

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
HOUSE COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON COMMERCE, TRADE AND CONSUMER PROTECTION
ON
PRIORITIZING CHEMICALS FOR SAFETY DETERMINATION

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I. Introduction

While estimates of the numbers and the amount of information available on particular chemicals 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.

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 detailing 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 regulation programs that waste time, money, and hundreds of thousands of animals while leaving human health and the environment unprotected. 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 notices¹ each year – review of existing chemicals would be in addition to these PMN reviews.

Evaluation of this tremendous backlog of chemicals, as well as providing robust information regarding new chemicals, is simply not feasible under the existing 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 1930's and 40's - tests that are time-consuming, expensive and use thousands of animals. 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 (Knight and Bailey 2006a & b; Ennever and Lave 2003) and an even poorer record in leading to actual regulation of hazardous chemicals (PETA 2006).

In light of these concerns, the Environmental Protection Agency (EPA) realized that the current toxicity testing paradigm is in urgent need of overhaul and contracted the National Academy of Sciences' National Research Council (NRC) to assess the current system and recommend actions

¹ <http://www.epa.gov/oppt/ar/2007-2008/reviewnewchem/index.htm>

to improve it. The NRC Committee on Toxicity Testing and Assessment of Environmental Agents (NRC Committee)² 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 that vision and how to implement it (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*³ cell and tissue assays instead of whole-animal tests for hazard assessment and regulatory decision-making.

Not only would use these new technologies broaden the depth and breadth of information available about each chemical, they would dramatically decrease the time required to evaluate each chemical. 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 a reduced reliance on whole-animal testing leads to a more predictive and efficient toxicity testing paradigm, leading to increased protections for people and the environment.

II. Short-Term Solutions

While the NRC, 2007 report describes a way forward that will take time to fully achieve available methods and technologies can be applied to the prioritization of chemicals today. For example, as a first “tier” in order to characterize the potential mechanisms of action of test chemicals (Andersen 2009). In another example, data from the EPA Office of Research and Development’s ToxCast Program⁴ has been used to create prioritization scheme for detecting chemicals with the potential to interact detrimentally with endocrine system.⁵ 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 NCGC published results of a mechanism-of-action study that used 26 assays in 13 different cell types to 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).

² 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.

³ *In vitro* refers to assays that take place in a culture dish or test tube.

⁴ 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.

⁵ Kavlock, Robert. Nov. 11, 2009. Presentation given at Johns Hopkins University School of Public Health, Center for Alternatives to Animal Testing, Chemical Information Day.

Recent changes in legislation regulating toxic chemicals in Europe, the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), has presented a similar challenge of scale (EC 2006). In an attempt to ensure that REACH is successful, European, American, and multi-national bodies like the Organization for Economic Cooperation and Development are working to further develop strategies to improve streamlined toxicity testing and risk assessment. In addition to the incorporation of 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 strategies, international efforts are collaborating with the Organization for Economic Co-operation and Development (OECD) to develop and standardize computer algorithm-based models, known as Quantitative Structure Activity Relationship models (QSARs). These models can group and classify chemicals based on similar structure or activity profiles, help extend information about similar chemicals to chemicals 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 be—and why they 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 principles for chemical prioritization

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 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 controls in to 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.

IV. Summary and Conclusion

As the National Research Council and the Environmental Protection Agency⁶ both state, advances in computational and cellular technologies will allow more predictive and protective toxicological assessments of chemicals. Until this vision is in place, 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, inaccurate, open to uncertainty and manipulation, and does not adequately protect human health.

⁶ 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>.

Prioritization of chemicals and endpoints to be tested by potential for hazard and exposure is essential in order to avoid unmanageable bottlenecks that would further stymie environmental protections.

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