT. AGENCY (Aug. 11, 2011), http://www.epa.gov/endo/pubs/edspoverview/primer.htm#3.

[172] FFDCA § 408(p)(3), 21 U.S.C. § 346a(p)(3).

to EPA.[173] To the extent practicable, EPA is required to minimize testing of the same substance for the same endocrine effect.[174]

These testing provisions suggest no limitations on EPA in pursuing implementation of the NRC Vision. The provisions may, in fact, provide an opportunity with respect to implementation—insofar as there is a mandate to minimize redundancy in effects testing (thus also potentially reducing the number of animals sacrificed).

2. *Legislative History of FIFRA and the Food Quality Protection Act of 1996*

Research on the legislative history of FIFRA, as enacted in 1972,[175] discloses no indication that Congress intended to limit toxicity testing methodologies available under the pesticide laws to those relying exclusively on the use of animals. Nor, on the other hand, does the legislative history suggest any intent by Congress to move away from animal testing. Unlike the legislative history supporting TSCA, FIFRA's legislative history reveals little about congressional intent regarding chemical testing.

Similarly, our research on the legislative history of the Food Quality Protection Act, which amended FIFRA and portions of the FFDCA, reveals no indication that Congress intended to limit toxicity testing methodologies available under the pesticide laws to those depending on the use of animals. Congress probably assumed a continued reliance on whole-animal testing while recognizing that EPA has the authority to set data-requirement standards under FIFRA.[176] The House Report accompanying the bill does reveal concerns that outdated testing requirements were contributing to a backlog of pesticide registrations.[177]

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[173] FFDCA § 408(p)(5)(A), 21 U.S.C. § 346a(p)(5)(A).

[174] FFDCA § 408(p)(5)(B), 21 U.S.C. § 346a(p)(5)(B).

[175] Research into the legislative history of subsequent amendments to FIFRA is beyond the scope of this article.

[176] *See, e.g.*, 142 CONG. REC. S8736 (daily ed. July 24, 1996) (discussing heightened uncertainty factors when using No Observed Effect Levels derived from animal testing to set child-safe standards); H.R. REP. NO. 104-699, pt. 1, at 56 (1996) (noting expectation that EPA will set data-requirement standards for endocrine disruptors within four years of enactment of FQPA under FIFRA §§ 3–4). *See also* FFDCA § 408(b)(2)(D)(ix), 21 U.S.C. §346a(b)(2)(D)(ix) (recommending EPA consider safety factors generally recognized as appropriate for animal experimental data).

[177] *See, e.g.*, H.R. REP. NO. 104-699, pt. 2, at 30–31 (1996) (noting that

3. *The Regulatory Framework for Toxicity Testing under FIFRA & the FFDCA (as Amended by the FQPA)*

As is the case with TSCA, the present FIFRA/FFDCA regulatory framework for toxicity testing presents obstacles to implementing the NRC Vision. Again, however, these barriers can be overcome through administrative action by EPA.

a. *EPA's Regulations*

EPA regulates toxicity testing under FIFRA and the pesticide residue provisions of the FFDCA by way of a set of formal regulations that have undergone a notice-and-comment rulemaking process.[178] Exercising its range of authority under FIFRA[179] and Section 408 of the FFDCA,[180] EPA has issued the following categories of regulations with respect to testing:

- General Provisions[181]
- How to Use Data Tables[182]
- Experimental Use Permits[183]
- Product Chemistry[184]

compilation of health and environmental data costs a registrant on average $8 million and takes five years); H.R. REP. NO. 104-699, pt. 1, at 122 (1996) (statement of Rep. George E. Brown, Jr.) (raising concerns about the backlog of registrations and noting that more scientific information results in ever-greater testing burdens). A relevant historical point bears noting: a 1954 amendment to the FFDCA, known as the Miller Amendment, inserted into the law a provision on pesticide residues that required manufacturers to supply scientific data on the toxicity of a chemical to "warm-blooded animals." This provision was eventually removed through the enactment of the Food Quality Protection Act of 1996. *See* Pub. L. No. 83-518, § 3, 68 Stat. 511 (1954) (codified at 21 U.S.C. § 346a(a) (1994)), *repealed by* Food Quality Protection Act of 1996, Pub. L. No. 104-170, 110 Stat. 1514.

[178] *See* 40 C.F.R. § 158 (2012); *Data Requirements for Pesticide Registration*, U.S. ENVTL. PROT. AGENCY (May 9, 2012), http://www.epa.gov/pesticides/regulating/ data_requirements.htm.

[179] FIFRA §§ 2–34, 7 U.S.C. §§ 136–136y.

[180] FFDCA § 408, 21 U.S.C. § 346a.

[181] 40 C.F.R. § 158(A). One of the regulations in this subpart includes a table containing instructions on how the results of various animal studies should be presented to EPA. 40 C.F.R. § 158.34 (flagging of studies for potential adverse effects). *See also* 40 C.F.R. § 160 (containing EPA's regulations on good laboratory practice standards. These include requirements for the proper housing and maintenance of test animals). *E.g.*, 40 C.F.R. § 160.90.

[182] 40 C.F.R. § 158(B).

[183] 40 C.F.R. §158(C). Various kinds of toxicology data required to support experimental use permits are derived from mammalian testing. *E.g.*, 40 C.F.R. § 158.230.

- Product Performance[185]
- Toxicology[186]
- Ecological Effects[187]
- Human Exposure[188]
- Spray Drift[189]
- Environmental Fate[190]
- Residue Chemistry[191]
- Biochemical Pesticides[192]
- Microbial Pesticides[193]
- Antimicrobial Pesticides[194]

Together, these regulations establish "the minimum data and information" typically required by EPA to support an application for pesticide registration or re-registration, the maintenance of a pesticide registration, or the setting of a pesticide residue tolerance.[195]

As with the regulatory structure EPA has established for toxicity testing under TSCA,[196] EPA's regulatory scheme for pesticides is heavily dependent on results derived from animal experimentation. The primary "toxicology" regulations include a table setting forth a range of toxicity data requirements.[197] With

[184] 40 C.F.R. § 158(D).

[185] 40 C.F.R. § 158(E).

[186] 40 C.F.R. § 158(F).

[187] 40 C.F.R. § 158(G). One regulation in this part sets forth testing requirements on a range of aquatic, terrestrial, and avian organisms. 40 C.F.R. § 158.630(d).

[188] 40 C.F.R. § 158(K).

[189] 40 C.F.R. § 158(L).

[190] 40 C.F.R. § 158(N).

[191] 40 C.F.R. § 158(O).

[192] 40 C.F.R. § 158(U). Data requirements depend heavily on animal testing, however, there are *in vitro* methodologies (e.g., mutagenicity testing: *in vitro* mammalian cell assay). 40 C.F.R. § 158.2050(d).

[193] 40 C.F.R. § 158(V). Data requirements depend heavily on animal testing. *E.g.*, 40 C.F.R. § 158.2140(c) (microbial pesticides toxicology data requirements).

[194] 40 C.F.R. § 161 (2012).

[195] 40 C.F.R. § 158.1(b)(1). Additionally, EPA has issued a separate set of detailed regulations addressing pesticide residue tolerances (and exemptions). *See generally* 40 C.F.R. § 180. Aspects of these regulations, not surprisingly, are correlated to toxicity testing in animals. *E.g.*, 40 C.F.R. § 180.1(j) (defining term "negligible residue" with reference to feeding studies performed on sensitive animal species).

[196] *See supra* Part I.A.3.a and accompanying notes.

[197] 40 C.F.R. § 158.500 (toxicology data requirements table). *See also* 40

rare exception,[198] the table specifies the use of animal experimentation methodologies.

EPA also has promulgated regulations on pesticide classification that expressly rely on results of lethal-dose testing as a means of determining whether to designate a pesticide as "restricted use."[199] Similarly, lethal-dose tests are among those whose results must be reported by a pesticide registrant to EPA as part of the registrant's duty to submit information regarding unreasonable adverse effects of a pesticide on the environment.[200]

As under TSCA, EPA has promulgated regulations pursuant to FIFRA and the FFDCA that are grounded mainly in *in vivo* testing. However, EPA's regulations emphasize the agency's flexibility under FIFRA with respect to requiring data and information and EPA notes that it will update its regulatory testing framework as necessary "to reflect evolving program needs and advances in science."[201]

Overall, this regulatory framework, as presently constructed, presents a challenge to implementation of the NRC Vision. At a minimum, implementing broad toxicity testing reform under FIFRA will require a major shift in the way in which the Agency conceives its regulatory testing requirements and reviews test results supplied by regulated industry. It will also require that EPA build an intellectual bridge to connect the current animal toxicology-centered framework with the evolving pathways framework consistent with the NRC Vision. This bridge must provide continuity in understanding how the presently available data, obtained through animal toxicology, can be used side-by-side with the information generated by newer, *in vitro* methods.

b. *EPA Policy/Harmonized Testing Guidelines*

As is the case with EPA testing policy under TSCA,[202] EPA policy under FIFRA and the FFDCA is manifested by the harmonized Series 870 Health Effects Test Guidelines issued by

C.F.R. § 158.510 (tiered testing options for nonfood pesticides).

[198] *E.g.*, 40 C.F.R. § 158.500(d) (mutagenicity testing: *in vitro* mammalian cell assay).

[199] *See* 40 C.F.R. §§ 152.170 (2012) (criteria for restriction to use by certified applicators), 152.3 (related definitions).

[200] 40 C.F.R. § 159.165 (2012) (toxicological and ecological studies).

[201] 40 C.F.R. § 158.30(a), (c) (2012).

[202] *See supra* Part I.A.3.b and accompanying notes.

EPA's Office of Chemical Safety and Pollution Prevention.[203] As previously noted, this current package of testing guidelines—rooted in traditional whole-animal testing methodologies—poses a challenge to implementation of the NRC Vision.

II. INCENTIVES TO MODERNIZE CHEMICAL TESTING: TSCA REFORM, THE ENDOCRINE DISRUPTOR SCREENING BILL, AND INTERNATIONAL HARMONIZATION OF TESTING

Looking beyond the current state of chemical regulation in the United States, there are at least three other emblematic legal efforts that could serve to hasten implementation of the NRC Vision and toxicity testing reform. The first is a long-awaited reauthorization of TSCA. The second is a legislative attempt to enhance endocrine disruptor screening in drinking water. The third is a shift by the European Union away from animal testing. We briefly discuss each in turn.

A. *TSCA Reform—The Safe Chemicals Act of 2011*

Less than a decade after the passage of TSCA, the National Research Council of the National Academy of Sciences published a study indicating that the amount and quality of toxicological information available about most chemicals in commerce was inadequate. This report, *Toxicity Testing: Strategies to Determine Needs and Priorities*,[204] selected 675 of the more than 65,000

[203] *See OCSPP Harmonized Test Guidelines, Series 870—Health Effects Tests Guidelines*, U.S. ENVTL. PROT. AGENCY (June 26, 2012), http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm.

[204] *See generally* NRC STRATEGIES, *supra* note 2, at 1. According to the report abstract:

> A "select universe" of 65,725 substances that are of possible concern to the National Toxicology Program (NTP) because of their potential for human exposure was identified. Through a random sampling process, 675 substances covering seven major intended-use categories were selected. From this sample, a subsample of 100 substances was selected by screening for the presence of at least some toxicity information. In depth examination of this subsample led to the conclusion that enough toxicity and exposure information is available for a complete health-hazard assessment to be conducted on only a small fraction of the subsample. On the great majority of the substances, data considered to be essential for conducting a health-hazard assessment are lacking. By inference, similar conclusions were made for the select universe from which the sample and the subsample were drawn. This report presents criteria for selecting substances and determining toxicity testing needs,

substances of concern because of their potential for human exposure. This subset was chosen from several categories, including pesticides, cosmetic ingredients, food additives, and chemicals in commerce. Based on an analysis of this sample, the report concludes that data for conducting a health hazard assessment was lacking for the great majority of these compounds. Approximately a decade later, the Environmental Defense Fund studied this issue and published a report that showed even the most basic toxicity testing results are unavailable for 75% of compounds used in commerce.[205]

Both of these studies indicate that the toxicity knowledge base for most of the compounds currently in the environment is inadequate. This inability to collect even the most rudimentary information has been attributed to some extent to the way in which the U.S. toxic chemicals laws, especially TSCA, are written.[206]

Faced with this and other perceived shortcomings of this law, and pushed by stakeholders, various members of Congress have embarked on efforts to amend TSCA. The current TSCA reform bill candidate, the Safe Chemicals Act of 2011, was introduced by Senator Frank Lautenberg.[207] The bill, if passed in its present form, would effect a significant overhaul of TSCA, whose key provisions have remained unchanged since the law was enacted over thirty years ago. The bill would, in essence, shift the burden of proving the safety of existing chemicals from EPA to industry. More specifically, according to Sen. Lautenberg, the new bill is designed to:

- Ensure that EPA has information on the health risks of all chemicals by requiring chemical companies to develop and

provides estimates of those needs, and describes some useful criteria for assigning priorities for toxicity testing.

[205] *See supra* note 3 (discussing the TOXIC IGNORANCE report).

[206] *See, e.g.*, *supra* notes 2–5 and accompanying text.

[207] S. 847, 112th Cong. (2011). Various TSCA reform bills have emerged from both Houses of Congress in recent years, including the Safe Chemicals Act of 2010, S. 3209, 111th Cong. (2010), and the Toxic Chemical Safety Act of 2010, H.R. 5820, 111th Cong. (2010). The Lautenberg bill was approved by the Senate Committee on Environment and Public Works on July 25, 2012, and at the time of publication, the bill was awaiting consideration by the Senate as a whole. Press Release, U.S. Sen. Comm. on Env't & Pub. Works, Chairman Boxer Lauds EPW Committee's Approval of Major Toxic Chemicals Reform and Wildlife Measures (July 25, 2012), *available at* http://epw.senate.gov/public/index.cfm?FuseAction=PressRoom.PressReleases&ContentRecord_id=BF8BF313-802A-23AD-40CA-09A3022EF8DF.

> submit a minimum data set for each chemical they produce; while EPA can access information more easily, the bill contains provisions to ensure that no duplicative or unnecessary testing occurs, and that EPA accepts and encourages the use of rapid, low-cost, non-animal tests that provide high quality data.
> - Require EPA to prioritize chemicals based on risk;
> - Expedite action to reduce risk from chemicals of highest concern;
> - Further evaluate chemicals that could pose unacceptable risk, with chemicals that present uncertainty about their ability to meet the safety standard being placed into the category of chemicals requiring a safety standard determination;
> - Provide broad public, market and worker access to reliable chemical information; and
> - Promote innovation, green chemistry, and safer alternatives to chemicals of concern.[208]

Importantly, the bill contains multiple provisions that would facilitate implementation of the NRC Vision. For example, in amending TSCA to require rules establishing the minimum data set requirements for chemicals, the bill mandates that EPA ". . . encourage and facilitate the use of alternative testing methods and testing strategies to generate information quickly, at low cost, and without the use of animal-based testing, including toxicity pathway-based risk assessment, *in vitro* studies, systems biology, computational toxicology, bioinformatics, and high-throughput screening."[209]

This language certainly alerts EPA to the need to consider alternatives if they are available. Under the bill, EPA's duty is articulated through the permissive terms "encourage and facilitate;" however, to implement the NRC Vision, more than hortative language is required. To ensure success of the paradigm shift for testing, EPA and other regulatory agencies must be charged explicitly with implementing the NRC Vision. Developing, validating, and utilizing *in vitro* toxicology should be

[208] OFFICE OF SENATOR LAUTENBERG, SAFE CHEMICALS ACT OF 2011 (2011), *available at* http://lautenberg.senate.gov/assets/SafeChem-Summary.pdf. *See also* RICHARD DENISON, ENVTL. DEF. FUND, SUMMARY OF CHANGES IN SAFE CHEMICALS ACT OF 2011 V. 2010 (2011), *available at* http://blogs.edf.org/nanotechnology/files/2011/05/Summary-of-key-changes-in-Safe-Chemicals-Act-of-2011-vs.-2010-v2.pdf.

[209] S. 847 § 5 (amending TSCA by adding new § 4(a)(1)(B)(iv)).

included within that charge. Absent a legal requirement to undertake this task, progress made toward implementation of the NRC Vision might stall or even end.

In prescribing methodologies in standards for test rules or orders issued under the proposed law, the Administrator may use *in vitro* or whole animal tests—but the latter may be used only in compliance with another new section of the law that would address the reduction of animal-based testing.[210] Ultimately, new TSCA § 30 would be the centerpiece of how the Safe Chemicals Act of 2011 implements the NRC Vision.[211] The amendments would:

[210] *Id.* § 5 (amending TSCA by adding new § 4(c)(3)(B)(i)(IV)–(V), which allows the use of whole animal tests only if they are consistent with new § 30, added by S. 847 § 26).

[211] The full text of § 30 is as follows:

> (a) ADMINISTRATION.—The Administrator shall take action to minimize the use of animals in testing of chemical substances or mixtures, including—
>
> (1) encouraging and facilitating, to the maximum extent practicable—
>
> (A) the use of existing data of sufficient scientific quality;
>
> (B) the use of test methods that eliminate or reduce the use of animals while providing data of high scientific quality;
>
> (C) the grouping of 2 or more chemical substances into scientifically appropriate categories in cases in which testing of 1 chemical substance would provide reliable and useful data on others in the category;
>
> (D) the formation of industry consortia to jointly conduct testing to avoid unnecessary duplication of tests; and
>
> (E) the parallel submission of data from animal-based studies and from emerging methods and models; and
>
> (2) funding research and validation studies to reduce, refine, and replace the use of animal tests in accordance with this subsection.
>
> (b) INTERAGENCY SCIENCE ADVISORY BOARD ON ALTERNATIVE TESTING METHODS.—
>
> (1) ESTABLISHMENT.—Not later than 90 days after the date of enactment of the Safe Chemicals Act of 2011, the Administrator shall establish an advisory board to be known as the 'Interagency Science Advisory Board on Alternative Testing Methods' (referred to in this subsection and subsection (c) as the 'Board').
>
> (2) COMPOSITION.—The Administrator shall—
>
> (A) appoint the members of the Board, including, at a minimum, representatives of—
>
> (i) the National Institute of Environmental Health Sciences;
>
> (ii) the Centers for Disease Control and Prevention;
>
> (iii) the National Toxicology Program;
>
> (iv) the National Cancer Institute; and
>
> (v) the National EPA-Tribal Science Council; and
>
> (B) ensure that no individual appointed to serve on the Board has a conflict of interest that is relevant to the functions to be

performed, unless—

(i) the individual promptly and publicly discloses the conflict; and

(ii) the Administrator determines that the conflict is unavoidable.

(3) PURPOSE.—The purpose of the Board shall be to provide independent advice and peer review to Congress and the Administrator on the scientific and technical aspects of issues relating to the implementation of this title with respect to minimizing the use of animals in testing chemical substances or mixtures.

(4) APPLICABLE LAW.—The Board shall be subject to subchapter II of chapter 5, and chapter 7, of title 5, United States Code (commonly known as the 'Administrative Procedure Act').

(5) REPORT.—Not later than 1 year after the date of enactment of the Safe Chemicals Act of 2011, and every 3 years thereafter, the Administrator, in consultation with the Board, shall publish in the Federal Register a list of testing methods that reduce the use of animals in testing under section 4.

(c) IMPLEMENTATION OF ALTERNATIVE TESTING METHODS.—To promote the development and timely incorporation of new testing methods that are not animal based, the Administrator shall—

(1) in consultation with the Board, and after providing an opportunity for public comment, develop a strategic plan to promote the development and implementation of alternative test methods and testing strategies to generate information used for safety standard determinations under section 6(b) that do not use animals, including toxicity pathway based risk assessment, in vitro studies, systems biology, computational toxicology, bioinformatics, and high-throughput screening;

(2) beginning on the date that is 2 years after the date of enactment of the Safe Chemicals Act of 2011 and every 2 years thereafter, submit to Congress a report that describes the progress made in implementing this section; and

(3) fund and carry out research, development, performance assessment, and translational studies to accelerate the development of test methods and testing strategies that are not animal-based for use in safety standard determinations under section 6(b).

(d) CRITERIA FOR ADAPTING OR WAIVING ANIMAL TESTING REQUIREMENTS.—On request from a manufacturer or processor that is required to conduct animal based testing of a chemical substance or mixture under this title, the Administrator may adapt or waive the animal testing requirement if the Administrator determines that—

(1) there is a sufficient weight of evidence from several independent sources of information to support a conclusion that a chemical substance or mixture has, or does not have, a particular property, in any case in which the information from each individual source alone is regarded as insufficient to support the conclusion;

(2) because of 1 or more physical or chemical properties of the chemical substance or mixture, testing for a specific endpoint is technically not practicable to conduct; or

(3) a chemical substance or mixture cannot be tested in animals at

- Require EPA to take action to minimize the use of animals in testing, through various technical and funding approaches;[212]
- Require EPA to establish an interagency science advisory board on alternative testing methods;[213]
- Require EPA to promote the development and timely incorporation of new test methods that are not animal-based;[214] and
- Waive an animal testing requirement on behalf a manufacturer or processor, where certain requirements are satisfied.[215]

In particular, one of the new provisions would require EPA to develop a "strategic plan to promote the development and implementation of alternative test methods and testing strategies to generate information used for safety standard determinations under [TSCA] section 6(b) that do not use animals, *including toxicity pathway based risk assessment, in vitro studies, systems biology, computational toxicology, bioinformatics, and high-throughput screening*."[216] Again, while this language is a clear and unmistakable nod toward the need to reform toxicity testing as set out in the NRC Vision, it does not go far enough.

From the perspective of implementing the NRC Vision, the bill shows clear promise. As discussed above, however, we believe that more assertive provisions are necessary (likely by way of non-discretionary duties placed on EPA) to ensure that the chemical testing reform policy that the bill seems to envision actually takes hold. In addition, some other caveats are necessary. First, the Safe Chemicals Act of 2011 is but one possible vehicle for an amended toxic chemicals law, and the contours of legislative reform will no doubt be subject to extensive give and take among stakeholders before anything like a final bill is considered by Congress or the President.[217] Second, as noted above, the encouraging aspects of

> concentrations that do not result in significant pain or distress, because of physical or chemical properties of the chemical substance or mixture, such as potential to cause severe corrosion or severe irritation to tissues.

Id. § 26 (amending TSCA by adding new § 30).

[212] *Id.* § 26 (amending TSCA by adding new § 30(a)).

[213] *Id.* § 26 (amending TSCA by adding new § 30(b)).

[214] *Id.* § 26 (amending TSCA by adding new § 30(c)).

[215] *Id.* § 26 (amending TSCA by adding new § 30(d)).

[216] *Id.* § 26 (amending TSCA by adding new § 30(c)(1) (emphasis added).

[217] Cal Dooley, president of the American Chemistry Council, the principal chemical industry trade association, said of Sen. Lautenberg's April 2011 bill:

the proposed new TSCA § 30 are couched in permissive, not mandatory, directives to the EPA Administrator: i.e., "encourag[e] and facilitat[e], to the maximum extent practicable;" "promote;" "accelerate;" and "may adapt or waive." As written, the bill nudges public policy in the direction of the toxicity testing future envisioned by the NRC. Instead, to greatly increase the odds of testing reform succeeding, we believe that the bill should insist on toxicity testing reform and expressly vest in EPA direct responsibility for implementing the NRC Vision.

It has been argued that the best route to implementing the NRC Vision is not a new legislative mandate, but rather an iterative, trial-and-error approach rooted in traditional federal agency administrative processes.[218] While sustained and robust administrative implementation efforts are necessary, it also seems clear that significant amendments to TSCA present an important opportunity to place the weight of a congressional imprimatur squarely behind the NRC Vision. More to the point, an amendment to TSCA that shifts to industry the burden to prove the safety of chemicals and affixes new, hard timelines—but does not incorporate aspects of the NRC Vision—could well lock in the status quo for whole-animal toxicity testing as industry and regulators race to catch up with an enormous backlog of untested chemicals using traditional toxicological methods. While we have argued that amending TSCA is not a pre-requisite to implementing the NRC Vision (in light of current law), it is nevertheless likely that amending TSCA *without* including drivers toward chemical testing reform could so de-prioritize toxicity testing reform as to jeopardize the long-term success of the NRC Vision.

B. *The Endocrine Disruptor Screening Enhancement Act of 2011*

Other potential legislative reforms also present opportunities for driving the modernization of toxicity testing.

"Unfortunately, it appears many of our concerns have not been addressed in this new version [of the TSCA reform bill], and the bill . . . could put American innovation and jobs at risk." Jeremy Jacobs, *Lautenberg tries again on TSCA reform legislation*, E&E NEWS PM (April 14, 2011), http://www.eenews.net/public/eenewspm/2011/04/14/4. Similarly, Christine Sanchez of the Society of Chemical Manufacturers and Affiliates, while calling for modernization of TSCA, nonetheless said that "[s]weeping changes like the ones proposed in this bill would negatively impact innovation and hasten the off-shoring of jobs." *Id.*

[218] *See, e.g.*, Cohen, *supra* note 105; Elliott, *supra* note 106.

In February 2011, for example, Representative Edward Markey introduced H.R. 553, the Endocrine Disruptor Screening Enhancement Act of 2011 (ED Act).[219] The ED Act would amend the Safe Drinking Water Act to require EPA to identify endocrine disrupting compounds in drinking water while carrying out its Estrogenic Substance Screening Program.[220] EPA would be required to publish a list of substances for testing and a schedule for issuing test orders within one year after the date of enactment.

Not later than two years after enactment, the Administrator would be required to publish guidance on developing or updating protocols for testing of possible endocrine disruptors.[221] The EPA science advisory board would have to be consulted in determining the appropriate guidance.[222] Substances that represent the highest public health concern would be addressed first.[223] Substances potentially impacting vulnerable populations, such as the elderly, infirm, or young, would receive priority consideration.[224]

The ED Act further calls for the Administrator to adopt a "structured evaluative framework" to assess the weight of the evidence about a compound's hazards.[225] This framework must include science-based criteria that would evaluate the endocrine mode of action. Under this Act, the term "testing" means testing of a substance under Section 408(p) of the FFDCA.[226]

The ED Act includes several provisions that call for testing and acceleration of testing for certain priority compounds[227] and the development of a structured framework for evaluating the weight of the evidence of endocrine disruption.[228] The bill also points out the need to evaluate the mode of action of potential endocrine damaging compounds.[229]

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[219] *See* Endocrine Disruptor Screening Enhancement Act, H.R. 533, 112th Cong. (2011), *available at* http://www.gpo.gov/fdsys/pkg/BILLS-112hr553ih/pdf/BILLS-112hr553ih.pdf.

[220] *Id.* § 2.

[221] *Id.* § 2(c)(1).

[222] *Id.*

[223] *Id.* § 2(b)(2)(A).

[224] *Id.*

[225] *Id.* § 2(f)(3) (amending section 1457 of the Safe Drinking Water Act).

[226] *See generally supra* notes 170–174 and accompanying text.

[227] H.R. 533 § 2(e).

[228] *Id.* § 2(f)(3).

[229] *Id.*

All of these provisions would benefit from application of *in vitro* alternatives and the approach set forth in the NRC Vision. In fact, it appears that EPA and NIEHS have begun to establish a scientific basis that is consistent with the requirements of this bill.[230] In short, the ED Act, if enacted in something like its current form, could serve as a driver for implementation of the NRC Vision—with far less controversy than broader TSCA reform is generating and will continue to generate.

C. *Harmonization of U.S. Chemical Regulation with the European Union Approach*

Many of the businesses that manufacture or use chemical compounds operate internationally in the global marketplace. As such, they are subject to the regulatory regimes of not only the United States, but also the many other countries in which they conduct business. In particular, those companies that have a presence in one or more of the nation states that are part of the European Union are faced with a series of laws and regulations that are moving toward the fuller utilization of in vitro toxicity testing.

In June 2007, the comprehensive European Community chemical regulation known as "REACH" came into force.[231] REACH greatly expands the requirements for testing chemicals and promotes alternatives to animal testing. REACH establishes a clear policy with respect to toxicity testing:

> [I]t is necessary to replace, reduce or refine testing on vertebrate animals. Implementation of this Regulation should be based on the use of alternative test methods, suitable for the assessment of health and environmental hazards of chemicals, wherever possible. The use of animals should be avoided by recourse to alternative methods validated by the [European] Commission or international bodies, or recognised by the Commission or the [European Chemicals] Agency as appropriate to meet the information requirements under this Regulation. To this end, the Commission, following

[230] *See supra* notes 98, 113. By incorporating data from *in vitro* assays, chemical descriptors, and biological pathways, a flexible ranking of the endocrine disruption capacity of 309 chemicals was created.

[231] Council Regulation 1907/2006, Concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals, 2006 O.J. (L 396) (EC).

> consultation with relevant stakeholders, should propose to amend the future Commission Regulation on test methods or this Regulation, where appropriate, to replace, reduce or refine animal testing. The Commission and the Agency should ensure that reduction of animal testing is a key consideration in the development and maintenance of guidance for stakeholders and in the Agency's own procedures.[232]

And the Seventh Amendment to the European Union's Cosmetics Directive, which took effect in 2003, is phasing out the use of animal testing for cosmetic products and their ingredients altogether—with a deadline of 2013.[233] These European moves are consistent with a robust implementation of the "three Rs:" *reducing* the number of animals being tested; *refining* the methodologies used; and *replacing* animal models.[234]

These relatively recent, ambitious European developments build on longstanding European authorities. In 1986, for example, the European Community adopted the Protection of Laboratory Animals Directive, with a stated purpose of reducing the number of animals used for experimentation, ensuring adequate care for them, avoiding or minimizing the infliction of unnecessary pain and distress, and avoiding unnecessary duplication of

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[232] *Id*. Preamble, at 17. REACH requires that "[i]n particular for human toxicity, information shall be generated whenever possible by means other than vertebrate animal tests, through the use of alternative methods, for example, *in vitro* methods . . . ." *Id.* art. 13, at 75 (general requirements for generation of information on intrinsic properties of substances). These methods are to be regularly reviewed and improved "with a view to reducing testing on vertebrate animals and the number of animals involved." *Id.*

[233] Council Directive 2003/15, 2003 O.J. (L 66) (EC), *amending* Council Directive 76/768/EEC, 1976 O.J. (L 262). *But see* Bibi van der Zee, *Cosmetics Industry Criticised as EU Set to Admit Delay in Animal Testing Ban*, GUARDIAN (Dec. 31, 2010), http://www.guardian.co.uk/world/2010/dec/31/animal-testing-cosmetics-industry-europe ("The final phase of European law designed to eradicate testing on animals of chemicals used in the cosmetics industry is set to be delayed for as long as four years because it is thought that alternative ways of testing the safety of ingredients' [sic] will not be ready in time.").

[234] W.M.S. RUSSELL & R.L. BURCH, PRINCIPLES OF HUMANE EXPERIMENTAL TECHNIQUE (1959), *available at* http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc. For more on alternatives to animal testing, see generally ALTTOX, http://www.alttox.org/ (last visited Oct. 29, 2012) (website, supported through a collaboration by Procter & Gamble Company and The Humane Society of the United States, that is "dedicated to advancing nonanimal methods of toxicity testing, both to better protect the health of humans, animals, and the environment and to reduce the numbers and suffering of animals used in current toxicology assessments").

experiments.[235] The Directive provided that "[a]n experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of an animal, is reasonably and practicably available."[236] In 2010, the EU adopted a strengthened directive to replace the 1986 legislation.[237]

III. THE ICCVAM PROCESS—EXPANDING THE PATH TO VALIDATION

Our analysis would be incomplete without a discussion of ICCVAM—an existing mechanism, legislatively enacted, with the potential to play an important role in driving implementation of the NRC Vision.

In 1997, the National Institute of Environmental Health Sciences (NIEHS), one of the National Institutes of Health (NIH), established the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM). ICCVAM is tasked with coordinating interagency reviews of new and revised toxicological methodologies, including non-animal alternatives, and coordinating cross-agency issues relating to validation, acceptance, and national and international harmonization of new methodologies.[238] In 2000, Congress enacted a law to formally create ICCVAM.[239]

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[235] Council Directive 86/609/EEC, 1986 O.J. (L 358), Preamble, at 1. This Directive provided the basis for the creation of the European Centre for the Validation of Alternative Methods (ECVAM). *Id.* art. 23, at 4.

[236] *Id.* art. 7, at 3.

[237] Council Directive 2010/63/EU, 2010 O.J. (L 276) (adopted September 2010). For an in-depth analysis of this directive, see Thomas Hartung, *Comparative Analysis of the Revised Directive 2010/63/EU for the Protection of Laboratory Animals with its Predecessor 86/609/EEC*, 27 ALTEX 285 (2011).

[238] *E.g.*, NAT'L TOXICOLOGY PROGRAM INTERAGENCY CTR. FOR EVALUATION OF ALT. TOXICOLOGICAL METHODS & INTERAGENCY COORDINATING COMM. ON VALIDATION OF ALT. METHODS, THE NICEATM-ICCVAM FIVE-YEAR PLAN (2008-2012) (Jan. 2008), *available at* http://iccvam.niehs.nih.gov/docs/5yrPlan/NICEATM5YR-Final.pdf (prefatory matter). In 2000, the ICCVAM Authorization Act, Pub. L. No. 106-545, 114 Stat. 2721 (2000) (codified at 42 U.S.C. §§ 201, 285*l* (2006)), established ICCVAM as a permanent interagency committee of NIEHS under NICEATM. It is noteworthy that federal agencies are not required to accept ICCVAM test recommendations with respect to testing alternatives. *See, e.g.*, *id.* § 4 (federal agency action). For more on validation, see Deborah Rudacille, *Summary of the July 2010 Workshop, "21st Century Validation Strategies for 21st Century Tools"*, 27 ALTEX 279 (2010).

[239] ICCVAM Authorization Act, Pub. L. No. 106-545, § 4(e), 114 Stat. 2721 (2000) (codified at 42 U.S.C. §§ 201, 285*l*-4(e) (2006)).

EPA is one of the fifteen U.S. federal agencies that comprise ICCVAM.[240] Administered by the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), ICCVAM brings together agencies that use, generate, and disseminate toxicological information, and it has a stated aim of "promot[ing] the scientific validation and regulatory acceptance of toxicological test methods that more accurately assess the safety or hazards of chemicals and products and reduce, refine (decrease or eliminate pain and distress), and/or replace animal use."[241] ICCVAM's mission is thus clearly aligned with the "three Rs" approach to laboratory animal welfare, which suggests that ICCVAM should prove to be an important vehicle for assisting EPA and other stakeholders implement the NRC Vision.[242] Unfortunately, in its almost fifteen-year history that has not proven to be the case.

Although ICCVAM provides a potentially powerful tool for the validation of promising non-animal testing approaches, and

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[240] NICEATM-ICCVAM, http://iccvam.niehs.nih.gov/ (last visited Oct. 29, 2012).

[241] *Id.*

[242] For a recent definition of the 3Rs under federal policy, see NAT'L RESEARCH COUNCIL, GUIDE FOR THE CARE AND USE OF LABORATORY ANIMALS 4–5 (8th ed. 2011). According to the Guide:

> *Replacement* refers to methods that avoid using animals. The term includes absolute replacements (i.e., replacing animals with inanimate systems such as computer programs) as well as relative replacements (i.e., replacing animals such as vertebrates with animals that are lower on the phylogenetic scale).
>
> *Refinement* refers to modifications of husbandry or experimental procedures to enhance animal well-being and minimize or eliminate pain and distress. While institutions and investigators should take all reasonable measures to eliminate pain and distress through refinement, IACUCs should understand that with some types of studies there may be either unforeseen or intended experimental outcomes that produce pain. These outcomes may or may not be eliminated based on the goals of the study.
>
> *Reduction* involves strategies for obtaining comparable levels of information from the use of fewer animals or for maximizing the information obtained from a given number of animals (without increasing pain or distress) so that in the long run fewer animals are needed to acquire the same scientific information. This approach relies on an analysis of experimental design, applications of newer technologies, the use of appropriate statistical methods, and control of environmentally related variability in animal housing and study areas.

See also W.M.S. RUSSELL & R.L. BURCH, PRINCIPLES OF HUMANE EXPERIMENTAL TECHNIQUE (1959).

thus for building regulatory acceptance for new *in vitro* methodologies, the interagency body has moved slowly in this regard—and been subject to criticism. As of April 2008, ICCVAM had approved ten or fewer *in vitro*-based alternatives—out of nearly 200 reviewed over ten years. By contrast, the European Centre for the Validation of Alternative Methods (ECVAM) had approved over 30 alternatives, with 170 more "in its pipeline."[243]

To be fair, ICCVAM faces inherent structural limitations. It lacks staff and independent funding, for example, and is supported through allocations by its members. Also, under the law, ICCVAM functions essentially in an advisory capacity: federal agencies are free to reject ICCVAM test recommendations for a variety of reasons, including on the seemingly catch-all basis that a test recommendation "is unacceptable for satisfactorily fulfilling the test needs for that particular agency and its respective congressional mandate."[244] Nor does the ICCVAM legislation purport to create an exclusive mechanism for the submission of test methods or scientific data to federal agencies by any party.[245]

In 2008, ICCVAM presented a five-year plan "to advance alternative test methods of high scientific quality to protect and advance the health of people, animals, and the environment."[246] The plan makes reference to the NRC Vision, then goes on to state

[243] *See* Gilbert M. Gaul, *In U.S., Few Alternatives to Testing on Animals: Panel Has Produced 4 Options in 10 Years*, WASH. POST, Apr. 12, 2008, at A01 (citing figures and various sources for proposition that existing system is broken). For additional criticism of ICCVAM, see also, e.g., PEOPLE FOR ETHICAL TREATMENT OF ANIMALS, REGULATORY TESTING: WHY IS THE U.S. SO FAR BEHIND EUROPE? (2008) (comparing approaches under ICCVAM and ECVAM frameworks for regulatory acceptance). For current information on methodologies accepeted by ICCVAM and ECVAM, respectively, see *Acceptance of Alternative Methods*, NICEATM-ICCVAM, http://iccvam.niehs.nih.gov/about/accept.htm (last visited Oct. 29, 2012), and EUROPEAN CTR. FOR VALIDATION OF ALT. METHODS, http://ecvam.jrc.it/ (last visited Oct. 29, 2012).

[244] ICCVAM Authorization Act, Pub. L. No. 106-545, § 4(e), 114 Stat. 2721 (2000) (codified at 42 U.S.C. §§ 201, 285*l*-4(e) (2006)) (recommending adoption).

[245] ICCVAM Authorization Act § 5(d), 42 U.S.C. § 285*l*-5(d) (application—submission of tests and data).

[246] NAT'L TOXICOLOGY PROGRAM INTERAGENCY CTR. FOR EVALUATION OF ALT. TOXICOLOGICAL METHODS & INTERAGENCY COORDINATING COMM. ON VALIDATION OF ALT. METHODS, THE NICEATM-ICCVAM FIVE-YEAR PLAN (2008-2012) (Jan. 2008), *available at* http://iccvam.niehs.nih.gov/docs/5yrPlan/NICEATM5YR-Final.pdf.

that ICCVAM "will facilitate reviews of the usefulness and limitations of defined [high-throughput screening] approaches, and also assist in the identification of assays and endpoints that are relevant for alternative test methods that have already been adopted."[247] The five-year plan continues to suggest that ICCVAM is positioned as an entity that can react to, but not lead, the development and regulatory acceptance of in vitro testing methods. Among the "3 Rs," the plan appears to make "refinement" the top priority, followed by "reduction"—with "replacement" being a lesser priority.[248]

Based on past performance and the limitations in the law that created ICCVAM, it seems unlikely that the ICCVAM mechanism will contribute meaningfully to the development and validation of alternative methodologies consistent with the NRC Vision. Progress to date in this regard has been inadequate, suggesting that the interagency body could also be perceived as presenting a challenge to full implementation of the NRC Vision.

Ultimately, a more flexible method—evidence-based toxicology (EBT)—has been suggested as a way to accelerate validation of alternative testing methodologies.[249] As in clinical medicine, an evidence-based process would be used to critically evaluate alternatives. Using an iterative process, new methods would be assessed by appraising their test characteristics, mechanistic basis, quality assurance, and other scientific parameters. These reviews would optimize the balance between safety, costs, and animal welfare, explicitly stating and, where possible, quantifying uncertainties. Under this modular approach, alternatives could be evaluated more quickly and brought into the regulatory arena as soon as possible, even if for limited purposes. In addition, gaps in tests would be identified and work could then be undertaken to strengthen them.[250]

Because the ICCVAM law does not require that alternatives be validated only through the ICCVAM system, an EBT approach would seem not to require any legislative changes. Rather, policy

[247] *Id*. at 30.

[248] *See* Paul Locke, *The Revolution in Toxicity Testing: Are We Ready for an In-Vitro Future?*, 116 AV MAGAZINE 18, 20 (2008).

[249] *See* Sebastian Hoffmann & Thomas Hartung, *Towards an Evidence Based Toxicology*, 25 HUM. & EXPERIMENTAL TOXICOLOGY 497 (2006).

[250] *Id*.

changes could be managed administratively: regulatory agencies must agree to participate in the EBT reviews and be ready to accept the consensus findings of EBT reviews. Additionally, the possibility of regulatory acceptance of EBT analyses will encourage the regulated community to engage in the EBT process.

CONCLUSION

Even as the science of toxicity testing continues to make great strides forward, the law lags behind. To date, there is no well-defined legal or regulatory requirement in place to ensure that promising new *in vitro* methodologies are validated or presented for regulatory acceptance in the United States, much less that they be used in practice. To be sure, the shift from primarily *in vivo* to *in vitro* testing for chemicals cannot occur overnight—in many respects, scientists are still making sense of the massive amounts of data that the new tests are generating. On the other hand, a strategy for implementation of chemical testing reform premised on waiting indefinitely for a perfect system to emerge is doomed to fail. The answer, as is often true, lies somewhere in the middle—with clear mandates for EPA and industry to make use of new methodologies whenever possible.

Certainly, existing U.S. statutes governing industrial chemicals and pesticides present no barrier to EPA and industry in implementing the NRC Vision. The enactment of new environmental laws is not required. The statutes currently on the books provide a sufficient legal foundation for implementing the NRC Vision. Successful implementation of the NRC Vision, however, will require a substantial change in chemicals policy by EPA—most likely in the form of amended or updated regulations, guidelines, policies, and programs. This conclusion is far from surprising. The regulatory and policy framework constructed by EPA pursuant to its authorities under the toxics laws represents a longstanding animal-based approach to testing for the adverse effects of chemicals. Despite modest support of *in vitro* methodologies and evidence that EPA is pursuing refinement activities and some new initiatives, the agency continues to operate primarily under the traditional paradigm of *in vivo* toxicity testing.

This article clarifies that there is a meaningful difference between the law *not standing in the way of implementation* of the landmark NRC Vision, on the one hand, and *affirmatively encouraging and driving implementation* of the NRC Vision, on

the other. The former situation describes the status quo in the United States. That is, federal chemical legislation now on the books presents few obstacles for federal agencies and stakeholders that, over the next several decades, would like to see the paradigm for toxicity testing move toward what the NRC has proposed. Will this be enough? Or are law and policy drivers needed?

There is no doubt that implementation of the NRC Vision will come sooner with a congressional mandate than by administrative restructuring—which is dependent upon EPA's political will—alone. When and if broad TSCA reform arrives, it will be crucial to include statutory drivers for implementing the NRC Vision. The current candidate bill for TSCA reform points policy in the right direction, but more is needed by way of mandatory language for EPA and industry. If TSCA reauthorization fails to meaningfully address toxicity testing reform, we likely risk locking in the *in vivo* testing status quo for the foreseeable future as EPA and industry are pressed into a mad dash to erase the vast data backlog for chemicals in commerce. This presents a very real question: can TSCA reform live up to its billing—providing more and better data, with the burden of safety on industry—*without* twenty-first century toxicology? We fear that a twenty-first century TSCA that does not clearly and actively incentivize the use of the latest science and *in vitro* methodologies will be too inflexible to meet modern demands: its success will depend almost entirely upon existing animal-testing methodologies and the slow pace at which these tests move. All the while, less controversial legislation, such as the Endocrine Disruptor Screening Enhancement Act, can generate positive pressure to develop and use new *in vitro* methodologies—as does the very practical need to harmonize testing requirements for industry across global markets, with the European Union setting the pace for alternatives.

In the immediate term, the best opportunities for implementing the NRC Vision may lie at the federal agency level, with EPA. Given the difficulties inherent in bringing about large-scale change, particularly among understandably risk-averse regulators and stakeholders, there is a need for discrete and concrete near- and intermediate-term steps to help ensure that the NRC Vision takes hold. Although there is important current activity in the agencies, we need more—for example, an administrative plan, or roadmap, that includes EPA, NIH, and especially ICCVAM, and builds on the content and trajectory of

the existing interagency memorandum of understanding. Despite its *raison d'etre*, ICCVAM does not appear poised to contribute meaningfully to implementation of the NRC Vision. Whether the reasons for this are primarily legal or institutional remains unclear, but it is certain that ICCVAM can serve as either a major driver of—or a major impediment to—implementation of the NRC Vision. Fortunately, validation can and should be supplemented by activities outside of the ICCVAM process. Sooner or later, EPA will assuredly need to promulgate fresh regulations that address pathways testing head-on. It will be important that policymakers embrace and move forward with the new and emerging science developed by their colleagues within and outside of government.

U.S. chemicals law and policy is grounded in the belief that the public should not be exposed to compounds that cause or exacerbate disease. The protection of human health and the environment from the toxic effects of chemicals begins, but does not end, with advances in scientific methodology and thinking. At the end of the day, these advances must be capable of delivering to regulators better data with which to make better decisions. Although questions of toxicity testing reform may have originated in the realm of science, these scientific issues are now intertwined with important legal questions and public policy concerns. Advances in science are thus a necessary, but not sufficient, step in law reform.

Ultimately, government officials must rely on the results of toxicity testing, together with other sources of scientific information, to make difficult regulatory decisions. The recommended path forward—implementation of the NRC Vision—provides a road map for marrying new science to old laws. But a scientific paradigm shift is only one ingredient of a successful formula to change the nature of toxicity testing in the United States. Full-throated implementation of the NRC Vision demands more. It requires engagement along the full spectrum of stakeholders: industry representatives, regulators, non-profit public health and environmental advocates, academics, scientists, and animal welfare advocates. These and perhaps other constituencies will have much to say about what happens next. It also demands that legislative reform, which has been sparked by the inadequacies uncovered through toxicology, embrace and contain provisions that implement the NRC Vision. Amending federal toxics legislation, while ignoring advances in science, risks

indefinitely miring chemical policy in the unsuccessful techniques of the past—and placing in jeopardy the success of the very legal reform that so many have worked for so long to achieve.