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## A Cautiously Pessimistic Appraisal of Trends in Toxics Regulation

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## A Cautiously Pessimistic Appraisal of Trends in Toxics Regulation

David E. Adelman\*

### INTRODUCTION

Many of the most dramatic and politically salient environmental disasters have involved toxic substances of one form or another. One need only think of Love Canal in New York, the Exxon Valdez in Alaska, Bhopal in India, Chernobyl in Ukraine, or the burning Cuyahoga River in Ohio.<sup>1</sup> Yet despite the iconic status of these events, regulation of toxic substances in the United States (and elsewhere) is criticized by a broad cross-section of stakeholders and experts. Among those on the left, the primary statute, the Toxic Substances Control Act (“TSCA”), is considered moribund and structurally unsound because of the high barriers it creates to regulatory action.<sup>2</sup> Critics on the right challenge the scientific bases for regulation and question, often on the basis of cost-benefit analyses, the rationality of the regulations that exist.<sup>3</sup> No one is particularly happy with the status quo.<sup>4</sup>

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1. See Bradley C. Karkkainen, *Panarchy and Adaptive Change: Around the Loop and Back Again*, 7 MINN. J. L. SCI. & TECH. 59, 66–67 (2005).

2. See John S. Applegate, *Synthesizing TSCA and REACH: Practical Principles for Chemical Regulation Reform*, 35 ECOLOGY L.Q. 721, 723, 734–36 (2008) [hereinafter Applegate, *Synthesizing TSCA and REACH*].

3. See David E. Adelman, *The False Promise of the Genomics Revolution for Environmental Law*, 29 HARV. ENVTL. L. REV. 117, 168–69 (2005). See generally RISKS, COSTS, AND LIVES SAVED: GETTING BETTER RESULTS FROM REGULATION (Robert W. Hahn ed., 1996) (citing evidence revealing the lack of success of recent government risk reduction expenditures); John D. Graham, *Legislative Approaches to Achieving More Protection Against Risk at Less Cost*, 1997 U. CHI. LEGAL F. 13 (1997) (arguing that more effective, less costly risk regulation could replace the current fragmentary regulations).

4. See, e.g., Dieter Pesendorfer, *EU Environmental Policy under Pressure: Chemicals*

The long winter, according to some commentators, may be ending.<sup>5</sup> Other countries are establishing innovative chemical regulatory programs, most notably in the European Union (“EU”) and Canada.<sup>6</sup> Recent scientific advances promise a new paradigm of environmental toxicology that will erase the uncertainties, delays, and high costs that have plagued toxics regulation for decades.<sup>7</sup> Efforts to reform toxics regulation are even beginning to make headway in the U.S., with promising legislation recently introduced in both the House and Senate.<sup>8</sup>

The brightest light in the firmament is surely the Registration, Evaluation, and Authorization of Chemicals (“REACH”) program recently enacted in the EU.<sup>9</sup> REACH, at least on the surface, corrects

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*Policy Change between Antagonistic Goals?*, 15 ENVTL. POL. 95, 111 (2006) (“The chemical policy reform under way is the result of serious anomalies of the current EU chemicals regulation concerning both environmental and health but also business and trade issues. These anomalies created a situation ‘in which all major coalitions view a continuation of the current situation as unacceptable.’”).

5. Gary E. Marchant, *Genomics and Toxic Substances: Part I-Toxicogenomics*, 33 ENVTL. L. REP. 10071, 10071 (2003); Kenneth Olden et al., *A Bold New Direction for Environmental Health Research*, 91 AM. J. PUB. HEALTH 1964, 1966 (2001) (“The new era of toxicogenomics, made possible by advances in human genomics, promises to revolutionize the practice of public health as it relates to environmental health protection.”); N. Rothman et al., *The Use of Common Genetic Polymorphisms to Enhance the Epidemiologic Study of Environmental Carcinogens*, 1471 BIOCHIMICA ET BIOPHYSICA ACTA C1, C8 (2001) (“Epidemiologic studies that measure susceptibility genes should provide opportunities to detect . . . gene-environment interactions that may give rise to new clinical and public health strategies aimed at preventing and controlling cancer.”); P. Trinia Simmons & Christopher J. Portier, *Toxicogenomics: The New Frontier in Risk Analysis*, 23 CARCINOGENESIS 903, 903–05 (2002) (discussing how new technologies, including transgenic animals, molecular epidemiology, toxicogenomics, alternative models to animals, and mechanism-based mathematics, are helping develop more scientifically accurate risk assessments); Lewis L. Smith, *Key Challenges for Toxicologists in the 21st Century*, 22 TRENDS PHARMACOLOGICAL SCI. 281, 282 (2001) (“The development of genomics, proteomics (the measurement of specific proteins) and metabonomics (the study of metabolite profiles of either intrinsic or xenobiotic molecules), combined with a greater knowledge of individual genetic polymorphisms, will offer new paradigms for hazard evaluation and risk assessment.”).

6. U.S. GOV’T ACCOUNTABILITY OFFICE, CHEMICAL REGULATION: OPTIONS EXIST TO IMPROVE EPA’S ABILITY TO ASSESS HEALTH RISKS AND MANAGE ITS CHEMICAL REVIEW PROGRAM, 29–31, app. II at 44–49 (2005) [hereinafter CHEMICAL REVIEW PROGRAM]; Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 741–43.

7. See, e.g., Marchant, *supra* note 5, at 10071, 10082.

8. See, e.g., Safe Chemicals Act of 2010, S. 3209, 111th Cong. 2d Sess. (2010).

9. David A. Wirth, *The EU’s New Impact on U.S. Environmental Regulation*, 31 FLETCHER F. WORLD AFF. 91, 100 (2007) (describing REACH entering into force on June 1,

many of the perceived defects in TSCA. Most significantly, it shifts the burden of proof to chemical manufacturers to demonstrate the safety of their products and requires them to make detailed information available to the public on the potential hazards of the chemicals they make and sell.<sup>10</sup>

Recent scientific advances are described in revolutionary terms.<sup>11</sup> This excitement is being propelled by expanding “knowledge of genes associated with disease states to the study of toxicology of chemical and physical agents” referred to collectively as “toxicogenomics.”<sup>12</sup> Toxicogenomics is touted as providing a new generation of powerful screening methods for determining whether a chemical is toxic and whether individuals have been exposed to or harmed by a toxic substance.<sup>13</sup> If this promise is realized, toxicogenomics will transform toxicology from its quasi-scientific status, subject to large uncertainties and inferential gaps, to a “true” science based on detailed understanding of chemical toxicity and precise testing methods.

As the title suggests, this Article adopts a guarded view of recent regulatory and scientific developments. While the regulatory advances in the EU will undoubtedly alter the landscape of toxics regulation in the United States and elsewhere, they incorporate many compromises that qualify their procedural and regulatory mandates. Antecedent laws, particularly the Food, Drug, and Cosmetics Act (“FDCA”) in the United States, suggest that the effect of procedural measures, notably burden shifting, can be muted by agency discretion over implementation of a law. This may be especially true of REACH, which opens the door to evasion through its tiered chemical

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2007, after the final vote of the European Parliament and approval of the EU Environment Council).

10. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 744–47.

11. See William E. Bishop et al., *The Genomic Revolution: What Does It Mean for Risk Assessment?*, 21 RISK ANALYSIS 983, 983 (2001) (predicting that toxicogenomics “will have profound impacts on the practice of risk assessment”); Olden et al., *supra* note 5, at 1966 (predicting that genomics methods “will lead to a revolution in our approach to the study of toxicity”).

12. Simmons & Portier, *supra* note 5, at 903.

13. Kenneth Olden & Janet Guthrie, *Genomics: Implications for Toxicology*, 473 MUTATIONS RES. 3, 4 (2001) (“The technology and knowledge generated by genomics offer new and exciting possibilities for improving predictiveness, relevance and precision of toxicolog[y].”).

classification scheme and the flexibility it affords manufacturers to use alternative testing methods.

The past thirty years have demonstrated that toxics regulation is inextricably tied to scientific understanding. Science informs the architecture of regulatory regimes and supplies the factual grounding for agency decisions. I will show that the likelihood is low, if not negligible, that advances in toxicogenomics will significantly improve toxics regulation over the next decade or so. Even proponents of toxicogenomics acknowledge that validation and refinement of its methods could take ten to twenty years.<sup>14</sup> Recent experience in the pharmaceutical industry suggests that this estimate may be overly optimistic. Despite aggressive use of genomics methods, drug development in the U.S. is in crisis—approvals of novel drugs hit a twenty-four year low in 2007<sup>15</sup> despite a doubling of spending on research and development over the last decade.<sup>16</sup> Moreover, far from simplifying drug development processes, scientific understanding of human genetics is making them more complex<sup>17</sup> and seemingly exacerbating the uncertainties that pervade drug development and toxicity testing.<sup>18</sup>

The enthusiastic embrace of toxicogenomics is nevertheless understandable, as scientific uncertainties are the source of severe

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14. Melvin E. Andersen & Daniel Krewski, *Toxicity Testing in the 21st Century: Bringing the Vision to Life*, 107 TOXICOLOGICAL SCI. 324, 328 (2009); see also NAT'L RESEARCH COUNCIL, TOXICITY TESTING IN THE 21st CENTURY: A VISION AND A STRATEGY 16 (2007) ("Implementing the [new toxicity testing strategy] will require improvements and focused effort over a period of decades.").

15. Avery Johnson & Ron Winslow, *Drug Makers Say FDA Safety Focus Is Slowing New-Medicine Pipeline*, WALL ST. J., June 30, 2008, at A1 (observing that in 2007 "the FDA approved just 19 new medicines, the fewest in 24 years").

16. See PRICEWATERHOUSECOOPERS, PHARMA 2020: THE VISION 1 (2007), <http://www.choruspharma.com/pharma2020final.pdf> (commenting that "the industry now spends far more on research and development (R&D) and produces far fewer new molecules than it did 20 years ago"); David Malakoff, *Spiraling Costs Threaten Gridlock*, 322 SCIENCE 210, 210 (2008) (describing how drug testing costs have "skyrocketed to nearly \$400 million on average, even as the number of major new treatments emerging from the pipeline has fallen").

17. See Elizabeth Pennisi, *Breakthrough of the Year: Human Genetic Variation*, 318 SCIENCE 1842, 1842 (2007) (reporting that *Science* chose "human genetic variation" as the scientific breakthrough of the year and that the studies completed during 2007 "drove home how complex the genome is").

18. GARY P. PISANO, SCIENCE BUSINESS: THE PROMISE, THE REALITY, AND THE FUTURE OF BIOTECH 64–68 (2006).

obstacles to effective regulation. The dearth of information and modest controls over the thousands of industrial chemicals sold in the United States are a recurring source of tension in the federal government and an outrage for many stakeholders. Yet, the information that science can provide is costly, time-consuming to obtain, and often of modest value given its large uncertainties.<sup>19</sup> These shortcomings invite industry opposition to regulatory testing and have had particular salience for the vast majority of chemicals that are produced in low quantities. The promise of resolving scientific uncertainties is therefore central to the hope that toxicogenomics will transform toxicology and the belief that science warrants large investments of time and resources.

I will argue that policymakers and stakeholders should be leery of claims, whether regulatory or scientific, that the tensions in toxics regulation can be resolved. For the foreseeable future, the problems are too complex and our understanding too modest for difficult choices to be avoided. This recognition does not imply that toxics regulation in the United States cannot be improved, such as by adopting certain elements of REACH, or that investments in toxicological science are futile. Rather, it suggests that toxics regulation, particularly in the near-term, must take into account the prevailing constraints. It should not be premised on transcending knowledge gaps, but instead on empowering agencies, in conjunction with stakeholders, to manage effectively the unavoidable uncertainties.

One straightforward implication of this approach is that toxics regulation should avoid the deep epistemic gaps to the extent that it can. New and existing regulatory regimes reflect this commonsensical approach by adopting proxies for chemical risk potential, such as the quantity of a chemical sold annually, its environmental persistence, and its potential to bioaccumulate.<sup>20</sup> Other

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19. See Thomas Hartung, *Toxicology for the Twenty-First Century*, 460 NATURE 208, 208 (2009) (stating that worldwide about two billion euros are spent annually on toxicological testing).

20. See *infra* Part I.A–B. This kind of tiered strategy predates the passage of TSCA; it informed the basic structure of the legislation. See, e.g., NAT'L ACAD. OF SCI., COMM. ON PRINCIPLES OF DECISION MAKING FOR REGULATING CHEMICALS IN THE ENV'T, DECISION MAKING FOR REGULATING CHEMICALS IN THE ENVIRONMENT app. J, at 224–27 (1975).

opportunities also exist to mitigate the informational burdens of toxics regulation, but they are more controversial and entail complex tradeoffs. For example, some laws permit use of toxicity testing data for structurally related or analogous compounds to alleviate testing burdens, but this strategy is often criticized for being scientifically unsound.<sup>21</sup> Relying more on post-marketing monitoring, as opposed to pre-manufacturing testing, can also mitigate the costs of regulatory delays and of testing itself. However, this necessarily trades off the possibility of preventing harm *ex ante* for the prospect of an enhanced likelihood of detecting risks after a chemical is marketed.

This Article will draw on the one-hundred year history of drug regulation, which represents the most stringent regulatory system for chemicals of any kind. An examination of this broader experience exposes several commonalities and tradeoffs inherent in chemical regulation. It also offers a comparative perspective on the strategies used in the regulation of chemicals that suggests an upper limit for the stringency of regulation that is politically and scientifically viable. Two important insights emerge from this comparative analysis: (1) the *ex ante-ex post* dichotomy that is often drawn between common law and statutory law is overstated—if not simply false—for chemical regulation, and (2) for most chemicals tiered “precautionary” systems like those embodied in REACH represent more of a change in rhetoric than a fundamental shift in substance over the status quo.

Complementing the comparative historical analysis, this Article will provide an overview of recent scientific developments and their implications for toxics regulation. I expect the direct impacts to be marginal, at least for the foreseeable future. More importantly, given the limited resources available to toxics programs and the steep opportunity costs that these financial constraints impose, I will advocate that the Environmental Protection Agency (“EPA”) and National Institute for Environmental Health Sciences (“NIEHS”) invest modestly in toxicogenomic research. The emerging complexity of human genetics suggests that it would be prudent to allow research

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21. See *infra* Part I.A–B.

to progress in the biomedical sciences before focusing more intensely on toxicogenomics.

The final part of the Article examines promising opportunities to improve the regulation of toxic substances, which is the subject of renewed interest in Congress and rising support from a broad cross-section of stakeholders.<sup>22</sup> It will evaluate three primary policies: the virtues of tiered regulatory regimes, the potential role of post-marketing testing, and the value of complementary innovation-oriented policies to promote development of “green chemistry” processes and compounds. Each will be discussed with an eye toward emerging legislative efforts to amend TSCA.

#### I. ESTABLISHED AND EMERGING TRENDS IN TOXICS REGULATION

“The objective [of TSCA] is to keep environmental thalidomides out of action.”<sup>23</sup>

The modern era of high-volume chemical manufacturing is a relatively recent creation. Chemical production experienced remarkable growth during the twentieth century—global quantities of manufactured chemicals increased four-hundred fold between 1930 and 2001, increasing from one million tons to more than 400 million tons annually.<sup>24</sup> In the United States alone, approximately 15.2 trillion pounds of chemicals are either manufactured or imported each year.<sup>25</sup> On average, manufacturers add over seven-hundred new chemicals each year to the more than eighty thousand that are already commercialized.<sup>26</sup> Yet, only 1134 chemicals—less than 1.5 percent of

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22. See, e.g., Lyndsey Layton, *Chemical Industry Lends Support to Reform*, WASH. POST, Aug. 9, 2009, at E4; Aaron Lovell, *Competing Groups Agree on Some TSCA Principles but Disputes Remain*, DEF. ENV'T ALERT (Inside EPA, Arlington, Va.) Aug. 18, 2009; see also Kid-Safe Chemicals Act of 2008, S. 3040, 110th Cong. (2008); Kid-Safe Chemicals Act of 2008 H.R. 6100, 110th Cong. (2008).

23. The Toxic Substances Control Act of 1971 and Amendment; Hearing on S.1478 before the Subcomm. on the Environment of the Comm. on Commerce, 92d Cong. 135 (1971) (statement of William H. Rodgers, Jr., Associate Professor of Law, University of Washington).

24. *Commission White Paper on Strategy for a Future Chemicals Policy*, at 4, COM (2001) 88 final (Feb. 27, 2001) [hereinafter *Commission Strategy*].

25. MICHAEL P. WILSON ET AL., CAL. POLICY RESEARCH CTR., GREEN CHEMISTRY IN CALIFORNIA: A FRAMEWORK FOR LEADERSHIP IN CHEMICALS POLICY AND INNOVATION 1 n.A (2006).

26. See CHEMICAL REVIEW PROGRAM, *supra* note 6, at 1–2.



those commercialized—are regulated under five major federal statutes, including TSCA.<sup>27</sup>

Progress in the area of toxics regulation, as the preceding numbers suggest, has been notoriously slow, and the track record for TSCA is especially troubling.<sup>28</sup> Over the course of thirty-three years, the EPA has issued formal regulations banning or restricting the production or use of just five chemicals of the approximately 62,000 that were in commerce at the time of TSCA's passage.<sup>29</sup> Similarly, of the more than 45,000 chemicals that the EPA has reviewed since 1979,<sup>30</sup> the vast majority had little or no health or safety data and only about 3800 chemicals were subject to any kind of regulatory action.<sup>31</sup> Of those actively reviewed, about half (1700) were withdrawn by the manufacturer, 1300 were subjected to specific workplace controls pursuant to consent orders under TSCA section 5(e), and 570 were commercialized on the condition that the manufacturer submit notices to the EPA of any significant new uses.<sup>32</sup>

Limited regulatory oversight has allowed production of health and safety information to stagnate. Several studies have exposed the dearth of data even for chemicals produced and used in the largest volumes. A 1997 report issued by Environmental Defense found that basic toxicology screening studies were available for only twenty-nine percent of the one hundred high-production volume ("HPV") chemicals in their sample.<sup>33</sup> A subsequent EPA study of 3000 HPV

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27. WILSON ET AL., *supra* note 25, at 13.

28. See U.S. GOV'T ACCOUNTABILITY OFFICE, CHEMICAL REGULATION: COMPARISON OF U.S. AND RECENTLY ENACTED EUROPEAN UNION APPROACHES TO PROTECT AGAINST THE RISKS OF TOXIC CHEMICALS 2 (2007) [hereinafter RISKS OF TOXIC CHEMICALS] ("Of the over 82,000 chemicals currently in the TSCA inventory, about 62,000 were already in commerce when EPA began reviewing chemicals in 1979.").

29. *Id.* at 18; see also U.S. GOV'T ACCOUNTABILITY OFFICE, CHEMICAL REGULATION: OPTIONS FOR ENHANCING THE EFFECTIVENESS OF THE TOXIC SUBSTANCES CONTROL ACT 10 (2009).

30. RISKS OF TOXIC CHEMICALS, *supra* note 28, at 8. Approximately 33,000 of the pre-manufacture notices ("PMNs") were subject to review beyond a determination that the chemical was exempt (e.g., low-volume chemicals, polymers). See *id.* at 22 & n.22.

31. *Id.* at 21–22.

32. *Id.* at 22. Under TSCA section 5(a)(2), EPA has issued significant new use rules for 160 existing chemicals. *Id.* at 18.

33. John S. Applegate, *Bridging the Data Gap: Balancing the Supply and Demand for Chemical Information*, 86 TEX. L. REV. 1365, 1382 (2008) [hereinafter Applegate, *Bridging the*

chemicals concluded: “[N]o basic toxicity information . . . is publicly available for 43% of the high volume chemicals manufactured in the US and a full set of basic toxicity information is available for only 7% of these chemicals.”<sup>34</sup> The findings of these studies were reinforced by a 1999 EU report, which found that basic toxicology data were available for only fourteen percent of HPV chemicals in the EU and no data existed for twenty-one percent of them.<sup>35</sup>

One must be careful, though, not to over-interpret these numbers. The volumes of individual chemicals produced are highly skewed—a small number of chemicals dominate the quantities sold annually. Just three hundred chemicals account for more than ninety-nine percent of the tonnage of all chemicals sold annually in the U.S.,<sup>36</sup> and fewer than 5500 chemicals are produced in amounts equal to or greater than 0.000066 percent of the total quantity sold (i.e., above ten thousand pounds per year).<sup>37</sup> Consistent with these numbers, a 2005 study found that 159 to 234 chemicals were detected in the umbilical cord blood of ten newborns, and a large representative study of the U.S. population found 116 chemicals in blood and urine samples.<sup>38</sup> Thus, while the quantities may not appear small in absolute terms, the great majority of chemicals in U.S. commerce are produced in minuscule quantities in relative terms.

The aggregate figures also ignore evidence indicating that a small subset of chemicals is likely to be toxic. Few compounds that have been tested over the past twenty-five years have tested positive for toxicity—approximately eighty-seven percent of tested chemicals were not found to be acutely toxic, ninety-three percent did not cause

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*Data Gap*]. The study defined “HPV” as any chemical produced in volumes exceeding one million pounds annually. *Id.*

34. *Id.*

35. *Commission Assessment of Additional Testing Needs under REACH: Effects of (Q)SARS, Risk Based Testing and Voluntary Industry Initiatives*, at 5 (Sept. 2003) (prepared by Finn Pedersen et al.) [hereinafter *Add'l Testing Needs Under REACH*].

36. RICHARD A. DENISON, ENVTL. DEF., HIGH HOPES, LOW MARKS: A FINAL REPORT CARD ON THE HIGH PRODUCTION VOLUME CHEMICAL CHALLENGE 9 (2007) (describing how “HPV chemicals comprise the bulk of industrial chemicals in commerce when measured by tonnage”).

37. *Id.* at 10. Similar production volumes exist in Europe, where about ten thousand chemicals are sold in quantities that exceed ten metric tons annually and a further twenty thousand are sold in one to ten metric tons. *Commission Strategy*, *supra* note 24, at 4.

38. WILSON ET AL., *supra* note 25, at 27, 31.

skin irritation, and about ninety-seven percent did not have discernible reproductive effects.<sup>39</sup> Similarly, under the European REACH program scientists estimate that of the pre-1981 chemicals produced in quantities equal to or greater than one-hundred metric tons annually, about 5500 substances, only about 2.5 percent of the total tested will be reproductive toxins.<sup>40</sup> In aggregate, regulators generally believe that no more than twenty percent of the chemicals tested will display sufficient toxicity to require regulatory action.<sup>41</sup>

Two important factors could enhance the tractability of regulating industrial chemicals. The first is the continuity of chemicals listed as HPVs and production processes generally. Of the many thousands of chemicals in commerce, just eight percent (248 in total) of the 2943 HPV chemicals in U.S. commerce today were introduced after 1979.<sup>42</sup> The second is the heterogeneity of chemical characteristics, production levels, and uses, which ought to enable use of relatively straightforward triage methods and tiered regulatory regimes. The Parts that follow analyze existing chemical regulation in the U.S. and recent regulatory developments in Europe. Several commonalities emerge from this comparative analysis that highlight the incremental nature of advances in toxics regulation.

#### *A. Current TSCA Regime and Pending Legislative Amendments*

Among the most striking features of toxics regulation in the U.S. is the degree to which the basic contours of the debate have remained the same. The issues that animated debates in 1971 over the legislation that ultimately became TSCA are essentially identical to the ones that dominate debate today. While there are new potential threats, such as endocrine-disrupting chemicals, the central scientific and legal issues have evolved very little. Concerns about the large uncertainties in toxicology testing, moral and technical objections raised against the use of cost-benefit analyses and economic discounting, and debate over whether manufacturers or the

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39. Hartung, *supra* note 19, at 209.

40. *Id.* In absolute terms, of course, this small relative number (i.e., about 138 compounds) may still be significant.

41. *See infra* Part I.A.

42. WILSON ET AL., *supra* note 25, at 43.

government should bear the burden of proof in regulatory decision-making are as alive today as they were in the 1970s.<sup>43</sup>

Regulating industrial chemicals has never been easy. It took Congress almost five years to pass TSCA.<sup>44</sup> Driven by widespread concerns about the risks from exposures to major chemicals such as mercury, vinyl chloride, and asbestos, the Nixon Administration elevated toxics regulation to the top of the environmental agenda.<sup>45</sup> In the 1971 annual report of the Council on Environmental Quality, the Nixon Administration went so far as to conclude that “from 60 to 90 percent of cancer is authoritatively attributed to environmental causes.”<sup>46</sup> In its opposition to new regulations, the chemical industry claimed that the annual costs of regulation could approach two billion dollars, with testing per chemical running upwards of \$100,000 and taking two to three years.<sup>47</sup> The government countered that the costs would be much lower, as only a small subset of commercial chemicals—it estimated twenty percent of the one thousand new chemicals introduced annually—would require testing.<sup>48</sup>

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43. See, e.g., NAT'L ACAD. OF SCI. *supra* note 20, at 12–14, 17–22, 39–44, 93–96; Valerie J. Brown, *REACHing for Chemical Safety*, 111 ENV'T HEALTH PERSPECTIVES A766, A768 (2003) (arguing that the “combination of the increased financial burden of testing, the bureaucracy of registration and authorization, and the requirement of applying the precautionary principle will discourage innovation and could ruin many small and medium-sized enterprises”).

44. See Gladwin Hill, *Congress Plans New Push to Control Toxic Chemical Products*, N.Y. TIMES, July 8, 1975, at 10; Steven Rattner, *A Law on Toxics Seems a Certainty*, N.Y. TIMES, Sept. 19, 1976, at 157.

45. See John W. Finney, *Senate Votes Regulation of Hazardous Chemicals*, 77–0, N.Y. TIMES, May 31, 1972, at 10 (“The legislation, which was sent to the House, is an outgrowth of concern that developed two years ago over the potential hazards of mercury poisoning from industrial wastes.”); Gladwin Hill, *U.S. Agency Urges a Drive to Bar Cancer by Screening Chemicals*, N.Y. TIMES, Feb. 28, 1976, at 38.

46. Hill, *supra* note 45. The CEQ report went on to argue that “[s]ome observed cancer undoubtedly arises from natural sources like radiation and asbestos, but much of the remainder is probably associated with carcinogenic agents produced by man.” *Id.*

47. Rattner, *supra* note 44; Harold M. Schmeck Jr., *Chemicals Face More Safety Testing*, N.Y. TIMES, Jan. 2, 1977, at 99.

48. See Schmeck, *supra* note 47; Rattner, *supra* note 44, at 157 (indicating that the General Accounting Office estimates the cost for chemical testing would be much lower at just \$100–200 million annually). Initial studies were consistent with the government’s estimates, finding that ten to sixteen percent of the chemicals tested by October of 1977 exhibited carcinogenic properties in animals. John Vinocur, *Major Enforcement Gaps Hobble Law to Control Toxic Substances*, N.Y. TIMES, Oct. 30, 1977, at 1.

The central sticking point in 1971 was whether all chemicals would be subject to pre-market approval and toxicity testing.<sup>49</sup> The Senate, which supported rigorous pre-market testing, and the House, which did not, split on the issue and did not resolve their differences until 1976.<sup>50</sup> Compromise was propelled by, among other events, the discovery of polychlorinated biphenyls (“PCBs”) in the Hudson River and in human breast milk.<sup>51</sup> Yet the Senate and House harmonized the competing legislation by opting largely for the weaker House bill. Environmental groups played an important role in passage of the law by withdrawing their demand for pre-market testing of all new chemicals.<sup>52</sup> The political calculus for supporting an inadequate bill was premised on what proved to be a false belief, namely, that the 1976 law would be a first step toward more comprehensive and rigorous regulation.<sup>53</sup>

The regulatory deficiencies of TSCA that emerged from this compromise have been recounted many times. I will highlight two provisions that are relevant to the central thesis of this Article and that contrast with those found in REACH and the FDCA. Unlike these other statutes, TSCA does not incorporate a regulatory approval

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49. Finney, *supra* note 45, at 10.

50. Hill, *supra* note 44, at 10.

51. *New Breed of Pollutants: The Dangers They Carry*, U.S. NEWS & WORLD REP., Feb. 7, 1977, at 42, 43–44 [hereinafter *New Breed of Pollutants*].

The major impetus for passage of the law came from PCB’s [sic]. . . .

. . . .

Traces of [PCBs] are found in nearly all human-tissue samples taken in industrialized countries. It is in mothers’ milk and in the flesh of fish of many fresh-water lakes and streams. The chemical has shown up in penguin eggs in Antarctica and in animals captured in Greenland.

*Id.* at 43; see also Richard D. Lyons, *House Votes Ban on Output of PCB’s [sic] within 3 Years*, N.Y. TIMES, Aug. 24, 1976, at 61. Other contributing events included the incident of Kepone poisoning of workers in July 1975 and the catastrophic explosion involving dioxin in Seveso, Italy, in July 1976. Peter Gwynne et al., *The Chemicals around Us*, NEWSWEEK, Aug. 21, 1978, at 25, 28.

52. Rattner, *supra* note 44, at 157 (describing how the Sierra Club withdrew support for required pre-market testing of all new chemicals).

53. See *id.* (“Supporters of stronger legislation believe that the current bill is better than no bill at all. ‘It’s a start,’ said Janie Kinney, counsel to the Consumer Protection and Finance Subcommittee of the House Commerce Committee: ‘In three years, when this comes up for renewal, there’ll be another chance.’”).

regime; instead, it requires chemical manufacturers to submit a “pre-manufacture notice” (“PMN”) prior to the marketing of a new (i.e., post-1976) chemical.<sup>54</sup>

The notice that a PMN provides is nominal, however, because TSCA does not impose any standards for the quality or type of information that must be submitted.<sup>55</sup> This omission is compounded by the perfunctory review to which the EPA subjects most PMNs—relying as it does on largely unvalidated screening models and conventions.<sup>56</sup> Regulatory oversight is cramped further by the ninety-day limit TSCA places on the EPA review process.<sup>57</sup> This narrow window often is preclusive of regulatory action, which must be based on a showing of “unreasonable risk,”<sup>58</sup> because the burden is on the EPA to demonstrate that regulation is warranted.<sup>59</sup>

The procedural barriers under section 6 of TSCA, which apply to new and grandfathered, pre-1976 chemicals, go beyond assessing the risk of the chemical in question. In addition to having the burden of proving that unreasonable risks exist, the EPA must show that the prohibitions, limitations, or requirements it imposes are “the least burdensome” available.<sup>60</sup> Furthermore, its decisions are subject to “searching review” by courts under the substantial evidence standard.<sup>61</sup> As a consequence, the EPA imposed regulations on pre-1976 chemicals only five times over the past thirty-four years, and it all but conceded this authority since its attempt to regulate asbestos was largely struck down by the Court of Appeals for the Fifth Circuit in 1991.<sup>62</sup> TSCA in effect has grandfathered ninety-five percent of

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54. 15 U.S.C. § 2604 (2006); *see also* Wirth, *supra* note 9, at 99.

55. Wirth, *supra* note 9, at 99.

56. CHEMICAL REVIEW PROGRAM, *supra* note 6, at 12 (discussing EPA’s use of simple, routinized screening models or classification schemes to conduct limited review for all but twenty percent of the PMNs that it receives); *see also* RISKS OF TOXIC CHEMICALS, *supra* note 28, at 13 (“In June 2005, we recommended that EPA develop a strategy for improving and validating the models that EPA uses to assess and predict the hazards of chemicals.”).

57. 15 U.S.C. § 2604(a)(1).

58. EPA interventions require a showing that chemicals “present an unreasonable risk,” 15 U.S.C. § 2605, as do EPA requests for information about chemicals, 15 U.S.C. § 2604, and urgent actions by the EPA (requiring “imminent and unreasonable risk”), 15 U.S.C. § 2606.

59. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 736–37.

60. 15 U.S.C. § 2605(a).

61. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 737.

62. RISKS OF TOXIC CHEMICALS, *supra* note 28, at 20.

the pre-1976 chemicals,<sup>63</sup> which account for ninety-nine percent of the volume of chemicals in commerce.<sup>64</sup>

The authority that the EPA possesses to require manufacturers to submit environmental- and health-effects data, so-called TSCA test rules, is similarly circumscribed by TSCA's procedural framework.<sup>65</sup> Typically with little or no data, the EPA is required to make formal findings about the potential toxicity, adequacy of other federal laws, and alternative options before it can demand that specific testing be conducted.<sup>66</sup> The EPA's findings are then subject to vigorous judicial review<sup>67</sup> and to a special hearing process that includes oral testimony and cross-examination.<sup>68</sup>

The procedures surrounding test rules add substantially to the time and cost of promulgating them. The cost for a single test rule is upwards of \$234,000, and the process takes two to ten years.<sup>69</sup> Consequently, the EPA has required testing of only about two hundred chemicals since 1979,<sup>70</sup> while it has entered into about three hundred testing agreements with manufacturers outside of this formal process.<sup>71</sup> The procedures also have impacted longer-term planning for chemical testing. The high-level committee established under TSCA to identify chemicals that require testing was moribund for years, as the EPA largely ignored its recommendations.<sup>72</sup> It was not

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63. Wirth, *supra* note 9, at 102 (noting also that the vast majority of pre-1976 chemicals have not undergone even the most basic toxicity testing).

64. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 732.

65. See 15 U.S.C. § 2607(a)-(c); see also Applegate, *supra* note 2, at 732.

66. DENISON, *supra* note 36, at 6. Specifically, EPA must find that "(i) [a chemical] 'may present an unreasonable risk' or is produced in substantial quantities and may enter the environment in substantial quantities or cause significant human exposure, and . . . (iii) testing is necessary to provide the needed information." *Id.*

67. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 730.

68. 15 U.S.C. § 2605(e)(3)(B).

69. RISKS OF TOXIC CHEMICALS, *supra* note 28, at 9-10.

70. *Id.* at 9.

71. *Id.* at 8. EPA authority under TSCA section 8 to promulgate rules for recordkeeping and submission is also underutilized. EPA has issued only about fifty section 8(d) rules covering about one thousand chemicals, which has led to the EPA receiving "nearly 50,000 studies covering environmental fate, human health effects, and environmental effects." *Id.* at 10-11.

72. John D. Walker, *The TSCA Interagency Testing Committee, 1977 to 1992: Creation, Structure, Functions and Contributions*, in ENVIRONMENTAL TOXICOLOGY AND RISK ASSESSMENT (Joseph W. Gorsuch et al. eds., 2d ed. 1993) (describing how, between 1977 and 1992, the Interagency Test Committee proposed testing of 175 chemicals, whereas EPA

until 2007 in the wake of the HPV Chemical Challenge (discussed below) that EPA revived its screening and chemical-testing prioritization program by establishing the Chemical Assessment and Management Program (“ChAMP”).<sup>73</sup>

The obstacles built into TSCA have led regulators to address data deficiencies through informal programs.<sup>74</sup> Recognition of the major gaps in data on high-production volume chemicals prompted the EPA, with significant spurring by environmental stakeholders, to establish the “HPV Chemical Challenge.” This voluntary program sought company sponsorship for the testing of, or collection of toxicological data on, specific HPV chemicals. The original list of HPVs included 2782 compounds, but this number was later reduced to 2164 due to exemptions or lack of sponsorship.<sup>75</sup>

The HPV Chemical Challenge has had mixed success. Among the positives, the EPA has received partial to complete toxicological data for eighty percent of the sponsored chemicals, with the remaining twenty percent having no data as of 2007.<sup>76</sup> While this represents a significant advance over the status quo, these numbers are deceptive because much of the new data are based on pre-existing studies or surrogate testing (i.e., use of estimation methods or data on structurally related analog chemicals)<sup>77</sup>—less than ten percent of the toxicological data were obtained through new testing.<sup>78</sup> Among the

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required testing for only twenty-five; by contrast, EPA and industry agreed on voluntary testing for thirty-four other chemicals).

73. United States Environmental Protection Agency, Chemical Assessment and Management Program: Basic Information, <http://www.epa.gov/CHAMP/pubs/basic.html> (last visited Apr. 26, 2010) (describing how ChAMP will generate “screening-level characterizations for an estimated 6,750 chemicals produced or imported in quantities of 25,000 pounds or more a year” and then prioritize them for subsequent toxicity testing or promulgation of control measures).

74. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 723.

75. DENISON, *supra* note 36, at 11.

76. *Id.* at 12.

77. *Id.* at 4. Also, the EPA has not promulgated test rules for most of the “orphaned” chemicals, and as of 2007 it had only issued test rules for sixteen, or six percent, out of 265 chemicals. Only forty percent of the six hundred newly emerged HPVs have been sponsored. *Id.* at 5.

78. *Id.* at 4; *Add'l Testing Needs under REACH*, *supra* note 35, at 15 (describing EPA’s review of 1024 substances in the HPV Chemical Challenge, in which it found that new testing was proposed for only two to eight percent of the substances). Either (Q)SAR or read-across methods were used to fill thirty-one to forty-six percent of the data points, which is the



negatives, the sponsors' over-reliance on "alternatives to new testing" has been the subject of significant criticism from the EPA and environmental stakeholders.<sup>79</sup>

### *B. Novel Regulatory Developments Abroad*

The EU's REACH program has been hailed as a major departure from the status quo of inadequate testing requirements and weak regulation of the production and uses of chemicals.<sup>80</sup> REACH shifts the burden to demonstrate the safety of chemicals—regardless of whether a chemical is new or pre-existing—from the government to manufacturers.<sup>81</sup> However, to mitigate the burden on industry, REACH provides a ten-year transition period during which testing will be conducted.<sup>82</sup> Equally important, REACH establishes three primary classes of chemicals with tiered levels of testing requirements.<sup>83</sup> Thus, while manufacturers bear the burden of demonstrating safety, testing requirements vary according to specified characteristics of a chemical and the manner in which it is used. This move to replace a uniform system with a calibrated, tiered framework was driven in large part by concerns about negative impacts on innovation,<sup>84</sup> and particularly "green chemistry." REACH

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equivalent of eighty-one to ninety-two percent of the missing data when available test data are excluded. *Id.*

79. DENISON, *supra* note 36, at 4. Further, "[f]or 83% of the industry submissions that Environmental Defense or EPA has reviewed, one or both of us indicated either that more testing than proposed was clearly needed . . . or might be needed." *Id.* at 18.

80. Wirth, *supra* note 9, at 100 (describing REACH establishing "the most rigorous testing requirements of any regulatory regime in the world").

81. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 741–43. It is important to note that more than ninety-nine percent of the substances likely to be regulated by REACH are "existing substances" that were in commerce prior to 1981. CHEMICAL REVIEW PROGRAM, *supra* note 6, at 29. The application of REACH to existing compounds therefore represents a dramatic expansion of the scope of EU chemical regulation.

82. Brown, *supra* note 43, at A769 (describing the provisions in REACH that allow up to ten years for research and development before a chemical must be registered).

83. *See id.* at A767.

84. *Commission Strategy*, *supra* note 24, at 20 (discussing the shift of REACH to a targeting testing regime from comprehensive risk assessments, which have been the primary cause of delays because "they require consideration of all dangerous effects, all exposed populations and all environmental compartments"). This focus stems in large part from the recognition that the pace of comprehensive chemical testing could not possibly overcome the existing backlog of chemicals, let alone keep pace with the introductions of new chemicals. *See*

is also notable for requiring that all toxicity testing data be made publicly available.<sup>85</sup>

Classification based on quantities in commerce and chemical characteristics are defining features of REACH. The quantity of a chemical manufactured or sold in the EU is the primary metric used to classify chemicals and to determine the level of testing required. For chemicals sold or manufactured in quantities of one to ten metric tons annually, testing should be limited to *in vitro* testing of acute hazards.<sup>86</sup> The testing requirements are elevated to a standard base set of toxicology testing for chemicals sold or manufactured in quantities of ten to one hundred metric tons annually.<sup>87</sup> Rigorous “substance-tailored testing for long-term effects” is required for quantities that exceed one thousand metric tons annually.<sup>88</sup>

REACH further refines categorization of chemicals based on their toxic characteristics; the chemicals of greatest concern trigger the highest levels of testing. Chemicals are labeled as being of “highest concern” if they exhibit toxicity (i.e., carcinogenic, mutagenic, or teratogenic), environmental persistency, bioaccumulative characteristics, or endocrine-disrupting capacities.<sup>89</sup>

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INST. FOR HEALTH & CONSUMER PROT., EUR. COMM’N, REACH AND THE NEED FOR INTELLIGENT TESTING STRATEGIES 3 (2005) (concluding that the existing focus on comprehensive testing had led to the current situation in which we “know a lot about a few chemicals (< 5%), but we have very little information on . . . most”); *see also Commission Strategy*, *supra* note 24, at 5 (“Recent experience has shown that innovation (e.g., in developing new and often safer chemicals) has been hindered by the burdens of the present notification system. Ecological, economic and social aspects of development have to be taken into account in an integrated and balanced manner in order to reach the goal of sustainability.”). The EU Commission goes on to argue that:

Regulations are a major factor in shaping the innovation behaviour of firms in the chemical industry. The Commission proposes to increase the current thresholds for notification and testing of new substances, to extend the conditions for derogation for research and development and enable test data to be used and submitted in a flexible way.

*Id.* at 8.

85. Commission Regulation 1898/2006, arts. 117–19, 2006 O.J. (L 396) 36–37 (EC), available at <http://eur-Lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:369:0001:0849:EN:PDF>; Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 750–51.

86. *Commission Strategy*, *supra* note 24, at 12.

87. *Id.*

88. *Id.*

89. *See* Wirth, *supra* note 9, at 100.

Thus, both a chemical's quantity in commerce as well as its properties determine the level of review. If a chemical is sold in low volumes and is relatively benign, simple registration will be adequate. As chemicals move along the spectrum toward higher volume and more dangerous properties, detailed evaluation and ultimately specific government authorization are required to market them.<sup>90</sup>

The EU Commission estimates that most chemicals will not require elaborate testing.<sup>91</sup> It projects that approximately eighty percent of the thirty thousand chemicals estimated to be covered by REACH will be subject to the lowest level of review under the registration program.<sup>92</sup> About 5000 substances, mostly those produced or sold in quantities over one hundred metric tons annually, are projected to require full substance-tailored testing.<sup>93</sup> At the highest level, about 1400 substances (five percent of the total) are likely to be classified as chemicals of very high concern that require formal authorization beyond the basic registration process.<sup>94</sup> REACH also promotes use and development of alternatives to animal testing, particularly *in vitro* testing methods and surrogate chemical structure-based predictors of toxicity, and thus encourages use of novel testing methods.<sup>95</sup> The aggregate cost for testing under REACH is estimated to be approximately €2.1 billion over the eleven-year transition period.<sup>96</sup>

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90. *Commission Strategy*, *supra* note 24, at 12; *see also* Wirth, *supra* note 9, at 100.

91. *Commission Strategy*, *supra* note 24, at 16.

92. *Id.*; *see also* Brown, *supra* note 43, at A767 (explaining the eighty-percent estimate is based primarily on the fact that the vast majority of chemicals are manufactured and sold in relatively low quantities). REACH also exempts chemicals used in either basic scientific research or medical applications. *Id.* at A769.

93. *Commission Strategy*, *supra* note 24, at 16.

94. *Id.* "Some 140 of these substances have been identified as priority substances and are subject to comprehensive risk assessment. . . ." *Id.* at 6.

95. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 751–52.

96. *Commission Strategy*, *supra* note 24, at 15 (discussing the potential range for the cost of direct testing of €1.2 to 2.4 billion); *see also* Brown, *supra* note 43, at A768 (describing industry estimates that the direct costs of registration and testing could be closer to \$4.2 billion, with indirect costs to industry and society of sixteen to eighteen billion dollars from program inception to 2020). The cost per chemical is projected to vary considerably, from €12,000 for one to ten metric tons per year to €208,000 for greater than ten thousand metric tons per year. This amounts to a cost of €404 per metric ton for a substance produced in an amount of three

The shift in the burden of proof for demonstrating safety is the most direct manifestation of the precautionary principle in the REACH program.<sup>97</sup> This burden shifting is muddled, however, by parallel requirements that producers show that the benefits of a toxic compound outweigh its costs, as well as that a “sound scientific basis” exists for restrictions on chemical sales and usage.<sup>98</sup> Equally important is the priority REACH places on developing testing methods that do not involve animals and replacing existing compounds with “suitable alternative substances or technologies where these are economically and technologically viable.”<sup>99</sup>

Canada has adopted a similar regulatory regime under the Canadian Environmental Protection Act of 1999 (“CEPA”). The basic framework is quite similar to that of REACH. The statute requires that all “existing chemicals” be evaluated and categorized according to the aggregate threat they pose to humans, their persistence in the environment or bioaccumulative properties, and their toxicity to humans or other species.<sup>100</sup> Under CEPA, the Canadian government has examined approximately 23,000 previously unassessed chemicals and found that 4300 chemicals warranted further assessment or control.<sup>101</sup> Listing of a chemical is significant because it triggers requirements that companies provide chemical testing data that could lead to regulation or restrictions.<sup>102</sup>

The failings of the EPA’s HPV Chemical Challenge, and TSCA generally, are exemplary of the pitfalls that pervade the regulation of industrial chemicals where scientific uncertainties are often

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metric tons per year, versus €7 per metric ton for a substance produced in an amount of 3000 metric tons per year. *Add'l Testing Needs under REACH*, *supra* note 35, at 29.

97. It is important to acknowledge that REACH is not without its critics. Some scientists worry that the broad application of existing test methods, many of which they claim have low predictive power and high rates of false positives, will lead to valuable chemicals being removed from commerce. *See, e.g.,* S. Hoffman & Thomas Hartung, *Toward an Evidence-Based Toxicology*, 25 HUMAN EXP. TOXICOLOGY 497, 503 (2006).

98. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 746, 760.

99. Commission Regulation 1907/2006, art. 1 (33) 2006 O.J. (396) 13 (EC) (listing the reduction of testing on vertebrate animals as an impetus for registration system reform). Authorization of a substance and imposition of any restrictions require the disclosure and assessment of substitute substances. Commission Regulation, 1907/2006, arts. 55, 60(4)–(5).

100. *See* CHEMICAL REVIEW PROGRAM, *supra* note 6, at 29.

101. DENISON, *supra* note 36, at 30.

102. CHEMICAL REVIEW PROGRAM, *supra* note 6, at 29–30.

overwhelming. Similar dangers exist under the newer REACH program, which relies on rough categories for triaging chemical testing and alternatives to new toxicity testing. These regulatory pitfalls anticipate issues that arise in the next part of this Article. The same problems, and the gaming that goes along with them, are found in related areas of chemical regulation (e.g., testing requirements for generic versions of pioneer pharmaceutical drugs).<sup>103</sup> This is not surprising given that chemical regulations as a class share many of the same technical and political constraints, and experience in one area of chemical regulation invariably informs efforts in others. Part II draws on experience in these other areas of chemical regulation.

## II. A COMPARATIVE ANALYSIS OF CHEMICAL REGULATION

The historical record is unequivocal on at least one aspect of chemical regulation: high-salience events have prompted significant legislative advances since 1902, when Congress passed the first law regulating “biologic drugs.” The 1902 law was spurred by the deaths associated with contaminated smallpox and diphtheria vaccines.<sup>104</sup> Passage of the Pure Food and Drugs Act (“PFDA”) in 1906 was prompted by numerous incidents of fraudulent mislabeling of drugs and the publication of Upton Sinclair’s *The Jungle*.<sup>105</sup> Similarly, the FDCA was passed in 1938 after more than one hundred people in Tennessee were poisoned by the antibiotic “Elixir Sulfanilamide.”<sup>106</sup> Perhaps most famously, the 1962 Drug Amendments were propelled

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103. See *infra* Part II.

104. Gary E. Gamerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 FOOD & DRUG L.J. 213, 216 (1994) (describing regulation as the “culmination of incidents in 1901 and 1902 in which batches of smallpox vaccine and diphtheria antitoxin were contaminated with tetanus-causing microbes”). Thirteen children died in St. Louis from exposure to diphtheria antitoxin that was contaminated with the tetanus bacterium. JAMES HARVEY YOUNG, *PURE FOOD: SECURING THE FEDERAL FOOD AND DRUGS ACT OF 1906* 148 (1989).

105. Aaron J. Ihde, *Food Controls under the 1906 Act*, in *THE EARLY YEARS OF FOOD & DRUG CONTROL* 40, 40–42 (Glenn Sonnedecker ed., 1982). See YOUNG, *supra* note 104, at 204, 281.

106. Richard A. Merrill, *The Architecture of Government Regulation of Medical Products*, 82 VA. L. REV. 1753, 1761–64 (1996) [hereinafter Merrill, *The Architecture of Government Regulation of Medical Products*] (explaining that a manufacturer recklessly used diethylene glycol in an elixir without testing it); see also Gamerman, *supra* note 104, at 218.

by an epidemic of severe birth defects linked to the drug thalidomide.<sup>107</sup> Replicating this pattern, the Federal Insecticide, Fungicide, and Rodenticide Act garnered political support following revelations about the ecological harm caused by dichlorodiphenyltrichloroethane (“DDT”), and TSCA gained legislative momentum from fears about mercury, asbestos, and most importantly PCBs.<sup>108</sup>

The commonality of dramatic triggering events, while by no means unique to these statutes,<sup>109</sup> reflects the strong opposition to and limitations of chemical regulation. Passage of the FDCA, for example, followed a series of legislative battles spanning twenty-seven years.<sup>110</sup> Evidence also exists that the public and policymakers lump chemicals together. With the dramatic growth in the production and use of chemicals by the 1970s,<sup>111</sup> the public came to view the rise of the new brand of chemicals collectively as a technological phenomenon that transcended the regulatory regimes into which they have been divided. Passage of TSCA, which occurred concurrently with the medical device amendments to the FDCA, was the last major legislative effort to regulate chemicals in this line of statutes.

The shadow of the FDCA loomed over TSCA. Allegations of the threats to innovation and delayed access to new technologies were the primary tropes of the opposition to both statutes. The incremental, multi-decadal evolution of the FDCA is a testament to their

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107. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1764 & n.35. More modest amendments to the FDCA in 1987, 1988, 1990, and 1992, most of which were directed at regulatory streamlining, were motivated by the AIDS crisis that emerged in the mid-1980s. Edward L. Korwek, *Human Biological Drug Regulation: Past, Present, and Beyond the Year 2000*, 50 *FOOD & DRUG L.J.* 123, 136–38 (1995). The 1976 amendments to the FDCA relating to regulation of medical devices were triggered in significant part by the fallout from defective intrauterine devices (“IUDs”) and numerous recalls of pacemakers. Susan Bartlett Foote, *Coexistence, Conflict, and Cooperation: Public Policies Toward Medical Devices*, 11 *J. HEALTH POL. POL’Y & L.* 501, 502–03 (1986).

108. *See New Breed of Pollutants*, *supra* note 51, at 42.

109. The significance of triggering is common to many pieces of environmental legislation. *See, e.g.*, Daniel A. Farber, *Politics and Procedure in Environmental Law*, 8 *J.L. ECON. & ORG.* 59, 67 (1992); Karkkainen, *supra* note 1, at 66–67.

110. *See generally* YOUNG, *supra* note 104 (chronicling the events between 1879 and 1906 that led to the passage of the FDCA).

111. Richard Lyons, *Can Regulators Keep Track of 1,000 New Substances a Year? Chemicals in Search of a Solution*, *N.Y. TIMES*, Dec. 25, 1977, at 108 (observing that the production of synthetic chemicals more than doubled between 1967 and 1977).

effectiveness.<sup>112</sup> Industry repeatedly raised the specter of onerous regulation causing research to move abroad and delay in access to innovative products.<sup>113</sup> The alleged impact on access to new drugs of the 1962 Drug Amendments, which imposed rigorous testing requirements, was still a major issue when TSCA was passed.<sup>114</sup> This concern was reinforced by fears about declining innovative output in the U.S. during the 1970s.<sup>115</sup>

The politics and science of toxics regulation contain formidable barriers to legislative reform of the TSCA. Two important themes run throughout the history of chemical regulation. The first is that obtaining adequate information is a costly part of the regulatory process, both in terms of time and dollars. The FDCA is the poster child in this respect, as the costs of clinical drug testing run upwards of \$600 million and involve years of work.<sup>116</sup> The second is that the uncertainties in assessing chemical toxicity make it exceedingly difficult to calibrate agency discretion, which tends toward a dichotomous all-or-nothing standard of judicial review. In particular, the courts have given the FDA broad discretion<sup>117</sup> while they subject the EPA to close scrutiny.<sup>118</sup> These core constraints suggest that toxics regulation may evolve, but without fundamental changes in the politics or science, dramatic reform is unlikely.

This Part provides a historical perspective on the regulation of chemicals and medical technologies more broadly. The characteristic that binds these areas of regulation together is the persistent

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112. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1756–57 (“The reformers believe that the need for advance FDA approval—not only to market new products, but to conduct, continue, or expand clinical trials, to build and operate new plants, to modify already approved products, to change labeling, to export—is *the* primary governmental obstacle to innovation.”).

113. John T. Kelly, *Three Years Later*, 21 FOOD DRUG COSM. L.J. 21, 25 (1966).

114. *Toxic Substances Control Act*, Hearings on H.R. 5276 and H.R. 10840 before the Subcomm. on Commerce & Finance, 92nd Cong. 131–32 (1972); Kelly, *supra* note 113, at 26 (describing how average review times increased from less than three months pre-1962 to about eighteen months after the 1962 Amendments).

115. See NAT’L RES. COUNCIL, A PATENT SYSTEM FOR THE 21ST CENTURY 18, 21 (2004); Henry Grabowski & John Vernon, *The Determinants of Pharmaceutical Research and Development Expenditures*, 10 J. EVOLUTIONARY ECON. 201, 201–02 (2000).

116. Joseph A. DiMasi & Henry G. Grabowski, *The Cost of Biopharmaceutical R&D: Is Biotech Different?*, 28 MANAGERIAL & DECISION ECON. 469, 475–76 (2007).

117. H. Thomas Austern, *Expertise in Vivo*, 15 ADMIN. L. REV. 46, 49–51 (1963).

118. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 736–38.

uncertainty in the risks associated with technologies that impact human health. The review that follows focuses on two issues: (1) the importance of allocating who has the burden of proof, and (2) the variation in testing requirements that is permitted based on either different classes of technologies or allowances for some form of surrogate testing. As demonstrated below, the two issues interact in important ways, such that the latter can limit or even undermine the significance of the former. Above all, this historical overview reveals that chemical regulations are converging to a loosely calibrated multi-tiered system that is emerging as the *de facto* model for chemical regulation going forward.

#### *A. Anticipatory Developments in Drug Regulation*

Regulation of chemicals, as exemplified by the FDCA, could easily, though mistakenly, be portrayed as a movement from weak information-oriented requirements to strict standards that must be met before a product can be marketed. This progressive narrative overlooks the Virus, Serum, and Toxin Act of 1902 (“1902 Act”), the first federal statute to impose stringent pre-market approval requirements on chemicals of any kind.<sup>119</sup> The 1902 Act, which later was amended as the Public Health Service Act (“PHSA”), regulates biologic drugs, such as vaccines,<sup>120</sup> and to this day represents a high-water mark in chemical regulation. The PHSA is also notable in that it began by regulating manufacturing processes, as opposed to end products *per se*, because testing methods for biologic drugs were virtually nonexistent at the time.<sup>121</sup>

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119. Virus, Serum, and Toxin Act of 1902, Pub. L. No. 57-244, 32 Stat. 728 (1902).

120. 42 U.S.C. § 262 (2006). The PHSA defines “biologic product” as “virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.” *Id.* § 262(i). Less formally, biologics are typically defined as “complex molecules or mixtures of biological origin, but do not include antibiotics or hormones.” Gamerman, *supra* note 104, at 215.

121. *See* Gamerman, *supra* note 104, at 216–17 (describing how regulation of the final product could not ensure safety, as minor variations in the manufacturing process could have severe and unpredictable results, in particular the high risk of contamination because biologics were typical crude extracts from human or other animal tissues).



The stars aligned for the PHSA, which was supported by federal agencies, the drug industry, and the medical community. Government-based public health departments initially developed and produced the biologic drug for treating diphtheria,<sup>122</sup> the blockbuster drug of its era, which gave federal officials exceptional authority in the eyes of congressional members. At the same time, the drug industry and medical community were in their formative years and saw the PHSA as protecting their interests.<sup>123</sup> The few established companies viewed the law as a means of limiting competition and promoting consumer confidence, which was threatened by unscrupulous producers.<sup>124</sup> In a similar vein, the medical community viewed the legislation as important to strengthening the still-tenuous credibility of medicine as a science.<sup>125</sup>

These unique circumstances led to rapid legislative action by Congress. After the Health Commissioners of the District of Columbia drafted the bill, with support from the District of Columbia Medical Society and the Hygienic Laboratory of the federal Public Health Service, the PHSA passed with essentially no congressional debate and no public involvement.<sup>126</sup>

The PHSA is a prototypical licensing statute. Under the statute, “[n]o person shall introduce or deliver for introduction into interstate commerce any biological product unless . . . a biologics license is in effect for the biological product.”<sup>127</sup> To market a biologic, a *manufacturer* is also required to obtain a license.<sup>128</sup> Biologics must be produced at properly licensed establishments, which are subject to “annual licensing renewal, unannounced inspections, [and

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122. JONATHAN LIEBENAU, *MEDICAL SCIENCE AND MEDICAL INDUSTRY: THE FORMATION OF THE AMERICAN PHARMACEUTICAL INDUSTRY* 51, 54–55 (1987) (describing how public health departments in cities like New York, Boston, Philadelphia, and Washington were instrumental in producing biologic drugs, most notably the antitoxin for diphtheria).

123. See David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 *FOOD & DRUG L.J.* 143, 149 (2005).

124. YOUNG, *supra* note 104, at 148–49.

125. See *id.* at 148 (describing how the drug industry and doctors were frustrated by opposing groups, such as “anti-vaccinationists,” who challenged the precepts of medicine during this period).

126. See *id.*

127. 42 U.S.C. § 262(a)(1) (2006).

128. *Id.* § 262(a)(2)(A).

requirements] that product samples be examined by the government laboratory for purity and potency.”<sup>129</sup> Beginning in 1944, biologic products themselves were required to “meet standards, designed to ensure the continued safety, purity, and potency.”<sup>130</sup> Throughout the process, the drug producer bears the burden of demonstrating the safety of its manufacturing processes, as well as the safety and efficacy of the product itself.<sup>131</sup>

For many decades the stringency of the PHSA licensing requirements were unique, a fact reflected by the modest scope of the Act’s amendments. Other than the 1944 amendments mentioned above, the only significant change to the law involved the transfer of concurrent regulatory authority to the FDA and National Institutes of Health in 1972.<sup>132</sup> Later, maintenance of a distinct regulatory regime for biologics came under significant fire with the advent of modern biotechnology, which nullified the distinctions between traditional drugs and biologics, and the regulatory failures associated with contaminated blood during the HIV/AIDS crisis of the 1980s.<sup>133</sup> But the statute withstood the political pressures brought on by these events and remains largely intact.<sup>134</sup>

Despite following closely on the heels of the PHSA, the politics and substance of the FDCA could not have been more different. While the PHSA garnered no public attention, passage of the FDCA was the culmination of hotly contested efforts to regulate food and drugs that dated back to 1879.<sup>135</sup> The limited scope and lengthy

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129. Gamerman, *supra* note 104, at 218. *See* 42 U.S.C. § 262(a)(2)(A). In addition, Phase III testing of biologics generally must be in a commercial-scale facility, and only the manufacturer of a biologic that meets this requirement can have marketing rights. Gamerman, *supra* note 104, at 214.

130. Ch. 373, § 351, 58 Stat. 702 (1944) (current version at 42 U.S.C. § 262(a)(2)(C)(i)(I)).

131. 42 U.S.C. 262(a)(2)(C) (explaining that a biologics license shall be approved upon demonstration that the biologic product “is safe, pure, and potent; and the facility in which the biologic product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent”); *see also* Korwek, *supra* note 107, at 125.

132. Edward L. Korwek & Michael N. Druckman, *Human Biologics*, in *FOOD AND DRUG L. AND REG.* 433, 437 (2008).

133. Gamerman, *supra* note 104, at 220–21. The lines were blurred earlier when the FDA was given regulatory jurisdiction over insulin in 1941 and antibiotics in 1945. *Id.* at 219.

134. *See* Korwek & Druckman, *supra* note 132, at 438–39 (noting that Congress has directed FDA to minimize the differences in the review processes under the PHSA and FDCA).

135. *See* YOUNG, *supra* note 104, at 45.

gestational period of the legislation were products of the strong opposition to the law. Unlike the strict approval standards of the PHSA, the FDCA eschewed formal regulatory review in favor of standards designed to preserve the integrity of product marketing and branding. The 1906 PFDA gave the government authority only to prohibit and penalize the marketing of drugs that were “adulterated or misbranded or poisonous or deleterious.”<sup>136</sup> Claims about the efficacy of a drug in treating a condition did not require any scientific support, and *actual* knowledge of adulteration had to be proven.<sup>137</sup>

The modest scope of the 1906 PFDA was upgraded after more than thirty years, following the deaths caused by the solvent-tainted antibiotic Elixir Sulfanilamide.<sup>138</sup> This first set of amendments marked the beginning of the FDCA’s movement toward the PHSA. The 1938 amendments established a TSCA-like form of pre-market review for all drugs regulated by FDA.<sup>139</sup> Under this regime, manufacturers were required to submit safety data in a new drug application (“NDA”), which became effective unless the FDA notified the manufacturer within sixty days that the effective date for the application was being postponed to permit further review.<sup>140</sup> Manufacturers were entitled to market a drug unless the FDA challenged its safety within the 180-day period given to conduct its pre-market review.<sup>141</sup>

The 1938 FDCA amendments anticipated TSCA insofar as they distinguished between new and existing drugs. All new drugs were subject to pre-market review, whereas manufacturers were given broad discretion to determine whether drugs reformulated with existing compounds “enjoyed a sufficient reputation for safety” in order to avoid FDA pre-market review altogether.<sup>142</sup> As a half-

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136. Federal Food and Drugs Act, ch. 3915, § 1, 34 Stat. 768 (1906) (current version at 21 U.S.C. § 301 (2006)). Specifically, marketing information could not be “false or misleading in any particular” as to the identity of a drug. Federal Food and Drugs Act § 1.

137. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1761, 1767, 1790.

138. *Id.* at 1761; *see also* Gamerman, *supra* note 104, at 218.

139. Gamerman, *supra* note 104, at 218–19.

140. *Id.* at 218.

141. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1764–65.

142. *Id.* at 1762.

measure, manufacturers were encouraged to consult informally with FDA prior to marketing such products.<sup>143</sup>

The adoption of a formal pre-market approval process took another twenty-four years and the political storm created by a much greater human tragedy. In 1962 the severe birth defects associated with thalidomide, an anti-morning sickness drug, reached a global scale.<sup>144</sup> This event fueled public pressure for more stringent regulation of the rapidly growing pharmaceutical industry.<sup>145</sup> The 1962 Drug Amendments to the FDCA established a rigorous pre-market approval process that placed the burden of proof on drug manufacturers to demonstrate, under a substantial evidence standard,<sup>146</sup> the safety and efficacy of their drug products.<sup>147</sup> Equally remarkable, these sweeping reforms were passed unanimously by the House and Senate,<sup>148</sup> despite substantial political opposition prior to the shock of the thalidomide debacle.

The 1962 Drug Amendments delegated unprecedented powers to FDA. One prominent commentator has referred to FDA's authority as akin to "jaw-bone enforcement" that combines drastic sanctions and strict criminal liability, both of which are based on vague, highly technical standards.<sup>149</sup> The broad legal framework and complex technical questions have led courts to be highly deferential to the FDA. In marked contrast to judicial review of EPA decisions under TSCA, the FDA has circumvented the formal hearing requirements for determinations of whether a pre-1962 drug meets the FDCA's

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143. *See id.* at 1763. The standard for product labeling was also increased to prohibit it from being "false or *misleading in any particular*" and to impose an affirmative duty on manufacturers "to reveal facts material in the light of such representations." *Id.* at 1762–63 (emphasis added).

144. *Id.* at 1764 n.35.

145. *See id.* at 1764.

146. *Id.* at 1766. The FDCA defines "substantial evidence" as "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified . . . to evaluate the effectiveness of the drug involved." 21 U.S.C. § 355(d) (2006). It also grants FDA very broad authority to determine the design and conduct of clinical trials, which FDA has exercised liberally. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1766–67.

147. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1765.

148. Austern, *supra* note 117, at 49.

149. *Id.* at 50, 55, 59.

efficacy standard.<sup>150</sup> FDA successfully avoided formal hearings by promulgating a high standard for demonstrating efficacy and disposing of manufacturer challenges on summary judgment.<sup>151</sup> This and many other decisions have led commentators to conclude that the FDA's rulemaking process "has virtual immunity from judicial intervention or correction."<sup>152</sup>

Changes in drug regulation have not been one directional. Countervailing pressures have caused Congress to whittle away at the absolute bar to the sale of drugs absent formal FDA pre-market approval. The pressure to relax standards has come from patient groups seeking access to new, promising drugs, as well as the drug industry. From the outset critics warned that the FDA drug approval process would have negative impacts on innovation and patient access to new drugs.<sup>153</sup> In partial recognition of this tension, the 1962 Amendments allowed drugs undergoing clinical testing to circumvent FDA pre-market approval if such investigational drugs were prescribed as part of a valid clinical study.<sup>154</sup>

It was not until the AIDS crisis, however, that patient groups seeking early access to potentially life-saving drugs succeeded in liberalizing this narrow exception.<sup>155</sup> During the late 1980s and early

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150. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1770.

151. *Id.* at 1770–72. FDA used a similar tactic to avoiding having to review follow-on drugs that were derivative of pre-1962 pioneer drugs; if the pioneer failed to meet the efficacy standard, all of the follow-on drugs were presumed to fail as well. *Id.* at 1773–74. Similarly, FDA was nominally given 180 days to conduct its review, but in practice every new submission of data restarted the clock and no manufacturer has had the fortitude to challenge FDA and risk receiving a rejection. *Id.* at 1766.

152. Austern, *supra* note 117, at 54; *see also* Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1782 ("FDA exercises effectively unchallengeable authority to dictate the number and kinds of studies required to support approval and nearly unreviewable discretion to interpret the results.").

153. *See* Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1792–93; Richard A. Merrill, *Modernizing the FDA: An Incremental Revolution*, 18 HEALTH AFF. 96, 98 (1999) [hereinafter Merrill, *Modernizing the FDA*] (observing that by the 1990s many critics of the "drug lag" were skeptical of administrative strategies for addressing it; they instead believed more fundamental changes were required).

154. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1777–79 (explaining that clinical studies are required to secure informed consent from participants, keep records, and adhere to FDA clinical testing regulations).

155. Korwek, *supra* note 107, at 136–38; Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1836–38 (commenting that the AIDS crisis

1990s, Congress passed amendments to the FDCA allowing the “treatment use” of promising new investigational drugs on a limited basis through, in effect, a pre-market notification process.<sup>156</sup> Under this scheme manufacturers were required to give FDA notice of proposed treatment uses, and FDA was given thirty days to object to them.<sup>157</sup> Subsequent amendments have instituted “fast track” approval processes for drugs that treat life-threatening diseases and broadened parallel access to investigational drugs (i.e., to patients not involved in a clinical trial) where patient entry into a clinical trial is not possible and no other therapeutic alternatives exist.<sup>158</sup> In essence, these amendments created distinct tiers of drugs that can be made available to patients on a limited basis through alternative FDA approval processes.

The Federal Insecticide, Fungicide, and Rodenticide Act (“FIFRA”), which governs the sale and marketing of pesticides,<sup>159</sup> and the 1976 Medical Device Amendments to the FDCA occupy a middle ground between the pre-market notice regime of TSCA (and the pre-1962 FDCA) and the current pre-market approval process for drugs. FIFRA is a licensing statute with a twist. While all pesticides must be registered for a specific use, the statutory standard is relatively weak—pesticides need only achieve their intended results and not cause “unreasonable adverse effects on the environment.”<sup>160</sup> This standard allows EPA to register pesticides suspected to be carcinogens so long as they achieve their purpose without causing “unreasonable adverse effects on the environment.”<sup>161</sup> Thus, whereas the focus of the FDCA is on absolute safety and efficacy, the

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marked the first time that effective pressure was put on FDA to approve drugs faster).

156. Korwek, *supra* note 107, at 136.

157. *Id.* at 137.

158. *Id.* at 138–39.

159. 7 U.S.C. § 136 (2006). FIFRA defines pesticide as “any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and any nitrogen stabilizer. . . .” *Id.* § 136(u).

160. *Id.* § 136a(c)(5)(C)–(D). FIFRA defines “unreasonable adverse effects on the environment” as “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 a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 346a of Title 21.” *Id.* § 136(bb).

161. *Id.* § 136a(c)(5)(C)–(D).

standard for registration of a pesticide is relative and calibrated to its benefits.<sup>162</sup> Further, although the burden of proof nominally lies with pesticide producers, for the nineteen thousand older pesticides on the market in the mid-seventies, the burden to obtain reliable data on their risks effectively lies with EPA.<sup>163</sup> One of the central lessons from FIFRA is that a licensing regime and burden shifting can be undermined by lax standards and expansive grandfathering of existing compounds. Despite the trappings of formal pre-marketing approval, some commentators have argued that FIFRA's weak regime is reflective of the waning power of environmentalism and the growing legislative sophistication of regulatory opponents.<sup>164</sup>

The Medical Device Amendments were influenced by experience with drug regulation and propelled by another regulatory failure: eleven maternal deaths from the Dalkon Shield intrauterine device.<sup>165</sup> In the end, Congress remained firm in its commitment to avoid the purported innovation-stifling effects of the FDCA medical device approval process.<sup>166</sup> Consistent with this perspective, the defining feature of the Medical Device Amendments is their tiered regulatory framework. Anticipating the framework adopted by the EU in REACH, Congress believed that it would be inefficient to regulate all medical devices, which range from bedpans to cardiac pacemakers, under a single regime.<sup>167</sup> A central premise of the law was therefore that "the great majority of devices would not require premarket approval."<sup>168</sup>

The new law established three categories: Class I contains general controls for the simplest devices; Class II contains categorical performance standards involving requirements for certain features and essential characteristics of devices; and Class III is for the most complex devices, and imposes a full-blown regulatory approval

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162. Donald T. Hornstein, *Lessons from Federal Pesticide Regulation on the Paradigms and Politics of Environmental Law Reform*, 10 YALE J. ON REG. 369, 389–90 (1993).

163. *Id.* at 437–38.

164. *Id.* at 434–35.

165. William H. Maisel, *Safety Issues Involving Medical Devices: Implications of Recent Implantable Cardioverter-Defibrillator Malfunctions*, 294 JAMA 955, 955 (2005).

166. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1800, 1807.

167. *Id.* at 1812.

168. *Id.*

process analogous to that for drugs.<sup>169</sup> Congress's decision to allow partial privatization of the review process for Class I and II devices is a distinctive element of the law.<sup>170</sup> Begun as a five-year experiment in 1997,<sup>171</sup> the program has since been extended and expanded.<sup>172</sup>

The Medical Device Amendments have had mixed success. FDA was mandated to classify medical devices into one of the three categories as a first step to regulating them, but the process took twelve years to complete.<sup>173</sup> Likewise, more than a decade passed before FDA made significant headway in reviewing and formally approving pre-enactment Class III devices—the silicone breast implant controversy being the most visible fallout from this delay.<sup>174</sup> It also remains unclear whether Congress struck the right balance between ensuring adequate regulatory oversight and not unduly delaying access to new technologies. A number of recent high-profile recalls, particularly of implantable cardiovascular devices such as pacemakers and defibrillators, have renewed pressure on FDA to strengthen its oversight.<sup>175</sup>

### *B. Convergent and Divergent Trends in Chemical Regulation*

The preceding survey of chemical regulation reveals several broad trends. First, placing the burden of proof on the producer has largely won out. Although relaxed to allow limited access to investigational

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169. 21 U.S.C. § 360c(a) (2006).

170. See Merrill, *Modernizing the FDA*, *supra* note 153, at 106. Under the Food and Drug Administration Modernization Act of 1997, the FDA has authority to accredit organizations to perform regulatory reviews, but only for pre-market notification of devices similar to products in Class I or II. 21 U.S.C. § 360m. Further, all third-party determinations must be submitted to FDA, which has thirty days to accept or reject the action. *Id.* § 360m(a)(2)(A).

171. Merrill, *Modernizing the FDA*, *supra* note 153, at 106.

172. See Judy Vale, *Expanding Expanded Access: How the Food and Drug Administration Can Achieve Better Access to Experimental Drugs for Seriously Ill Patients*, 96 GEO. L.J. 2143, 2155 (2008).

173. Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1807–09.

174. *Id.* at 1814.

175. See, e.g., Mike Mitka, *Medical Device Oversight under Scrutiny*, 295 JAMA 1109, 1009 (2006) (noting the recall of certain defibrillators and pacemakers manufactured by Guidant Corporation); Gardiner Harris, *Report Criticizes F.D.A. on Device Testing*, N.Y. TIMES, Jan. 16, 2009, at A17 (quoting the FDA commissioner's explanation that "sometimes it takes a crisis before" such recognition of the problems with current testing mechanisms occurs).



drugs, the FDCA exemplifies this shift and represents the high-water mark of chemical regulation in the United States. Second, tiered regulatory regimes such as those found in REACH and the Medical Device Amendments are emerging as the dominant regulatory framework. Third, regulation of industrial chemicals in the U.S. is trailing these developments. TSCA, the only statute that relies solely on regulatory review, continues to occupy the low-water mark for chemical regulation. FIFRA lies somewhere in the middle of the spectrum with its weak system of regulatory approval. The central role of cost-benefit balancing in each of these statutes further sets them apart.

The large scientific uncertainties and high costs of chemical regulation have created discord in the legal system. The tensions are perhaps most visible in divergent standards for judicial review of agency rulemaking—FDA’s open-ended discretion under the FDCA versus EPA’s cramped rulemaking authority under TSCA. The large scientific uncertainties have made it exceedingly difficult for courts to adopt an intermediate level of review, forcing them either to defer broadly to agency decisions or to use the technical uncertainties as a pretext for overturning agency rules. This dichotomous treatment of FDA and EPA persists despite the near identity of the sources of uncertainty with which each agency contends.

While this striking difference in judicial scrutiny is troubling, calibrating judicial review in this context is clearly difficult. It is made more so by the discrepancies in likelihoods and magnitudes of risks at stake. Although often overlooked, the difference in relative rates of regulatory rejections is an important systemic difference between regulating drugs and industrial chemicals. Ninety percent of drugs fail clinical trials due to problems with either toxicity or efficacy,<sup>176</sup> whereas conservative estimates based on existing studies find that about twenty percent of industrial chemicals exhibit some form of toxicity.<sup>177</sup>

The significance of these divergent base rates is best appreciated through representative testing numbers. Drawing on the REACH and EPA high-production volume testing programs, we can project that

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176. See PISANO, *supra* note 18, at 56–57.

177. See *supra* text accompanying note 48.

about five thousand chemicals will be tested using sophisticated animal bioassays.<sup>178</sup> If past studies are representative, approximately twenty percent of the tested chemicals will be human toxins of some form, and recent estimates suggest that the false-positive rate for animal bioassays is about ten percent.<sup>179</sup> Although it is much more difficult to determine the rate of false negatives, the available evidence suggests that the rate is low, as “[e]very known human carcinogen has tested positive in laboratory animals.”<sup>180</sup> I will assume conservatively that the false-negative rate is also ten percent. For comparison purposes, I will assume that the rates for false negatives and false positives in drug testing are both ten percent.

The difference in base rates—twenty percent versus ninety percent—dramatically impacts the actual numbers of false positives and negatives. If five thousand industrial chemicals are tested, four hundred false positives would be recorded. This translates to twenty-eight percent of the chemicals testing positive for toxicity when they are not in fact toxic.<sup>181</sup> By contrast, 2.5 percent of the chemicals testing negative would exhibit some toxicity.<sup>182</sup> The corresponding numbers for drugs are more divergent and inverted: forty-seven percent of drugs that make it through clinical testing should have tested positive, while just one percent of the drugs that fail clinical testing should have been found safe and effective.<sup>183</sup> These illustrative calculations reveal that false positives are more common than false negatives for toxicity testing of industrial chemicals, whereas false negatives are of much greater concern in drug testing.

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178. See *supra* text accompanying note 48.

179. William H. Farland et al., *Cancer Bioassays*, 5 BRIT. MED. J. E390, E391 (2005).

180. *Id.*

181. The math is straightforward: (1)  $5000 * 0.8 * 0.1 = 400$  false negatives, (2)  $5000 * 0.2 = 1000$  true positives, and (3)  $400 / (400 + 1000) * 100 = 29$  percent of compounds that test positive are in fact nontoxic.

182. The basic math is the same: (1)  $5000 * 0.2 * 0.1 = 100$  false negatives, (2)  $5000 * 0.8 = 4000$  true negatives, and (3)  $100 / (100 + 4000) * 100 = 2.5$  percent of compounds that test negative are in fact toxic.

183. False negatives: (1)  $1000 * 0.9 * 0.1 = 90$ , (2)  $1000 * 0.1 = 100$ , (3)  $90 / (90 + 100) * 100 = 47$  percent; false positives: (1)  $1000 * 0.1 * 0.1 = 10$ , (2)  $1000 * 0.9 = 900$ , (3)  $10 / (10 + 900) * 100 = 1$  percent. I am using, somewhat arbitrarily, one thousand for the number of drugs because this is the number of applications that are submitted for new drugs to FDA annually. Schmeck, *supra* note 47, at 99.

A naive interpretation of these results would favor the current asymmetric approach to judicial review. Courts would be deferential to EPA decisions not to regulate and apply greater scrutiny to its decisions to regulate, while judicial review of FDA rulemaking would be the opposite. But EPA decisions not to regulate typically are much harder to challenge because they often involve informal decisions outside of administrative rulemaking processes, limited data, or neither data nor formal processes.<sup>184</sup> EPA decisions to regulate thus are already much more likely to be challenged.<sup>185</sup> This is not the case for the FDA, which is required to affirmatively make a decision regarding every drug it reviews, so that judicial review of its decisions is not subject to the same bias.<sup>186</sup> The complicating dynamic for FDA rulemaking stems from the broad judicial deference courts grant FDA, which discourages legal challenges altogether.<sup>187</sup>

The multidimensional nature of chemical regulation qualifies the inferences one can draw from the contrasting base rates between drugs and industrial chemicals. For one, decisions are not simply whether to regulate—the stringency of regulation is of equal importance. Additionally, absolute numbers matter. The impacts of failing to detect the toxicity of four hundred industrial chemicals could be severe, particularly if any of them are used in large quantities, bioaccumulative, or environmentally persistent (e.g., DDT, PCBs).<sup>188</sup> Multiple factors therefore must be considered in structuring a regulatory regime that defies a binary rule. The regulatory base rates provide, at best, a rough rationale for the different frameworks and standards that have evolved between the regulation of industrial chemicals and drugs.

These complexities help to explain recent efforts to moderate chemical regulation at both ends of the spectrum. Under the FDCA,

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184. Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 737–39.

185. *See, e.g., id.* at 737.

186. *See* Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, at 1792.

187. *See supra* Part II.

188. *See* Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 725; Environmental Protection Agency, Polychlorinated Biphenyls (PCBs), Basic Information, <http://www.epa.gov/epawaste/hazard/tsd/pcbs/pubs/about.htm> (last visited Apr. 26, 2010).

Congress has created limited exceptions to the stringent drug approval process, while passage of REACH in Europe strengthens regulation of industrial chemicals. This convergence, which affects the stringency of regulation and its structure, provides an attractive model for renewed efforts to amend TSCA in the U.S. In particular, the tiered regimes found in REACH and the Medical Device Amendments have the dual advantage of political viability and respectable scientific grounding.

Regulatory error rates also highlight the permeability of prospective chemical regulation. This is particularly true of drug regulation, where the extraordinary costs of clinical testing and substantial rates of false negatives create conditions in which, as a practical matter, gaps in regulatory protection are unavoidable. The same statistical obstacles affect regulation of industrial chemicals, but the bias favors over-regulation. Statistical base rates, particularly in drug regulation, qualify the customary distinction made between *ex post* common law actions and *ex ante* statutes. So long as agencies are reliant on traditional modes of toxicity testing, chemical pre-regulation will have prospective aspirations that it can meet only partially, and follow-up monitoring will be an important supplement.

### III. SCIENTIFIC DEVELOPMENTS CHALLENGING THE TOXICOGENOMICS PARADIGM

“Fast, inexpensive testing methods currently under development ‘are the potential foundation for a national cancer policy that would prevent this menacing disease.’”<sup>189</sup>

The slow progress of toxicology suggests that science is unlikely to come to the aid of regulators in the foreseeable future.<sup>190</sup> The

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189. *Environmental Prevention of Cancer Urged*, WILMINGTON MORNING STAR, Feb. 28, 1976, at 2.

190. INST. FOR HEALTH & CONSUMER PROT., *supra* note 84, at 23–24.

Science currently is the bottleneck for the development and validation of *in vitro* methods for the replacement of complex *in vivo* toxicological tests . . . However, from a scientific point of view it is known that *in vitro* methods and (Q)SARs (either separately or together) will never be able to *fully* replace the animal tests for the most complex endpoints, within the timeframe required by current and proposed legislation.

*Id.*

standard suite of toxicology tests have changed very little over the last half-century.<sup>191</sup> Use of animal models subjected to high doses of a chemical remains the methodology of choice in toxicity testing,<sup>192</sup> despite longstanding concerns about their large uncertainties. A typical objection is that “uncertain extrapolations, first from high doses to environmental levels that are usually orders-of-magnitude lower than those used in the animal studies, and then from animals to humans”<sup>193</sup> lead to significant uncertainties.

A new school of toxicology is importing powerful methods and biological insights from the biomedical sciences, especially from pharmaceutical research.<sup>194</sup> These methods focus on changes in gene activity levels and the associated concentrations of proteins and metabolites in specific cells and tissues.<sup>195</sup> Potential uses could include triaging contaminants and contaminated sites; environmental and human health monitoring; regulatory reporting metrics; and risk assessment.<sup>196</sup> High-throughput genomics methods provide a platform technology that allows more than 100,000 compounds to be screened per day in the pharmaceutical industry.<sup>197</sup> They hold the potential to radically reduce the costs of and increase the rate at which industrial chemicals can be evaluated for toxicity.<sup>198</sup>

Incorporation of toxicogenomic methods represents a paradigm shift in the field of toxicology that will require a fundamental change

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191. Andersen & Krewski, *supra* note 14, at 324 (commenting that the basic methods date back thirty to sixty years); Hartung, *supra* note 19, at 208; Michael P. Holsapple et al., *The “Vision” for Toxicity Testing in the 21st Century: Promises and Conundrums*, 107 TOXICOLOGICAL SCI. 307, 307 (2009).

192. Andersen & Krewski, *supra* note 14, at 324.

193. *Id.*

194. Andersen & Krewski, *supra* note 14, at 328 (discussing the use of new genomics methods in the pharmaceutical sector, including *in silico* modeling and *in vitro* screens); David J. Dix et al., *The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals*, 95 TOXICOLOGICAL SCI. 5, 7 (2007) [hereinafter Dix et al., *The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals*] (“HTS [high-throughput screening] technology optimized for drug discovery is now being refocused to applications in toxicological screening.”).

195. David J. Dix et al., *A Framework for the Use of Genomics Data at the EPA*, 24 NATURE BIOTECHNOLOGY 1108, 1108 (2006).

196. *Id.* at 1109.

197. Francis S. Collins et al., *Transforming Environmental Health Protection*, 319 SCIENCE 906, 906 (2008).

198. *See id.*

in the field's scope, knowledge base, and methods.<sup>199</sup> At the most basic level, scientists believe that the rise of toxicogenomics will shift the focus of testing from animal models to *in vitro* testing of changes in specific biological processes using isolated cells.<sup>200</sup> Scientists anticipate that this move to *in vitro* systems will reduce the need for inferential judgments to interpret study findings, enhance the accuracy of testing methods, and lower testing costs significantly.<sup>201</sup>

Changes of this magnitude do not come cheaply and will not occur overnight. A recent report issued by the National Research Council predicted that development of toxicogenomics methods—and use of them as a basis for regulatory decision-making—would take ten to twenty years to implement and require investments of one billion dollars.<sup>202</sup> As I will discuss further below, these estimates are probably overly optimistic. If experience in the pharmaceutical sector is relevant—and it should be—recent scientific developments suggest that progress will be slow. The productivity of drug development, which uses the same collection of “omics” methods, is actually declining. Further, scientists are discovering new layers of complexity that implicate human disease processes and chemical toxicity. Cancer, for example, is strongly associated with still-poorly understood “epigenetic” processes that govern the regulation of gene activity, as are a variety of environmental exposures.<sup>203</sup>

In this Part, I will review the potential impacts of toxicogenomics methods and evaluate critiques that suggest its capacity to inform

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199. See, e.g., Andersen & Krewksi, *supra* note 14, at 329 (arguing that the emergence of toxicogenomics “will require significant revision of the curricula currently used to train students for careers in toxicology”).

200. Holsapple et al., *supra* note 191, at 307 (discussing the shifting “focus [to] *in vitro* methods that evaluate chemicals’ effects on biological processes using cells, cell lines, or cellular components”).

201. Collins et al., *supra* note 197, at 906 (stating that use of toxicogenomics will serve to “rely increasingly on human as opposed to animal data; and to offer increased efficiency in design and costs”).

202. Andersen & Krewksi, *supra* note 14, at 328.

203. Stella Marie Reamon-Buettner et al., *The Next Innovation Cycle in Toxicogenomics: Environmental Epigenetics*, 659 MUTATION RES. 158, 159–60 (2008) (discussing the “growing body of evidence that environmental exposures, particularly in early development, can induce epigenetic changes that may be transmitted in subsequent generations and may serve as a basis of diseases developed later in life” and noting that many forms of cancer are not linked to epigenetic changes).

regulatory decision-making will be limited and require decades of research. It is here that my skepticism is perhaps greatest but also most uncertain given the inherent unpredictability of a rapidly changing field like the biomedical sciences.

#### *A. The Promise of Genomics Methods*

The purported benefits of toxicogenomic methods are remarkable. Proponents claim that it will greatly enhance the accuracy of animal models,<sup>204</sup> allow direct measurements of chemical toxicity at very low levels of exposure,<sup>205</sup> permit rapid high-throughput screening of compounds for toxicity,<sup>206</sup> enable multiple chemicals to be tested simultaneously for toxicity,<sup>207</sup> and establish new means for assessing harm to organisms beyond humans.<sup>208</sup> If these predictions are realized, dose-response relationships, which currently rely on extrapolating from high levels of exposure, could be mapped across multiple concentrations that match realistic levels of human exposure.<sup>209</sup>

Gene expression profiling is toxicogenomics' foundational technology. It tracks the biological effects of a toxic substance by monitoring genes that are activated (i.e., transcribed) or deactivated

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204. See Cynthia A. Afshari et al., *Application of Complementary DNA Microarray Technology to Carcinogen Identification, Toxicology, and Drug Safety Evaluation*, 59 *CANCER RES.* 4759, 4760 (1999); Olden et al., *supra* note 5, at 1966.

205. Marilyn J. Aardema & James T. MacGregor, *Toxicology and Genetic Toxicology in the New Era of "Toxicogenomics": Impact of "-omics" Technologies*, 499 *MUTATION RES.* 13, 18 (2002); Simmons & Portier, *supra* note 5, at 904.

206. Richard A. Lovett, *Toxicologists Brace for Genomics Revolution*, 289 *SCIENCE* 536, 536 (2000) (asserting that toxicogenomics will reduce the costs and time associated with toxicity testing); William D. Pennie et al., *The Principles and Practice of Toxicogenomics: Applications and Opportunities*, 54 *TOXICOLOGICAL SCI.* 277, 277 (2000).

207. Scott W. Burchiel et al., *Analysis of Genetic and Epigenetic Mechanisms of Toxicity: Potential Roles of Toxicogenomics and Proteomics in Toxicology*, 59 *TOXICOLOGICAL SCI.* 193, 193–94 (2001); Olden et al., *supra* note 5, at 1966.

208. See Michael Waters et al., *Systems Toxicology and the Chemical Effects in Biological Systems (CEBS) Knowledge Base*, 111 *ENVTL. HEALTH PERSP.* 811, 821 (2003) (asserting that toxicogenomics will allow comparative analysis of impacts between different species).

209. See Andersen & Krewski, *supra* note 14, at 326 (describing high-throughput testing based on a suite of assays that could reveal dose-response relationships over a very broad range of doses); Collins et al., *supra* note 197, at 906 (claiming that toxicogenomic methods will allow testing of compounds "at as many as 15 concentrations, generally ranging from ~5  $\mu$ M to ~100 mM, to generate a concentration-response curve").

by exposure to a chemical.<sup>210</sup> Gene expression levels are used as signatures of specific toxicity pathways being activated in response to chemical exposure.<sup>211</sup> For example, if a chemical causes direct damage to DNA (e.g., polyaromatic hydrocarbons) or interferes with hormonal regulators (e.g., endocrine disruptors), a genome-wide assay following an exposure would reveal aberrant activity levels among those genes vulnerable to the tested chemical.<sup>212</sup> Scientists believe that such gene expression profiling, by virtue of its capacity to monitor dynamic biological responses, will enable them to understand the underlying mechanisms of chemical toxicity.<sup>213</sup>

Using known toxic compounds, scientists believe that toxicogenomic methods will enable them to identify toxicity pathways and how they are affected by toxic substances.<sup>214</sup> This process will allow toxic effects to be catalogued, toxic chemicals to be identified by their specific signatures of toxicity, and efficient screening of new compounds for potential toxicity.<sup>215</sup> The major challenges to validating these *in vitro* methods are believed to be twofold. First, the observed impacts on toxicity pathways will have to be related to actual disease onset and progression.<sup>216</sup> Put more simply,

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210. Mark R. Fielden & Tim R. Zacharewski, *Challenges and Limitations of Gene Expression Profiling in Mechanistic and Predictive Toxicology*, 60 TOXICOLOGICAL SCI. 6, 7 (2001). “The underlying hypothesis for ToxCast is that toxicological response is driven by interactions between chemicals and biomolecular targets. In most cases, these targets are part of the cellular proteome (e.g., receptors, ion channels, kinases).” Dix et al., *The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals*, *supra* note 194, at 6.

211. When a gene is activated, its genetic sequence of nucleotides is transcribed (i.e., transferred) to a complementary molecule, messenger RNA (“mRNA”), which is then transported to a unit of the cell that uses the mRNA as a template for constructing the protein for which the gene codes. Lawrence H. Lash et al., *Genetics and Susceptibility to Toxic Chemicals: Do You (or Should You) Know Your Genetic Profile?*, 305 J. PHARMACOLOGY & EXPERIMENTAL THERAPEUTICS 403, 407 (2003). The number of mRNA generated during the transcription process correlates with the level of activity of the gene in question. *Id.*

212. Simmons & Portier, *supra* note 5, at 904.

213. See Michael D. Waters et al., *Toxicogenomic Approach for Assessing Toxicant-Related Disease*, 544 MUTATION RES. 415, 419 (2003) [hereinafter Waters et al., *Toxicogenomic Approach for Assessing Toxicant-Related Disease*].

214. Andersen & Krewski, *supra* note 14, at 325 (explaining the process of resolving dose-response relationships from perturbations of toxicity pathways using *in vitro* methods and then linking them back to *in vivo* processes).

215. See *id.* (discussing the identification of toxicity pathways (i.e., biological signaling pathways) in conjunction with a suite of high-throughput tests to expose “the range of significant perturbations of human biology that might occur as a result of chemical exposure”).

216. *Id.* at 327 (“Understanding the relationships between early perturbations and more



toxicity signatures based on model cellular systems must be shown to be predictive of much larger biological harm. The second challenge involves relating *in vitro* test results at specific chemical concentrations to the relevant exposure levels *in vivo*. Metabolic processes that break-down chemicals have a dramatic impact on the levels of a chemical *in vivo*, and this introduces a large source of uncertainty in determining the levels of exposure to relevant target organs or cell types given a specific level of exposure from environmental sources.<sup>217</sup> Continued ignorance about this relationship is likely to require that animal testing remain an important tool.<sup>218</sup>

The EPA is supporting the development of toxicogenomic methods under its ToxCast program. In its simplest form, the objective of ToxCast is to identify the protein targets and biological effects associated with environmental toxins.<sup>219</sup> In the near-term, the program's objective is to develop tools that will facilitate the prioritization of compounds for standard toxicity testing.<sup>220</sup> The ToxCast program is in the process of using gene expression profiling to identify signatures of toxicity for over three hundred well-characterized toxins (primarily pesticides) across more than four hundred end points (e.g., endocrine disruption).<sup>221</sup> Scientists will complement this experimental work by developing elaborate computer models for "*in silico*" testing, with a focus on the liver, because it is the target of more than five hundred environmental pollutants.<sup>222</sup>

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integrated apical responses will require co-ordination of *in vitro* and *in vivo* studies in the near term.").

217. *Id.* at 326 ("Accounting for metabolism in biological systems *in vitro* remains a difficult problem. . . .").

218. *Id.*

219. Dix et al., *The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals*, *supra* note 194, at 6. The National Institutes of Health Chemical Genomics Center has taken an alternative approach to identifying toxicity pathways via the international HapMap Project, which evaluates the differential sensitivity of cell lines. Collins et al., *supra* note 197, at 907. "The ultimate goal [of HapMap] is to establish *in vitro* 'signatures' of *in vivo* rodent and human toxicity." *Id.*

220. Collins et al., *supra* note 197, at 907; Dix et al., *The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals*, *supra* note 194, at 5.

221. Collins et al., *supra* note 197, at 907.

222. *Id.*

Scientists acknowledge that major obstacles remain to applying toxicogenomic methods in a regulatory setting. The interpretation of experimental results is likely to be particularly complex. As one expert has explained: “[n]o single assay or endpoint will have a large impact on interpretation of the fingerprint or bioactivity profile. It will be the overall pattern across many assays and data types that will be the predictor of toxicity used for prioritizing chemicals.”<sup>223</sup> The qualitative balancing that integration of a broad assortment of data will entail suggests that difficult scientific judgments and discretion will not be eliminated by adoption of toxicogenomic methods. The judgments no doubt will be different and, one can only hope, less subject to uncertainty and disagreement among experts.

*B. Shooting for Mars: Signs of Increasing Genetic Complexity*

“It would be difficult to overstate the importance of the cloning of the cystic fibrosis gene. . . . The implications of [the] research are profound; there will be large spin offs in basic biology . . . but the largest impact will be medical.”<sup>224</sup>

The decoding of the gene for cystic fibrosis in 1989 is a cautionary example of the persistent chasm between the promise of genomics methods and their medical benefits. Cystic fibrosis was supposed to be a relatively tractable case that would demonstrate the huge potential of genomics science to revolutionize medicine.<sup>225</sup> This discovery was a watershed event because it involved the first use of genomics methods to decode the gene associated with a human disease.<sup>226</sup> Yet, as the scientists who decoded the gene now acknowledge, “[t]he disease has contributed much more to science than science has contributed to [treating] the disease.”<sup>227</sup>

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223. Dix et al., *The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals*, *supra* note 194, at 11.

224. P. N. Goodfellow, *Steady Steps Lead to the Gene*, 341 NATURE 102, 102 (1989).

225. *See id.*; Daniel W. Nebert et al., *From Human Genetics and Genomics to Pharmacogenetics and Pharmacogenomics: Past Lessons, Future Directions*, 40 DRUG METABOLISM REVIEW 187, 190 (2008); Esther F. Schmid & Dennis A. Smith, *Pharmaceutical R&D in the Spotlight: Why is There Still Unmet Medical Need?*, 12 DRUG DISCOVERY TODAY 998, 1000–01 (2007).

226. Helen Pearson, *One Gene, Twenty Years*, 460 NATURE 165, 165 (2009).

227. *Id.*

The genetic complexity of cystic fibrosis has consistently outpaced scientific understanding. The number of mutations associated with cystic fibrosis is stunning—more than 1500 have been identified, each requiring a different therapeutic approach.<sup>228</sup> Further, despite expenditures of several hundred million dollars, a broadly effective treatment has yet to be discovered,<sup>229</sup> and basic questions remain unresolved regarding the mechanism for the disease and how specific mutations cause it.<sup>230</sup> Moreover, while some of the impediments may be particular to the cystic fibrosis gene, many are not, such as the importance of other associated genes to its functionality.<sup>231</sup>

This experience has led Jack Riordin, one of the co-discoverers of the cystic fibrosis gene, to conclude that a central lesson from the work on cystic fibrosis is the remarkable complexity of human biology.<sup>232</sup> Riordin has expressed the challenge of applying genomics to medicine in the following terms: “It’s not like going to the Moon—it’s going to Mars.”<sup>233</sup>

### 1. The Intricacies of Interpreting Toxicogenomic Indicators

The intuitive appeal of using gene activity levels to identify toxicity pathways has often obscured the underlying complexities.<sup>234</sup> Biologists know, for example, that changes in gene expression can be caused by a host of processes, such as defensive or adaptive responses, that are unrelated to toxicological harm.<sup>235</sup> Further,

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228. *Id.* at 167.

229. *Id.* at 165, 167. Two promising drugs, however, are currently in clinical testing that appear to mitigate the severity of cystic fibrosis for patients with certain rare mutations. *Id.* at 167.

230. *Id.* at 165.

231. *Id.* at 169.

232. *Id.* at 165.

233. *Id.*

234. See Fielden & Zacharewski, *supra* note 210, at 6; Holsapple et al., *supra* note 191, at 307–08 (describing long-debated problems with *in vitro* toxicogenomic methods: “(1) the role of metabolism, (2) the ability to extrapolate *in vitro* concentrations to relevant *in vivo* doses, (3) the ability to understand[] organ interactions, (4) the ability to detect epigenetics and other unknown mechanisms, and (5) the fact that cell lines have a lot of abnormal biology”).

235. Fielden & Zacharewski, *supra* note 210, at 8 (offering DNA repair and breakdown as examples of defensive responses and rapid cell growth or atrophy as examples of adaptive responses); Jeremy K. Nicholson et al., *Metabonomics: A Platform for Studying Drug Toxicity*

chemical toxins may not directly impact gene expression, as they can cause gene mutations that affect protein function without altering gene expression levels, or they may not cause genetic mutations at all.<sup>236</sup>

Changes in gene expression levels can be extremely difficult to detect. This is particularly true where changes in gene expression levels are localized in a small number of cells or where they are highly variable, or even random, because of sensitivities to dose, timing, and duration of exposure.<sup>237</sup> External factors, such as seasonal variations in sunlight, or internal molecular influences, such as hormone levels, can be important and are difficult to anticipate.<sup>238</sup> The pain reliever acetaminophen, which causes liver damage through random modifications of cellular proteins, illustrates this point.<sup>239</sup> Acetaminophen is not associated with consistent changes in gene expression levels. Changes vary from exposure to exposure according to the nature of the proteins affected. This variability creates a chicken-and-egg problem: a central objective of gene expression studies is to obtain a mechanistic understanding of a chemical's toxicity, but it is this mechanistic knowledge that is critical to interpreting gene expression data.

Complex disease processes add to the thicket of gene expression patterns upon which toxicogenomic methods are based. Unlike

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*and Gene Function*, 1 NATURE REVIEWS DRUG DISCOVERY 153, 159 (2002) (“The distinction between adaptive and toxic effects remains a challenge with all the ‘omics’ platforms.”).

236. Gary A. Boorman et al., *Toxicogenomics, Drug Discovery, and the Pathologist*, 30 TOXICOLOGIC PATHOLOGY 15, 17 (2002) (noting that many toxins inhibit cellular functioning by “binding to proteins or altering macromolecules, not by directly altering gene expression”); Olden & Guthrie, *supra* note 13, at 7 (explaining that in many cases, there will be a weak association between gene expression and protein levels, and that post-translational modifications, independent of gene expression levels, may be essential to the biological activity of a protein).

237. Fielden & Zacharewski, *supra* note 210, at 7–9. For example, alloxan and streptozotcin are highly toxic but only affect a certain type of cell in the pancreas that constitutes less than two percent of the pancreatic cell population. *Id.* at 9. See also Collins et al., *supra* note 197, at 907 (acknowledging that in a preliminary study “[s]ome compounds were cytotoxic across all cell types and species, whereas others were more selective”).

238. Boorman et al., *supra* note 236, at 18; Fielden & Zacharewski, *supra* note 210, at 9 (explaining that it is very difficult to control for externally induced variability, such as that caused by nutritional or hydration status, time of last meal, hormonal fluctuations, and seasonal and light-induced fluctuations in hormones).

239. Fielden & Zacharewski, *supra* note 210, at 7.

simple diseases, the causal connection of any one gene to a complex disease is weak and thus difficult to resolve even with powerful high-throughput methods.<sup>240</sup> Specific genes associated with complex traits may also marginally contribute to toxic susceptibility; therefore, it makes little sense to treat them as meaningful predictors of toxicity. Further, it may be very difficult to establish connections between exposure and harm, because impacts on toxic pathways may be many steps removed from sites of damage.<sup>241</sup> These and other challenges have prompted scientists to embrace a highly integrated approach<sup>242</sup> that compiles the results of complementary “omics” studies, such as proteomics<sup>243</sup> and metabonomics.<sup>244</sup> Scientists now believe that this kind of holistic approach will be essential to successfully studying the mechanisms that underlie toxic responses given the complexities outlined above.<sup>245</sup>

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240. Eric S. Lander & Nicholas J. Schork, *Genetic Dissection of Complex Traits*, 265 SCIENCE 2037, 2037 (1994) (explaining that the multigenic nature of complex toxin-induced diseases means that any single mutation may “affect the probability of disease, but not fully determine the outcome,” making toxicogenomic studies much more difficult because a mutation “may be present in some unaffected individuals or absent in some affected individuals”).

241. Bette Meek & John Doull, *Pragmatic Challenges for the Vision of Toxicity Testing in the 21st Century in a Regulatory Context: Another Ames Test? . . . or a New Edition of “the Red Book”?*, 108 TOXICOLOGICAL SCI. 19, 19 (2009).

242. PIERRE BALDI & G. WESLEY HATFIELD, DNA MICROARRAYS AND GENE EXPRESSION: FROM EXPERIMENTS TO DATA ANALYSIS AND MODELING ix (2002) (“[A]rray data must be integrated with sequence data, with structure and function data, with pathway data, with phenotypic and clinical data, and so forth. New biological discoveries will depend strongly on our ability to combine and correlate these diverse data sets along multiple dimensions and scales.”); Meek & Doull, *supra* note 241, at 19–20 (highlighting the importance of distinguishing between effects and adverse effects in a scientifically grounded manner).

243. Proteomics is the study of proteins in biological systems, particularly their functionality and the levels at which they are produced; cells typically contain thousands of different proteins. Pennie et al., *supra* note 206, at 278.

244. Metabonomics involves the study of chemical metabolism (i.e., biological breakdown of chemicals, including foreign toxins) using methods that allow visualization of tissue-wide patterns of chemical metabolites. Waters et al., *Toxicogenomic Approach for Assessing Toxicant-Related Disease*, *supra* note 213, at 418. Importantly, “[m]etabolic changes are real-world end points, whereas gene expression changes are not; [gene expression levels] merely indicate the potential for an end-point change.” Nicholson et al., *supra* note 235, at 153.

245. See Fielden & Zacherewski, *supra* note 210, at 7–8. It is important to note, however, that the process of combining these different sources of information (genomic, proteomic, metabolic, etc.) is far from trivial and successful examples of this approach are still relatively rare. See Mark Gerstein et al., *Integrating Interactomes*, 295 SCIENCE 284, 285 (2002).

## 2. Implications of Inter-Individual Variability

Identifying signatures of toxicity is made more challenging by differences in toxic susceptibility between individuals. Studies have shown, for example, that metabolic processes involved in neutralizing exposures to toxic substances vary by as much as eighty-five to five hundred percent across the U.S. population “with correspondingly high variability in cancer risk.”<sup>246</sup> These differences suggest both that identifying consistent patterns will be challenging and that the key processes may differ substantially between people.<sup>247</sup> Multiple patterns may have to be resolved in order to set regulations that are protective of subpopulations.<sup>248</sup>

Interpersonal variation in toxic susceptibility, although still poorly understood, can be attributed to simple genetic disorders, complex genetic interactions, developmental differences, epigenetic causes, environmental factors, or combinations of all five.<sup>249</sup> Toxicity pathways are also complex assemblages of enzymes (and their associated genes) that are designed to compensate for discrete mutations and mitigate the impacts of toxic compounds. Yet, interpretation of test results and identification of reliable signatures of toxicity are undermined by processes that mediate and buffer the impacts of toxic exposures.

The obstacles to validating toxicogenomics methods raise substantial questions about their viability. However, over the past few years deeper scientific challenges have emerged as the intricacy of human genetics has come into focus. Reflecting the significance of this deepening complexity, *Science* selected “human genetic variation” as the scientific breakthrough of 2007.<sup>250</sup> The editors

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246. Frederica P. Perera & I. Bernard Weinstein, *Molecular Epidemiology: Recent Advances and Future Directions*, 21 *CARCINOGENESIS* 517, 520 (2000).

247. Frederica P. Perera, *Molecular Epidemiology: On the Path to Prevention?*, 92 *J. NAT'L CANCER INST.* 602, 608–09 (2000).

248. *Id.*

249. See RUTH HUBBARD & ELIJAH WALD, *EXPLODING THE GENE MYTH: HOW GENETIC INFORMATION IS PRODUCED AND MANIPULATED BY SCIENTISTS, PHYSICIANS, EMPLOYERS, INSURANCE COMPANIES, EDUCATORS, AND LAW ENFORCERS* 58–60 (3d ed. 1999); R. C. LEWONTIN, *BIOLOGY AS IDEOLOGY: THE DOCTRINE OF DNA* 27, 43–44 (Harper Collins 1993) (1991).

250. Pennisi, *supra* note 17.

observed that researchers had started “appreciat[ing] the extent to which our genomes differ from person to person and the implications of this variation for deciphering the genetics of complex diseases and personal traits.”<sup>251</sup> These observations reinforce growing concerns among experts that scientific developments are increasing uncertainty in biomedical research and development, not resolving it.<sup>252</sup>

Scientific developments are forcing scientists to reconsider established theories about genes,<sup>253</sup> to acknowledge that most genetic conditions are complex and influenced by environmental factors,<sup>254</sup> and to begin to understand a new class of “epigenetic” heritable traits that control gene regulation.<sup>255</sup> To give one example, only about 1.2 percent of the human genome codes directly for proteins (i.e., biologically active compounds), but almost five percent of the genome is subject to natural selection, which suggests that so-called “non-coding” sections of the genome have some functional significance to an organism’s survival.<sup>256</sup> These processes are only now being factored into biomedical research.

The emergence of new layers of complexity is already being felt in the pharmaceutical industry, which has led the way in the

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251. *Id.* at 1842.

252. PISANO, *supra* note 18, at 64–68.

253. See Mark B. Gerstein et al., *What is a Gene, Post-ENCODE? History and Updated Definition*, 17 GENOME RES. 669, 669 (2007), available at <http://genome.cshlp.org/content/17/6/669.full.html#ref-list-1> (“The discrepancy between our previous protein-centric view of the gene and one that is revealed by the extensive transcriptional activity of the genome prompts us to reconsider now what a gene is.”).

254. David Altshuler et al., *Genetic Mapping in Human Disease*, 322 SCIENCE 881, 881 (2008) (“Despite great hopes, [the attempt to find Mendelian traits] proved unsuccessful for common forms of human diseases—such as diabetes, heart disease, and cancer—that show complex inheritance in the general population.”); David F. Horrobin, *Modern Biomedical Research: An Internally Self-Consistent Universe with Little Contact with Medical Reality?*, 2 NATURE REVIEWS DRUG DISCOVERY 151, 154 (2003) (describing studies of identical twins that suggest environmental factors may account for forty to ninety percent of disease susceptibility).

255. Romulo M. Brena et al., *Toward a Human Epigenome*, 38 NATURE GENETICS 1359, 1359 (2006) (describing “epigenetic” processes as those involving “the interplay of DNA methylation, histone modifications and expression of noncoding RNAs, in the regulation of gene expression patterns from early development to adulthood”).

256. Gerstein et al., *supra* note 253, at 673. A recent study found that “a vast amount of DNA, not annotated as known genes, is transcribed into RNA . . . . While the majority of the genome appears to be transcribed at the level of primary transcripts, only about half of the processed (spliced) transcription detected across all the cell lines and conditions mapped is currently annotated as genes.” *Id.*

development and use of genomics methods. As experience with cystic fibrosis vividly shows, even putatively simple genetic conditions are proving to have numerous variants.<sup>257</sup> Metabolic proteins important to drug metabolism and implicated in many adverse drug reactions display similar intricacies. In one prominent case, scientists found that seventy-eight percent of the adverse drug reactions tied to the TPMT enzyme were not associated with the mutation presumed to be dominant.<sup>258</sup> Similarly, although more than seventy mutations have been identified for a related metabolic enzyme (CYP2D6), no genetic test exists for predicting its behavior despite the enzyme's sixty-fold variance in activity.<sup>259</sup> Even the now-famous BRCA1 and BRCA2 genes associated with breast cancer, upon closer study, are subject to much more genetic variation than previously thought.<sup>260</sup>

Scientists now believe that “most, if not all, human genes have about 3 to 10 major [mutations], and dozens or hundreds, of rare [ones].”<sup>261</sup> An important corollary of these findings is that rare, detrimental mutations (i.e., a population frequency of less than one percent) are likely to be undiscoverable prior to an adverse reaction.<sup>262</sup> In essence, the high degree of human genetic variability that exists will circumscribe, if not preclude, clinical uses of genetic tests for many complex diseases.<sup>263</sup> Use of toxicogenomic methods to understand and identify broadly applicable signatures of toxicity will fail for the same reasons when the underlying genetics are complex—so-called signatures of toxicity will be poorly representative of the population at large or impossible to resolve from the background variation.

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257. See Daniel W. Nebert & Elliot S. Vesell, *Advances in Pharmacogenomics and Individualized Drug Therapy: Exciting Challenges that Lie Ahead*, 500 EUROPEAN J. PHARMACOLOGY 267, 272 (2004) (“[V]irtually no examples can be cited in which a single DNA variant site (genotype) is always associated with a particular trait (phenotype)—in all subjects within all human populations.”).

258. *Id.* at 268.

259. *Id.* (cautioning that this may be overly optimistic but noting that some scientists have suggested that “predictive genotyping for *CYP* genes will improve clinical efficacy for all drug therapy by 15% to 25%, thereby decreasing adverse drug reactions by 10–20%”).

260. See Nebert et al., *supra* note 225, at 195.

261. Nebert & Vesell, *supra* note 257, at 268.

262. *Id.*

263. *Id.* at 272.



### 3. Newly Discovered Layers of Biological Complexity

Recent developments in the field of epigenetics, which involves heritable changes to gene regulation that do not involve DNA mutations, exacerbate these problems by further eroding the generality of gene expression signatures of toxicity.<sup>264</sup> Epigenetic traits involve modifications to compounds closely associated with DNA, such as chemicals associated with its translation or the scaffolding on which DNA is organized.<sup>265</sup> However, “unlike the genome, the epigenome is highly variable between cells and fluctuates in time according to conditions even within a single cell.”<sup>266</sup> Thus, while epigenetic traits are heritable, they can be affected by environment conditions over the course of an organism’s life and can be highly variable from cell to cell.<sup>267</sup>

Epigenetic processes are likely to be highly relevant to chemical toxicity. The role of epigenetic processes in cancer and asthma, both of which are associated with environmental toxins, is well established.<sup>268</sup> Epigenetic processes and genetics “cooperate at all stages of cancer development.”<sup>269</sup> Further, a recent high-resolution map of a genome segment revealed that only sixty percent of actively

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264. See Peter A. Jones & Stephen B. Baylin, *The Epigenomics of Cancer*, 128 CELL 683, 683 (2007).

265. *Id.* (describing how epigenetic “[g]ene silencing at the level of chromatin . . . is particularly important in orchestrating key biological processes, including differentiation, imprinting, and silencing of large chromosomal domains such as the X chromosome”). “Epigenetic mechanisms include, among other things, histone modification, positioning of histone variants, nucleosome remodelling, DNA methylation, small and non-coding RNAs. . . . These mechanisms interact with transcription factors and other DNA-binding proteins to regulate gene-expression patterns inherited from cell to cell.” Peter A. Jones et al., *Moving AHEAD with an International Human Epigenome Project*, 454 NATURE 711, 711 (2008).

266. Miho M. Suzuki & Adrian Bird, *DNA Methylation Landscapes: Provocative Insights from Epigenomics*, 9 NATURE REVIEWS GENETICS 465, 465 (2008); see also Florian Eckhardt et al., *DNA Methylation Profiling of Human Chromosomes 6, 20 and 22*, 38 NATURE GENETICS 1378, 1381 (2006) (DNA methylation patterns have been shown to differ significantly between different cell types).

267. Adrian Bird, *Perceptions of Epigenetics*, 447 NATURE 396, 396 (2007).

268. Nebert et al., *supra* note 225, at 199; Suzuki & Bird, *supra* note 266, at 474 (“The role of aberrant DNA methylation in cancer has been persuasively argued.”).

269. Jones & Baylin, *supra* note 264, at 683; see also Editorial, *Between Genotype and Phenotype*, 38 NATURE GENETICS 1355, 1355 (2006) (describing studies showing that certain colon cancers in humans correlated with specific patterns of DNA methylation, specifically CpG island methylation).

translated DNA subsequences coded for proteins, suggesting that many regulatory elements for genes are completely uncharacterized, and that the inter-gene interactions were far more complicated than anticipated.<sup>270</sup>

The still-emerging complexity of human genetics helps to explain the modest success of genomics methods beyond basic scientific research,<sup>271</sup> despite the high levels of funding over the last decade.<sup>272</sup> Yet, if successful utilization of genomics methods is proving elusive in the pharmaceutical sector, which benefits from far greater resources and much stronger public support, it is hard to see how toxicogenomics could fare better. In fact, at least one commentator has suggested that the validation problems for toxicogenomics could be more difficult than those for drug development.<sup>273</sup>

None of these factors bodes well for rapid advances in toxicogenomics or its widespread integration into toxics regulation. To the contrary, regulatory uses of toxicogenomic methods appear to be receding further into the future and are highly unlikely to be viable within the next one or two decades. The magnitude of interpersonal variation exposed by recent developments in human genetics is even

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270. Nebert et al., *supra* note 225, at 202 (explaining how scientists found “many new transcription start-sites, with an arrangement of far more complex regulatory sequences and binding of transcription factors than heretofore imagined”). See also George M. Weinstock, *ENCODE: More Genomic Empowerment*, 17 *GENOME RES.* 667, 667 (2007), available at <http://genome.cshlp.org/content/17/6/667.full>.

271. See, e.g., Holsapple et al., *supra* note 191, at 308 (acknowledging that high-throughput “approaches have already been extensively studied and have arguably not performed to their anticipated promise”); PISANO, *supra* note 18, at 118–22 (commenting on the “crisis” in R&D productivity in the pharmaceutical industry, particularly for new drug therapies, and noting that biotech does not have any higher R&D productivity).

272. See Pedro Cuatrecasas, *Drug Discovery in Jeopardy*, 116 *J. CLINICAL INVESTIGATION* 2837, 2837 (2006) (noting that the pharmaceutical industry’s discovery and development budget has increased thirty-fold since 1970, and that it spends \$30 billion on R&D per year, which is greater than the total NIH budget of \$28 billion); *Billion Dollar Pills*, *ECONOMIST*, Jan. 27, 2007, at 69, 70 (chronicling the increased spending and decreased production in the pharmaceutical industry: “[I]n most years in the 1990s the industry spent roughly \$35 billion–40 billion on research and development and produced 35–40 new drugs. By 2004 spending had swept past \$50 billion, but the number of new drugs had fallen below 30. Now annual spending exceeds \$60 billion, but the number of new drugs has still to grow.”).

273. Dix et al., *The ToxCast Program for Prioritizing Toxicity Testing of Environmental Chemicals*, *supra* note 194, at 10 (suggesting that the diversity of environmental chemicals and issues relating to “solubility, volatility, or confounding cytotoxicity” are greater for toxicogenomics than for drug-related application of genomics methods).

more sobering. Absent advances in a mechanistic understanding of toxicological processes, many subpopulations of individuals with heightened chemical sensitivities will lie beyond detection because their populations are simply too small. These results have important implications for safety factors and efforts to set conservative standards as a means of ensuring broad public protection. The risks posed by some chemicals could be substantial but unquantifiable for a significant number of people.<sup>274</sup>

It is doubtful that the many complicating problems described above can be resolved in the near-term. As a purely practical matter, the time and costs required of the research appear to lie far outside the reach of environmental toxicology. Thus, despite the great excitement that toxicogenomics is generating, and despite its alluring potential, the EPA or NIEHS should not expend significant amounts of their limited resources on toxicogenomics research and development. For the foreseeable future, they would be better off investing opportunistically in discrete projects with significant potential and otherwise waiting for the biomedical sector to resolve the critical questions raised above. Until that time, regulators should focus on using the existing suite of tools as openly and efficiently as possible.

#### IV. LOW-TECH POLICY OPTIONS: MITIGATING ENDEMIC SCIENTIFIC UNCERTAINTIES

The preceding Parts highlight the gradual convergence of regulatory programs and the halting developments in toxicity testing. Toxics regulation operates in a distinctive environment characterized by large scientific uncertainties, graduated and escalating testing costs, highly skewed production volumes (a small number of high-volume chemicals dominate the market for commercial chemicals), and relatively modest rates of chemical toxicity.<sup>275</sup> Other areas of chemical regulation share these basic characteristics, with the important exception of drug regulation, which must contend with

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274. Insofar as current test methods are sensitive to certain types of toxic response, population heterogeneity could cause estimates of false-negative rates to be misleadingly low.

275. *See supra* Part I.

much higher rates of failure in clinical drug testing. The severity of these constraints across different chemical market sectors helps to explain the parallels between different areas of chemical regulation.

The historical record reveals that stringent and weak forms of chemical regulation—even of closely related types—have coexisted since its emergence in the first decade of the 1900s. Strict pre-market approval processes complemented by detailed testing requirements were written into the PHSA of 1902,<sup>276</sup> while the 1906 PFDA was limited to weak market-oriented information disclosure requirements.<sup>277</sup> The 1938 FDCA amendments introduced the first intermediate level of regulation based on pre-market review, which empowered the FDA to intervene prior to commercial sale if it could show that a drug posed a substantial risk to the public.<sup>278</sup> Subsequent statutes regulating chemicals incorporate at least one of these frameworks.<sup>279</sup>

The 1970s was a decade of prolific legislative action. Congress amended FIFRA twice<sup>280</sup> and passed TSCA.<sup>281</sup> But it was also a period of growing concern about the negative economic impacts of regulation. Passed in the shadow of the 1962 Drug Amendments, the Medical Device Amendments clearly reflect congressional concerns about the costs of and delays created by stringent regulation.<sup>282</sup> The tiered system of testing incorporated into the Medical Device Amendments combines all three forms of regulation—information disclosure, pre-market review, and pre-market approval—into a single integrated framework.<sup>283</sup> Subsequent laws have adopted variants of this pluralistic regulatory model. The EU's REACH

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276. See *supra* notes 122–31 and accompanying text.

277. See *supra* notes 135–37 and accompanying text.

278. See *supra* notes 138–41 and accompanying text.

279. See *supra* notes 132–34, 138–52 and accompanying text.

280. See Act to Amend the Federal Insecticide, Fungicide, and Rodenticide Act, Pub. L. No. 95-396, 92 Stat. 819 (1978); Federal Environmental Pesticide Control Act of 1972, Pub. L. No. 92-516, 86 Stat. 973.

281. 15 U.S.C. § 2601 (2006) (original version at Ch. 53, § 2601, 90 Stat. 2003 (1976)).

282. See Travis P. Meek, *Proper Preemption or Contrived Construction?: Why Section 360K(A) of the FDCA Should Not be Interpreted to Preempt State Common Law Tort Claims*, 3 *IND. HEALTH L. REV.* 231, 250 (2006).

283. Jordan Paradise et al., *Evaluating Oversight of Human Drugs and Medical Devices: A Case Study of the Implications for NanoBiotechnology*, 37 *J.L. MED. & ETHICS* 598, 602 (2009).

program is the most visible example, but the FDCA contains categorical exceptions for certain investigational drugs that also mirror a tiered regulatory model.

A central theme of this Article is that, barring dramatic advances in toxicological testing, there is little reason to believe that toxics regulation in the United States will advance to a strict pre-market approval system. It took almost sixty years for non-biologic drugs to be regulated under a formal pre-market approval system, and each regulatory advance was precipitated by catastrophic regulatory failures involving human casualties. Over the years, industrial chemicals have had their fair share of disasters (e.g., Love Canal, Bhopal, environmental PCBs), but these often iconic disasters have never triggered the political momentum needed to pass prospective regulations as stringent as those governing drugs.

Ironically, TSCA itself may be an impediment to major regulatory reform. Insofar as TSCA succeeds in reducing the likelihood that catastrophic events will occur, the galvanizing forces needed to promote reform may never materialize. In fact, from an industry perspective, an optimal level of regulation would minimize the likelihood of politically salient catastrophes occurring while allowing low-level chronic exposures to persist.<sup>284</sup> The history of chemical regulation in the United States demonstrates that the business sector ignores the potential for extreme events at its peril, as they have the unique possibility of precipitating major legislative action.

Despite the absence of a precipitating event, the passage of REACH in Europe reinforces my skepticism. The most telling fact is that, although public support for stringent environmental regulation is much higher in Europe than in the U.S.,<sup>285</sup> in practice REACH is closer to a TSCA pre-marketing notice model than to the FDCA drug approval process. While critical for “chemicals of highest concern,” the shift in burden of proof under REACH is irrelevant for most

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284. Industry appears, at times, to understand these dynamics. Subsequent to the shock created by the thalidomide tragedy, the pharmaceutical industry had committed to supporting the 1962 amendments of the FDCA. See RICHARD HARRIS, *THE REAL VOICE* 142–47 (1964). But this strategy was largely a preemptive one—the industry recognized that legislative action was inevitable. *Id.* at 143. They supported amendment only to protect against more stringent regulation in the future. *Id.*

285. Wirth, *supra* note 9, at 97–98.

chemicals—the limited testing requirements effectively give them the benefit of the doubt. Similarly, the availability of alternative testing methods, particularly structure-based testing models, has the potential to erode testing standards for all chemicals. This flexibility contrasts with drug testing under the FDCA, which combines burden shifting with stringent testing requirements.<sup>286</sup> Moreover, experience with alternative testing methods under EPA’s HPV Chemical Challenge has demonstrated that the scientific uncertainties endemic to toxicology can be readily turned to the advantage of chemical producers who are reluctant to test their products rigorously.

This analysis is not to suggest that REACH is of marginal importance. On the contrary, its data disclosure requirements alone are significant. Nevertheless, REACH should not be read as a move toward a full-blown pre-marketing approval system. REACH is a major advance toward something quite different, namely, a pluralistic regulatory framework that reflects the heterogeneity of the products it covers and the complexities of the scientific knowledge that informs regulatory determinations.

The prevailing political and scientific conditions strongly suggest that toxics regulation in the U.S. will not advance beyond a tiered framework like that found in REACH. This point is useful insofar as it helps to frame the debate over toxics regulations. Policymakers will be more effective if they confront the scientific and political constraints that bound toxics regulation than if they ignore them. Being a negative conclusion, however, it does little to provide much positive guidance. The Parts that follow attempt to fill this gap by discussing several promising measures, including key elements of REACH, that would enhance toxics regulation in the U.S. This analysis is of particular importance now because, in the wake of the EU’s passage of REACH, there are signs that Congress seriously plans to consider significant amendments to TSCA.<sup>287</sup>

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286. *See supra* Part II.A.

287. *See Layton, supra* note 22; Lovell, *supra* note 22.

### *A. Promising Legislative Opportunities*

Notwithstanding the challenging scientific and political circumstances, opportunities exist for enhancing toxics regulation in the U.S. I will focus on three primary types of policies: (1) tiered systems for toxicity testing and regulatory review; (2) enhanced post-marketing monitoring and independent meta-reviews of toxicological studies; and (3) development of parallel policies designed to promote innovation (i.e., green chemistry). These proposals range from the well-established, tiered regulatory systems, to the more controversial, enhanced post-marketing monitoring. Each of them will be analyzed below, but the space devoted to them will vary according to the details needed to explore them, not because they are particularly favored or disfavored.

#### 1. Tiered Regulatory Frameworks

TSCA's system of pre-market review reflects Congress's decision to minimize the negative impacts of regulation by defaulting to the least common denominator. Under this reasoning, because most chemicals are non-toxic and sold in modest quantities, pre-market review best reflects the low level of risk typically at stake. This regulatory minimalism is compounded by TSCA's complete absence of testing requirements and the difficulty of demonstrating harm under traditional tort actions—both discourage chemical producers from conducting toxicity tests.<sup>288</sup>

A tiered regulatory structure avoids the false dichotomy presented by the choice between pre-market review and pre-market approval, and it better reflects the heterogeneity of industrial chemicals and their markets. In a tiered regulatory structure, much will turn on the metrics used to categorize chemicals, as experience with EPA's HPV Chemical Challenge suggests. Fortunately, several factors are well established and defined, including quantities produced or used, direct evidence of human exposures (e.g., presence in human blood

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288. Applegate, *Bridging the Data Gap*, *supra* note 33, at 1368–69, 1387; Wendy E. Wagner, *Choosing Ignorance in the Manufacture of Toxic Products*, 82 CORNELL L. REV. 773, 774 & n.1, 784–85 (1997).

samples), environmental persistence, and potential to bioaccumulate. Each of these should to be incorporated into any tiered framework contemplated by Congress.

A central benefit of a tiered regulatory framework is its capacity to mitigate the scientific uncertainties endemic in toxics regulation. Simple proxies, such as quantities in commerce, cannot be the sole basis upon which testing requirements and regulatory standards are based, as even relatively small quantities of certain chemicals can impact human health or the environment (e.g., persistent organic pollutants).<sup>289</sup> Proxies are most useful in setting the type of testing that is required. If testing reveals evidence of toxicity, this result can be used to elevate the level of testing and the regulatory procedures to which a chemical is subject. REACH uses both strategies to triage chemicals that may require formal pre-market approval.

Agency discretion remains a significant factor in tiered regimes. It enters the process in two principal forms: judgments about how to classify a chemical and decisions about the adequacy of test methods. Insofar as the proxies used to classify chemicals are simple and objective, classification decisions will be straightforward. However, where ambiguities are significant and the available evidence is equivocal, classification decisions can invoke significant controversy because they may be determinative of whether a chemical is regulated at all. Disputes over the classification of medical devices have sometimes been problematic for this reason.<sup>290</sup>

Assessing alternatives to standard test methods, such as mathematical models and the testing of structurally related chemical analogues, presents a much more challenging problem. It is also one that already has led to significant controversy, most notably under the EPA's HPV Challenge Program.<sup>291</sup> Drug regulation avoids this dilemma by imposing a high standard for clinical testing of all

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289. See, e.g., U.S. ENVTL. PROT. AGENCY, PERSISTENT ORGANIC POLLUTANTS: A GLOBAL ISSUE, A GLOBAL RESPONSE 1, 7 (2002), <http://www.epa.gov/international/toxics/pop.pdf>; Applegate, *Synthesizing TSCA and REACH*, *supra* note 2, at 725.

290. See, e.g., U.S. GOV'T ACCOUNTABILITY OFFICE, FDA SHOULD TAKE STEPS TO ENSURE THAT HIGH-RISK DEVICE TYPES ARE APPROVED THROUGH THE MOST STRINGENT PREMARKET REVIEW PROCESS 6-7 (2009), <http://www.gao.gov/new.items/d09190.pdf>.

291. See Applegate, *Bridging the Data Gap*, *supra* note 33, at 1392-94.



drugs.<sup>292</sup> But this is not a feasible strategy for industrial chemicals given their diverse characteristics, generally small markets, and sheer numbers. In this context, spending hundreds of thousands of dollars per chemical on toxicity testing is a political non-starter. Yet, once regulators move beyond rigid standards or conventions, a potential morass opens up of often unproven alternatives to direct testing.<sup>293</sup>

No easy solution exists to this dilemma. A tiered system can minimize these uncertainties by categorizing chemicals according to straightforward metrics, but this strategy goes only so far before complex, technical, value-laden judgments reenter the regulatory process. One could use essentially arbitrary conventions or rules (e.g., “alternative testing methods cannot be used in more than thirty percent of the chemicals reviewed”), but this strategy is questionable given the large uncertainties in the standard test methods. Reliance on rigid rules would risk replacing one form of imperfect, convention-driven testing for another presumably more costly and time-consuming form of imperfect testing. The relatively low base rates of chemical toxicity provide a further basis for rejecting a blanket limit.

The epistemic limits on decision-making created by these constraints suggest that a procedural, transparency-maximizing approach is preferable to a rigid, easily administrable rule. Strict substantive standards, almost by definition, are ill-suited to the present circumstances in which scientific uncertainties are large and the heterogeneity of chemicals broad. Reforms could come in two forms given these conditions: (1) applying enhanced procedures to EPA decisions to accept alternatives to standard test methods, and (2) establishing a requirement that all toxicity data, models, and analysis used to support regulatory decisions be publicly available. The first of these could be formulated very simply. The enhanced procedures would create a presumption against reliance on alternative testing methods and would require agency officials to provide a detailed justification whenever they accept alternatives to direct testing.

Proposals to eliminate the secrecy of toxicity testing data date back at least to the early 1970s, and they now are an important

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292. See Merrill, *The Architecture of Government Regulation of Medical Products*, *supra* note 106, 1765.

293. See *supra* Part I.

component of the emerging debate over TSCA reform.<sup>294</sup> The status quo already has been upended, though, following passage of REACH and its requirement that testing data be made public.<sup>295</sup> It therefore would be a modest, complementary step to require that, as a condition for using alternative test methods, any relied upon data, models, and analysis be made public. These measures would not, of course, prevent overuse of dubious alternatives to standard testing, but they would make it substantially harder to use alternatives indiscriminately and would empower stakeholders to challenge the more egregious misuses of standard testing.

## 2. Enhanced Post-Marketing Monitoring and Scientific Meta-Reviews

There are technical and practical limits to the level of pre-market testing that can be required of chemical producers. As we have seen, a tiered regulatory framework mitigates both of these limits by calibrating testing requirements using rough proxies of potential risk. Post-marketing monitoring and meta-studies are alternative mechanisms for mitigating these constraints. Post-marketing studies can be less expensive, use different methods (i.e., epidemiological studies), and avoid additional regulatory delays. Their downside—and it is a serious one—is that they cannot preempt human exposures. Scientific meta-reviews also operate retrospectively. Their great virtue lies in leveraging existing data through transparent processes overseen by reputable, independent organizations. In the biomedical sector, the Cochrane Collaboration has pioneered meta-reviews of studies on medical interventions.<sup>296</sup> If toxicity data are made available to the public, Cochrane-like meta-reviews would offer much needed independent analysis.

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294. Layton, *supra* note 22; Lovell, *supra* note 22.

295. *See supra* Part I.B.

296. COMM. ON COMPARATIVE EFFECTIVENESS RESEARCH PRIORITIZATION, INST. OF MED. OF THE NAT'L ACADS., INITIAL NATIONAL PRIORITIES FOR COMPARATIVE EFFECTIVENESS RESEARCH (forthcoming) (prepublication copy at 2–18, on file with author); Mark Starr & Iain Chalmers, *The Evolution of the Cochrane Collaboration, 1988–2003*, (2003), <http://www.update-software.com/history/clibhist.htm>.

After many years of being essentially moribund,<sup>297</sup> post-marketing monitoring is receiving belated but significant attention in the pharmaceutical and medical device sectors.<sup>298</sup> The favorable economics and the potential to conduct statistically powerful studies are driving this movement.<sup>299</sup> The economics of drug testing are particularly stark. Because drug research and development take many years and are very costly, time is extremely valuable. Economists estimate, for example, that increasing the duration of clinical testing of a drug by just one month reduces the net present value of a drug in year one by about \$2.9 million.<sup>300</sup> By contrast, post-marketing testing avoids regulatory delays altogether,<sup>301</sup> and its costs can be offset by revenues from drug sales, as opposed to consuming capital when it is in short supply. This asymmetry makes post-marketing testing economically attractive and thus less susceptible to interest group opposition.

The prospect of greater statistical power is equally important. Many rare adverse effects of drugs cannot be detected by standard clinical testing and could not be cost-justified because the numbers of test subjects would have to be very large.<sup>302</sup> Post-marketing

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297. See Alan M. Garber, *Is Having More Preapproval Data the Best Way to Assure Drug Safety?*, 27 HEALTH AFF. w371, w371 (2008), available at <http://content.healthaffairs.org/cgi/reprint/27/5/w371> (“Despite long-standing plans to improve postmarketing surveillance, such efforts often take the form of a requirement for more data on safety and effectiveness before a drug is approved.”); Alastair J.J. Wood, *A Proposal for Radical Changes in the Drug-Approval Process*, 355 NEW ENG. J. MED. 618, 621 (2006) (describing an FDA report finding that “of 1191 open post-marketing commitments, only 114 (9.6 percent) had been met, yet none of the drugs . . . have been withdrawn from the market”).

298. Garber, *supra* note 297, at w373 (arguing that “the optimal information strategy for new drugs will likely consist of a shifting balance of pre- and postapproval data collection,” as post-approval studies do not have the same deterrent effect on small under-capitalized companies, and also allow the costs of studies to be offset by revenue from concurrent sales); Mitka, *supra* note 175, at 1109 (describing a recent proposal by FDA to strengthen its post-marketing monitoring of medical devices); Shelby D. Reed et al., *How Changes in Drug-Safety Regulations Affect the Way Drug and Biotech Companies Invest in Innovation*, 25 HEALTH AFF. 1309, 1314 (2006) (making the case that “sizeable increases in spending for postmarketing safety evaluations are likely to have a much less detrimental economic impact on manufacturers”).

299. Reed et al., *supra* note 298, at 1310, 1313 (discussing econometric study data on drug testing showing that it is likely much more cost-effective to strengthen post-marketing study requirements than pre-market clinical testing).

300. *Id.* at 1314.

301. *Id.* at 1315.

302. See F.M. Scherer, *Uncertainty and Choice: The Challenges of Pharmaceutical*

monitoring is less subject to these constraints, as drugs with substantial markets will have patient numbers sufficient to detect relatively rare adverse conditions. Moreover, the ease of conducting post-marketing studies is projected to increase substantially with the rising use of electronic medical records.<sup>303</sup> All of these factors auger well for the rising importance of post-marketing monitoring of drugs and the added information that it alone can provide.

Similar benefits exist for toxicity testing of industrial chemicals. A central criticism of toxics regulation has revolved around its negative impacts on innovation, which are driven by the costs of toxicity testing and regulatory delays.<sup>304</sup> Enhanced post-marketing monitoring does not contribute to regulatory delays and is less capital-intensive than pre-market toxicity testing. However, because the costs and duration of chemical toxicity testing would be much less than for clinical testing of drugs, these benefits are far less pronounced. Further, the expected level of false negatives, estimated above to be about 2.5 percent or roughly four hundred compounds in total, is significantly lower than that for drugs. The anticipated numbers of additional toxic chemicals identified therefore should be substantially lower than for drugs.

The relatively small economic advantages and reduced potential for toxic chemicals to be removed from the market suggest that the value of post-marketing monitoring will have to be scrutinized carefully. Post-marketing monitoring is most likely to be justifiable for chemicals produced or used in large quantities or with a significant or uncertain potential to bioaccumulate. For these chemicals, their heightened significance and the larger numbers of potential exposures may be justification alone. On the other side of the equation, reducing the costs and increasing the value of

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*Efficacy, Safety, and Cost*, 28 *MANAGERIAL DECISION ECON.* 267, 279 (2007) (“[T]he adverse side effects that have typically attracted public debate are intrinsically small-numbers events, with occurrence probabilities too low to yield significant indications of user risk with the clinical trial sample sizes customarily required by the FDA.”).

303. PriceWaterhouseCoopers, *Pharma 2020: Marketing the Future, Which Path Will You Take?* 7 (2009), [http://www.pwc.com/en\\_GR/gr/surveys/assets/pharma-2020-marketing-future.pdf](http://www.pwc.com/en_GR/gr/surveys/assets/pharma-2020-marketing-future.pdf) (predicting that “[b]y 2020, electronic medical records, e-prescribing and remote monitoring will . . . [provide] access to extensive outcomes data”).

304. *See supra* Part I.B.

biomonitoring ought to be high priorities for EPA and NIEHS. A stronger case for post-marketing monitoring will also exist where multiple chemicals can be monitored simultaneously and per-chemical costs reduced. The Kids-Safe Chemicals Act, pending in Congress, adopts an innovative approach to post-marketing monitoring under a provision that requires government-based biomonitoring (e.g., monitoring of humans for the presence of certain classes of commercial chemicals), and this information is then available as a potential basis for further regulatory action.<sup>305</sup> As this example suggests, the value of post-marketing monitoring ultimately will have to be evaluated on a case-by-case basis; blanket endorsement or rejection is not possible.

Meta-reviews offer an alternative cost-effective means for evaluating the risks posed by industrial chemicals. This strategy is becoming increasingly important in the biomedical sector.<sup>306</sup> The Cochrane Collaboration, which is exemplary of this movement, is dedicated to conducting and updating meta-reviews of medical interventions, but it is by no means the only one.<sup>307</sup> Begun in 1993 as an international non-profit organization, the Cochrane Collaboration conducts meta-reviews that are published and updated regularly and prepared according to strict quality-control standards.<sup>308</sup> Cochrane reviews, which include technical abstracts and summaries for laypeople, are made broadly available to the public.<sup>309</sup> As of January 2010, the Cochrane database listed more than six thousand reviews of medical treatments and diagnostic tests.<sup>310</sup>

The viability of this independent, collaborative model is obviously contingent on toxicity study data becoming publicly available. As described above, provisions in REACH will force the public release

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305. S. 3040, §§ 505–506, 110th Cong. (2008); H.R. 6100, §§ 505–506, 110th Cong. (2008).

306. Hoffman & Hartung, *supra* note 97, at 503–05 (arguing that the most important methods used to assess and evaluate the treatment options for a given medical question are systematic reviews and meta-analyses).

307. COMM. ON COMPARATIVE EFFECTIVENESS RESEARCH PRIORITIZATION, *supra* note 296, at 2–18.

308. *Id.*

309. *Id.*

310. The Cochrane Library, Record Counts, <http://ww3.interscience.wiley.com/cgi-bin/mrwhome/106568753/ProductDescriptions.html#creviews> (last visited Apr. 26, 2010).

of a great deal of the privately held toxicity data and should make the collaborative approach possible.<sup>311</sup>

Independent meta-reviews would provide an alternative to government reviews, such as those conducted under EPA's Integrated Risk Information System ("IRIS"),<sup>312</sup> and would augment the resources available for this work. EPA reviews are deficient both in number and on substantive grounds. The IRIS system repeatedly has been criticized for the deficiencies in its peer review processes and its failure to involve a representative range of stakeholders.<sup>313</sup> The IRIS database is also far from complete, with many commercial chemicals yet to be reviewed and many existing reviews significantly outdated.<sup>314</sup> Moreover, the significant procedural obstacles and budgetary constraints experienced by the EPA suggest that significant improvements in the IRIS database will be difficult to achieve.<sup>315</sup>

The establishment of the Cochrane Collaboration was prompted by similar circumstances, namely, a critical need for reliable information about the safety and efficacy of medical treatments.<sup>316</sup> The success of the Cochrane Reviews demonstrates the great value of this collaborative, open-science-based approach to conducting scientific reviews. Modeled off the Cochrane Collaborative, an international non-governmental organization dedicated to conducting

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311. *See supra* Part I.B.

312. Similar to the Cochrane reviews, IRIS studies generate a consensus opinion on the potency of toxic chemicals regulated by EPA based on an assessment of the available toxicological studies. *See* Integrated Risk Information System (IRIS), <http://www.epa.gov/NCEA/iris/> (last visited Apr. 26, 2010) (stating EPA's descriptions IRIS); *see also* MARK R. POWELL, SCIENCE AT EPA: INFORMATION IN THE REGULATORY PROCESS 31 (1999). EPA uses potencies/reference doses and modeling methods to calculate regulatory standards for each of the chemicals it regulates. *Id.* at 31–32. As such, the IRIS toxicological reviews provide the final toxicological information used by EPA to calculate regulatory standards for toxic substances.

313. U.S. GOV'T ACCOUNTABILITY OFFICE, HUMAN HEALTH RISK ASSESSMENT: EPA HAS TAKEN STEPS TO STRENGTHEN ITS PROCESS, BUT IMPROVEMENTS NEEDED IN PLANNING, DATA MANAGEMENT, AND TRAINING 13–14 (2006), <http://www.gao.gov/new.items/d06595.pdf> [hereinafter GAO, EPA IMPROVEMENTS].

314. U.S. GOV'T ACCOUNTABILITY OFFICE, CHEMICAL ASSESSMENTS: LOW PRODUCTIVITY AND NEW INTERAGENCY REVIEW PROCESS LIMIT THE USEFULNESS AND CREDIBILITY OF EPA'S INTEGRATED RISK INFORMATION SYSTEM, 3–4, 15–16, 18–21 (2008), <http://www.gao.gov/new.items/d08440.pdf> [hereinafter GAO, EPA'S IRIS].

315. *Id.* at 55–58.

316. Starr & Chalmers, *supra* note 296.

meta-reviews of toxicity studies could take advantage of global human resources and avoid the problems with peer review and scientific independence that have undermined IRIS.<sup>317</sup>

Creation of such an independent scientific organization would not experience the controversy common in other areas of environmental science and policy (e.g., The Nature Conservancy's sponsorship of ecological science and monitoring).<sup>318</sup> Scientists, non-governmental organizations, and citizens play critical roles in collecting, updating, and maintaining data relevant to environmental regulation and policy.<sup>319</sup> Their growing importance is reflected in the willingness of federal agencies, particularly the EPA, to work with them and provide both technical and financial support.<sup>320</sup> More recently, federal agencies have begun to recognize and utilize non-profit and citizen-generated data by incorporating this work into official reports.<sup>321</sup> Citizen groups and non-profit organizations are now frequently at the forefront of efforts to develop innovative technologies and programs.<sup>322</sup> Strong precedent therefore exists for the viability of the Cochrane Collaboration approach to enhance the quality and breadth of toxicity information on industrial chemicals.

### 3. Affirmative Policies to Promote Innovation

A recurring criticism of toxics regulation is that it threatens innovation, particularly environmentally beneficial innovation such as new forms of "green chemistry," by raising the costs of

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317. See, e.g., GAO, EPA IMPROVEMENTS, *supra* note 313, at 13–14; GAO, EPA's IRIS, *supra* note 314, at 26.

318. See The Nature Conservancy, Conservation Science, <http://www.nature.org/tnc/science/> (last visited Apr. 26, 2010).

319. David E. Adelman, *The Challenge of Abrupt Climate Change for U.S. Environmental Regulation*, 58 EMORY L.J. 379, 400–02 (2008).

320. See, e.g., Barton H. Thompson, Jr., *The Continuing Innovation of Citizen Enforcement*, 2000 U. ILL. L. REV. 185, 223 (2000) (making the point that "charitable tax deductions thus permit the government to leverage its monitoring budget with private contributions that exceed the foregone tax revenue"); EPA's Volunteer Monitoring Program, <http://www.epa.gov/owow/monitoring/volunteer/epasvmp.html> (last visited Apr. 26, 2010).

321. See, e.g., Thompson, *supra* note 320, at 219 (describing how organizations receiving direct governmental support now monitor "portions of almost 1000 streams and rivers; 2800 ponds, lakes, and wetlands; and 4 major estuaries").

322. *Id.* at 224 (describing how groups have developed sophisticated monitoring systems that rival and sometimes exceed the capabilities of local public enforcement agencies).

commercializing new chemicals.<sup>323</sup> While the increased costs associated with chemical regulation cannot be eliminated, they can be mitigated or offset by complementary innovation-oriented policies.<sup>324</sup> In the context of climate change regulation, compelling evidence exists for the effectiveness of parallel regulatory and innovation policies.<sup>325</sup> For example, Denmark experienced unique success in its efforts to reduce greenhouse gas emissions, and a critical feature of its approach is the use of policies designed to promote technology development and adoption.<sup>326</sup> Recent economic analyses confirm the value in combining environmental regulations with complementary innovations policies.<sup>327</sup>

In the context of chemical regulation, precedent for an integrated approach also exists. In the pharmaceutical sector, the Orphan Drug Act of 1983 (“ODA”) maintains regulatory objectives while providing incentives for innovation.<sup>328</sup> The term “orphan drug” refers to the absence of drugs available for rare diseases<sup>329</sup> whose small markets are insufficient to justify the large costs of drug

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323. See *supra* Part I.A.

324. See David E. Adelman and Kirsten H. Engel, *Reorienting State Climate Change Policies to Induce Technological Change*, 50 ARIZ. L. REV. 835, 858–60 (2008) (discussing ability of states to adopt an advantageous program that couples innovation-related policies with climate change regulation).

325. *Id.*

326. *Id.* at 860; Monica Prasad, *On Carbon, Tax and Don't Spend*, N.Y. TIMES, Mar. 25, 2008, at A27 (arguing that facilitating technology shifting is essential to reducing carbon emissions). See also Monica Prasad, *Taxation as a Regulatory Tool: Lessons from Environmental Taxes in Europe*, (Feb. 1–3, 2008), [http://www.sociology.northwestern.edu/faculty/prasad/Taxation\\_3\\_25\\_08](http://www.sociology.northwestern.edu/faculty/prasad/Taxation_3_25_08).

327. LAWRENCE H. GOULDER, PEW CENTER ON GLOBAL CLIMATE CHANGE, INDUCED TECHNOLOGICAL CHANGE AND CLIMATE POLICY iv (2004), [http://www.pewclimate.org/docUploads/ITC\\_Report\\_F2.pdf](http://www.pewclimate.org/docUploads/ITC_Report_F2.pdf) (“To promote ITC and reduce GHG emissions most cost-effectively, two types of policies are required: policies to reduce emissions and incentives for technological innovation.”).

328. Wesley Yin, *Market Incentives and Pharmaceutical Innovation*, 27 J. HEALTH ECON. 1060, 1060–62 (2008). Indeed, the success of the ODA has led other countries such as Japan, Australia, and the EU to adopt similar laws. Paul D. Maher & Marlene Haffner, *Orphan Drug Designation and Pharmacogenomics*, 20 BIODRUGS 71, 72 (2006).

329. The Act covers “any disease or condition which . . . affects less [sic] than 200,000 persons in the United States.” 21 U.S.C. § 360bb(a)(2) (2006). It provides for a streamlined FDA review process with technical support to assist in the development of clinical testing regimens. See David Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?*, 31 AM. J.L. & MED. 365, 374–76 (2005).



development. Using an eclectic mix of policy instruments, the ODA has overcome this market failure. In the decade preceding passage of the ODA, thirty-four orphan drugs were produced.<sup>330</sup> In contrast, over the first twenty years following its passage, 229 orphan drugs were commercialized.<sup>331</sup> These developments have led to a substantial increase of more than sixty-nine percent in the number of clinical trials conducted on drugs for rare diseases.<sup>332</sup>

The ODA policies range from regulatory streamlining to more traditional market-based incentives. By streamlining clinical trials and providing technical assistance,<sup>333</sup> FDA has reduced the time for drug approvals by fifty percent. In effect, this streamlining has added one to two years to the duration of patent protection for each drug.<sup>334</sup> Direct economic support and incentives are also key elements of the ODA, including a fifty percent tax credit for the costs of clinical trials, which amounts to a rebate of millions of dollars on the large up-front costs associated with drug development.<sup>335</sup>

The ODA has not been free of criticism, and concerns have been raised about its susceptibility to gaming and over-inclusiveness. Drugs with blockbuster potential (i.e., billions in annual revenues) have received orphan drug status when they can be used to treat

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330. Loughnot, *supra* note 329, at 370; *see also* Maher & Haffner, *supra* note 328, at 71 (noting that fewer than ten orphan drugs were commercialized in the decade prior to the passage of the ODA, whereas 269 orphan drugs were commercialized less than twenty-five years after its passage).

331. Loughnot, *supra* note 329, at 370.

332. Yin, *supra* note 328, at 1061 (noting scholarship finding that after the ODA, the increase in the variety of drugs was higher for rare diseases than for non-rare diseases).

333. *See* OFFICE OF TECH. ASSESSMENT, PHARMACEUTICAL R&D: COSTS, RISKS, AND REWARDS 71 (1993), <http://www.fas.org/ota/reports/9336.pdf> (observing that orphan drugs “may have a very different cost structure from other NCEs, not only because of the tax credit but also because they may involve smaller and shorter clinical trials than other drugs”); Henry Grabowski, *Increased R&D Incentives for Neglected Diseases—Lessons From the Orphan Drug Act* 16–17 (July 2003), [http://www.econ.duke.edu/Papers/Other/Grabowski/Orphan\\_Drug.pdf](http://www.econ.duke.edu/Papers/Other/Grabowski/Orphan_Drug.pdf) (finding that the number of subjects in clinical trials for orphan drugs was much smaller than the average for all drugs and that “the representative orphan drug has R&D costs that are significantly lower than non-orphan compounds”).

334. *Cf. id.* at 71–72 (stating that, for the period 1985–1990, the average approval time for drugs classified as “A” by the FDA was 25.7 months for non-orphans and only 18.1 months for orphans).

335. Loughnot, *supra* note 329, at 369. The aggregate value of this tax credit is significant—through 2007 it cost nearly \$2 billion, and it is projected to cost \$1.9 billion between 2008 and 2012. Yin, *supra* note 328, at 1062.

multiple diseases, one of which is sufficiently rare.<sup>336</sup> Although recent studies suggest that such cases are the exception to the rule,<sup>337</sup> these tensions highlight the importance of carefully structuring innovation policies to ensure that they stimulate new development as opposed to merely providing windfalls for work that would have occurred in their absence.

The examples described above are illustrative of the approaches that could be adopted to mitigate the impacts of regulatory costs on innovation. Experience with climate change policies and orphan drugs shows that when traditional regulations and innovation policies work in tandem they can guide innovation in directions with high social value. Further, insofar as the technical challenges are more tractable—and given the stasis of toxicology, it is hard to see how they could not be—focusing limited government and private-sector resources on green innovation has the potential to circumvent the deep uncertainties that have come to characterize regulation of industrial chemicals.

Experience in other areas also demonstrates that integrating regulation and innovation policies cannot be done haphazardly. Success is dependent on identifying the barriers both to new innovation and to adoption of underutilized existing technologies. These obstacles must be evaluated against the gaps left by the relevant regulatory framework. Similarly, as the ODA example suggests, careful consideration must be given to the scope of the incentives provided to avoid windfalls and to ensure that socially beneficial innovation is being effectively targeted. Designing policies to promote green chemistry, for example, is likely to be more difficult than designing policies for orphan drugs, as the attributes of “green” chemicals and processes are complex and thus not amenable to a simple numerical cutoff like that used in the ODA.

None of these considerations precludes development of parallel innovation policies. They instead highlight the care that must be

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336. Loughnot, *supra* note 329, at 365, 370–71. The multi-billion dollar anemia drug, Epopen, is the most glaring example of this occurring. *Id.* at 370–71.

337. Grabowski, *supra* note 333, at 16 (describing evidence that the average sales peak for an orphan drug is about \$100 million annually versus an average peak of \$500 million annually for standard drugs).

taken in coordinating traditional regulatory and newer innovation policies to capitalize on the valuable synergies that often are overlooked.

#### CONCLUSIONS

Cautious pessimism is perhaps an overly negative framing of my perspective, and yet I do not feel comfortable resorting to the obvious alternative “realism” because it comes across as presumptuous. Further, the scientific and regulatory uncertainties implicated by toxics regulation leave ample room for a broad range of “realist” positions; I am merely on the pessimistic end of this spectrum.

My primary objectives in this Article are to place toxics regulation in the broader historical context of chemical regulation as a general class and to make the case that a great deal of work is still needed before toxicogenomics will become widely used in toxics regulation. The history of chemical regulation in the United States suggests basic limits on regulatory regimes for industrial chemicals. I argue that a tiered regime similar to that found in REACH is the brand of regulation most likely to emerge if TSCA reform were to move forward. The obdurate limitations of toxics science reinforce this view.

My pessimism is not nearly as unyielding as the scientific uncertainties. The relative weakness of TSCA standards coupled with its inertia-filled procedures leave substantial room for effective reforms. Tiered systems for regulating industrial chemicals, enhancement of post-marketing monitoring, and innovation policies directed at promoting new chemicals and processes each holds significant promise. REACH very well may be instrumental in opening the door to such reforms in the United States.

I am very pessimistic about two things. The first is that seeking to replicate the model of strict pre-marketing approval exemplified by drug regulation under the FDCA is untenable from both a political and scientific perspective. The second is that investing heavily in toxicogenomics research and development with the hope that it will rescue toxics regulation from deep scientific uncertainties is premature at best and may prove illusory in the long term.