

TESTIMONY OF
PHYSICIANS COMMITTEE FOR RESPONSIBLE MEDICINE
AND
PEOPLE FOR THE ETHICAL TREATMENT OF ANIMALS
AND
THE HUMANE SOCIETY OF THE UNITED STATES, HUMANE SOCIETY INTERNATIONAL,
HUMANE SOCIETY LEGISLATIVE FUND
BEFORE THE
US SENATE COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS AND ITS
SUBCOMMITTEE ON SUPERFUND, TOXICS, AND ENVIRONMENTAL HEALTH
ON THE
TOXIC SUBSTANCES CONTROL ACT

DECEMBER 15, 2009

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I. Introduction

While estimates of the number of chemicals in commerce differ, there could be environmental exposure to anywhere between 10,000 and 100,000 chemicals. Understanding the potential health and environmental risks posed by chemicals currently in the environment, while ensuring new chemicals are safe for use, presents a monumental challenge. For ethical, scientific, and practical reasons, this challenge cannot be met using toxicity test methods that use animals.

In order to effectively assess both existing and new industrial chemicals, we must reform the way in which toxicity testing is conducted, including the science used to evaluate chemicals. If carried out thoughtfully, reform of the Toxic Substances Control Act (TSCA) represents an unprecedented opportunity to implement an effective program of chemical assessment and management that is consistent with the National Academy of Sciences' recent landmark report presenting a vision and strategy for toxicity testing in the 21st Century (NRC, 2007). Without the committee's careful consideration of all stakeholders' concerns and subsequent careful drafting, TSCA reform could result in more ineffective chemical testing programs that waste time, money, and hundreds of thousands of animals while leaving human health and the environment unprotected.¹ Incorporation of the approach outlined in the NRC report is essential to creating a feasible and effective program. While some of the elements outlined in the report will require research and development before they can be implemented, a number of existing methods and approaches can be used now for prioritization.

The current TSCA Inventory contains approximately 80,000 chemicals; in order to review this number of chemicals over 10 years, the EPA would have to review approximately 6,000 – 8,000 chemicals each year (approximately 20 each day), at heavy expense to the taxpayer. Currently, the EPA's Office of Pollution, Prevention, and Toxics—the office that would be charged with implementing this legislation—reviews about 1000 pre-manufacture notices² each year – review of existing chemicals would be in addition to these PMN reviews.

Evaluation of this tremendous backlog of existing chemicals, as well as the generation of robust information regarding new chemicals, is simply not feasible under the current toxicity testing paradigm used by the EPA and other regulatory agencies. This paradigm is largely based on experiments on animals, particularly rodents, rabbits, and dogs, and uses methods that were developed as long ago as the 1930s and 40s - tests that are time-consuming, expensive, and in some cases use thousands of animals apiece. For example, a single two-generation reproductive toxicity study requires a minimum of two years, \$380,000, and 2,600 animals. There are simply not enough laboratories in the world to conduct all the testing required in a reasonable time-frame. In addition, the current testing paradigm has a poor record of predicting effects in humans (Seidle and Stephens, 2009; Knight and Bailey 2006a, 2006b; Ennever and Lave 2003) and an even poorer record in leading to actual regulation of hazardous chemicals (Seidle 2006).

¹ The High Production Volume Chemical Challenge Program is a recent example of a chemical testing program that has not resulted in better regulation of chemicals. For more information, please see the June 17, 1999 testimony by animal advocates before the Subcommittee on Energy and the Environment of the House Committee on Science (106th Congress, Serial No. 106-18).

² <http://www.epa.gov/oppt/ar/2007-2008/reviewnewchem/index.htm>

In light of these concerns, the Environmental Protection Agency (EPA) realized that the current toxicity testing paradigm is in urgent need of overhaul and requested the National Academy of Sciences' National Research Council (NRC) assess the current paradigm and recommend actions to improve it. The NRC Committee on Toxicity Testing and Assessment of Environmental Agents (NRC Committee)³ set out to create a vision for the future of toxicity testing and a strategy that, once implemented, would improve the depth and breadth of toxicology and its usefulness as a predictive—and protective—science (Edwards and Preston 2008). *Toxicity Testing in the 21st Century: A Vision and Strategy* outlines such a vision, together with an initial roadmap for its implementation (NRC 2007). The NRC Committee envisions an iterative process of chemical characterization, toxicity testing, and dose-response and extrapolation modeling informed by population-based data and human exposure information. The report calls for the development of a suite of human-based *in vitro*⁴ cell and tissue assays instead of whole-animal tests for hazard assessment and regulatory decision-making.

Not only would use of these new technologies increase the depth and breadth of information available about each chemical, they would dramatically decrease the time required to evaluate each substance. The result is that a vastly larger number of chemicals could be evaluated within a shorter period of time. This approach could also address currently intractable problems such as the toxic effects of chemical mixtures and nanoparticles, synergistic effects of chemicals, susceptibility of sensitive sub-populations, sensitivity at different life stages, gene-environment interactions, the need to test the effects of chemicals over wider dose ranges, and the effects of chemicals at very low, environmentally relevant doses (Gibb 2008). The conclusion of the report is that the reduced reliance on whole-animal testing leads to a more human-relevant and efficient toxicity testing paradigm, resulting in increased protections for people and the environment.

II. Short-Term Solutions

While the 2007 NRC report outlines a way forward that will take time to fully achieve, available methods and technologies can be applied to the prioritization of chemicals today (Andersen 2009). For example, *in vitro* or *in silico* models can be relied upon as a first “tier” in order to characterize the potential mechanisms of action of test chemicals. In another example, data from the EPA Office of Research and Development's ToxCast Program⁵ has been used to create a prioritization scheme for detecting chemicals with the potential to interact detrimentally with the endocrine system.⁶ Shaw et al. (2008) showed the feasibility of a similar process for prioritizing 50 different nanomaterials based on likely biological reactivity according to differences in material characteristics. Last year, scientists at the NIH Chemical Genomics Center (NCGC) published results of a mechanism-of-action study that used 26 assays in 13 different cell types to

³ The Committee on Toxicity Testing and Assessment of Environmental Agents is an ad-hoc committee convened by the National Academies' National Research Council to create a vision and strategy for 21st-century toxicity testing at the request of the Environmental Protection Agency.

⁴ *In vitro* refers to assays that take place in a culture dish or test tube.

⁵ High-throughput systems capable of running hundreds of chemicals at many different doses through suites of different cell-based and biochemical assays are being used to generate information predictive of the modes of action of test chemicals, to create clusters of chemicals with similar mechanisms of action, and to prioritize chemicals for immediate investigation or regulation.

⁶ Kavlock, Robert. Nov. 11, 2009. Presentation given at Johns Hopkins University School of Public Health, Center for Alternatives to Animal Testing, Chemical Information Day.

cluster 1,408 compounds given at 14 different concentrations according to mechanism of action. The results compared favorably with current information about the chemicals' toxic profiles, and provide support for such approaches (Huang et al. 2008).

Recent changes in chemical legislation in Europe, i.e. the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation, has presented a similar challenge of scale (EC 2006). In an attempt to ensure that REACH is successful, European, American, and multi-national bodies such as the Organization for Economic Cooperation and Development (OECD), are working to further develop strategies to streamline toxicity testing and risk assessment. The REACH legislation also requires that animal tests be used only as a last resort, after all avenues to obtain the required information without animals (i.e. existing data, read-across from similar chemicals) have been exhausted.

In addition to the mandatory use of suitable non-animal testing methods, REACH includes:

- An emphasis on the acquisition and use of existing information
- Use of chemical categories with similar properties
- Use of weight-of-evidence approaches
- Incorporation of non-guideline test results in weight-of-evidence approaches
- Criteria for identifying situations where testing is not feasible
- Exemption of chemicals with no exposure potential

In addition to these sensible strategies, an international collaboration including the OECD is developing and standardizing computer algorithm-based models, known as Quantitative Structure Activity Relationship models (QSARs) for use in chemical assessment. These models can group and classify chemicals based on similar structure or activity profiles, help extend information about similar chemicals to substances with little data (known as bridging), and provide data for classification or risk assessment. Scientists and regulators influential to the REACH legislation are currently demonstrating how these models can—and must—be used in order to quickly assess chemical hazards in the scientific literature (Schaafsma et al. 2009; vanLeeuwen et al. 2009).

Incorporating these strategies into TSCA reform will allow the U.S. to take advantage of the experiences of other regions in regulating industrial chemicals and create the best and most protective policies.

III. Common-sense guidelines for chemical prioritization

A first step in implementing updated TSCA regulations will be setting priorities for assessment and regulatory action. We suggest the following guidelines when determining how to set priorities:

1. Review of TSCA inventory: It is important to get a true picture of the chemicals currently manufactured or imported within the U.S., and the current and near future use and exposure patterns, in order to evaluate and prioritize information needs.

2. Tabulate and review all existing data: Companies should submit to the EPA all unpublished studies for manufactured or imported chemicals relating to physical-chemical properties, environmental dispersal, toxicity, and human and environmental exposure. The EPA should also gather information from other governmental bodies, such as Health and Environment Canada and the European Chemicals Agency, and solicit any additional information from public sources.
3. Make regulatory determinations where possible: Using available data, make determinations of safe use or put necessary risk management controls in place where possible and warranted. Here, special emphasis should be placed on chemicals with known high exposure profiles or those with high potential to remain in the environment after an accidental release.
4. Group chemicals according to common modes of action or structural class: Assessing chemicals as members of scientifically-supported categories has several advantages, the strongest of which is that in some cases hazard information from one or more chemicals can be extrapolated to other members of the category lacking information. Methods mentioned in (5) can support the formation of categories, as can regulator or scientist experience.
5. Apply QSAR and high-throughput biological methods to prioritize chemicals and design integrated strategies for further testing, if warranted. For some chemicals, cellular and computation methods can be used to fill information needs; in other cases these methods can be used to detect priority chemicals and endpoints that require further study.
6. Determine and fulfill information needs according to exposure: Prioritization should be based on potential risk, including potential exposure. For example, chemicals that are produced within a verified closed system may not need extensive hazard information. In addition, a data “gap” is not necessarily a data “need,” and the EPA should be given the flexibility to determine the information needed to make a regulatory decision without requiring a fixed list of data requirements that would apply comprehensively to all chemicals. Testing should be tailored to the chemical based on its toxicity profile and expected exposure. Testing beyond such a determination would waste time, money, and animal lives.
7. Prevent duplicative testing by providing incentives for data sharing. Companies should be required to form consortia and share data where appropriate, in order to prevent duplicative testing on the same chemical or category of chemicals.
8. Where appropriate, allow waivers for tests that are not practical to conduct or clearly redundant, such as inhalation testing of solid materials or aquatic testing for insoluble substances (Sandusky et al 2006).

IV. Ensure Implementation of New Technology

The next decade will see extensive development of new high-throughput and high-content cell, tissue, and computer-based toxicity testing methods. Any effective modernization of TSCA must allow for and encourage adoption of this evolving technology. By providing legislative support to this effort as it modernizes TSCA, Congress will also send a strong message: that more effective chemical regulation is dependent on more effective and humane testing methods. To do this, we urge the Congress to be mindful of the following considerations:

1. The principle of animal testing as a “last resort” should be a foundation of US policy.
2. Computational, cell and tissue-based methods can be used now to prioritize chemicals or groups of chemicals that are of primary concern. These methods can also be used to satisfy information needs for some chemicals. Further development and application of these methods for use in risk assessment should be encouraged in the new legislation.
3. New legislation should be flexible enough to allow the inclusion of new testing methods and Integrated Testing Strategies as they are developed, and should not prescribe a minimum data set/check-list of toxicity tests to which all substances must be subject.
4. New legislation should provide EPA with significant funding and organizational support, guidelines for an efficient and flexible peer review process, and clear benchmarks of success, to ensure rapid implementation of better testing methods.
5. New legislation should offer strong incentives for companies to fund, develop, and use new methods and testing strategies; and, as non-animal/alternative methods become available, require the use of such methods in place of animal tests.

V. Summary and Conclusion

As the NRC and EPA⁷ both state, advances in computational and cellular technologies will allow more predictive and protective toxicological assessments of chemicals. While this vision is being progressively realized, existing methods and approaches can be used in addition to exposure variables, physical-chemical information, and existing knowledge to prioritize chemicals for regulation or further study.

Protecting human health and the environment is the critical goal of effective chemical regulation. In order to achieve this goal, it is necessary to reform chemical testing methods along with policy. The current toxicity-testing paradigm relies on animal testing and is slow, sometimes misleading, open to uncertainty and manipulation, and as a consequence of these factors, can not adequately protect human health. Prioritization of chemicals and endpoints to be tested, based on potential for hazard and exposure, is essential in order to avoid unmanageable bottlenecks that would further stymie environmental protections.

⁷ See The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals, located at: <http://www.epa.gov/spc/toxicitytesting/index.htm>.

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