TESTIMONY OF
THE HUMANE SOCIETY OF THE UNITED STATES and the
HUMANE SOCIETY LEGISLATIVE FUND

BEFORE THE
HOUSE COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON ENVIRONMENT AND THE ECONOMY

ON ISSUES PERTAINING TO
REAUTHORIZING THE TOXIC SUBSTANCES CONTROL ACT
SECTION 4

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I. Introduction

Thank you Chairman Shimkus and Ranking Member Tonko for the opportunity to testify on behalf of The Humane Society of the United States (HSUS), the nation's largest animal protection organization, and the Humane Society Legislative Fund on Section 4 of the Toxic Substances Control Act (TSCA). We strongly support animal protection, public health and environmental safety for people and the animals in our environment and believe the Environmental Protection Agency should have the tools necessary to appropriately regulate chemicals in the United States.

The current law authorizing the EPA to regulate chemicals, the Toxic Substances Control Act (TSCA), enacted in 1976, has many shortcomings that have been extensively documented and have led to a chorus of disparate voices urgently calling for an update of this now 28 year-old legislation. [1] Our testimony focuses on one critical aspect of this reform: the process used to evaluate chemical safety in Section 4.

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 the current assessment approaches that rely heavily on animal testing.

The current TSCA Inventory contains approximately 80,000 chemicals; in order to review this

[1] Including several non-governmental organizations (http://www.edf.org/health/policy/chemicals-policy-reform; http://www.saferchemicals.org/resources/tsca.html), the Environmental Protection Agency (http://www.epa.gov/oppt/existingchemicals/pubs/principles.html), and the American Chemistry Council (http://www.americanchemistry.com/Policy/Chemical-Safety/TSCA).

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 if current assessment approaches are used. 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 notices (PMN) each year[2] – 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 $380,000, 2,600 rats and two years to perform (data interpretation and regulatory decisions based on that information would involve additional costs).

According to EPA's 2009 Strategic Plan for Evaluating the Toxicity of Chemicals, the traditional approach of animal testing has "…led over time to a continual increase in the number of tests, cost of testing, use of laboratory animals, and time to develop and review the resulting data. Moreover, the application of current toxicity testing and risk assessment approaches to meet existing, and evolving, regulatory needs has encountered challenges in obtaining data on the tens of thousands of chemicals to which people are potentially exposed and in accommodating increasingly complex issues (e.g., lifestage susceptibility, mixtures, varying exposure scenarios, cumulative risk, understanding mechanisms of toxicity and their implications in assessing dose-

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

response, and characterization of uncertainty)." [3] 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; Olson et al., 2000) and an even poorer record of leading to actual regulation of hazardous chemicals (Seidle 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 with the National Academy of Sciences' National Research Council (NRC) to assess the current system and recommend actions to improve it. The resulting report, "Toxicity Testing in the 21st Century: A Vision and Strategy" outlines a testing paradigm that, rather than relying on a battery of animal tests, envisions an iterative process of chemical characterization, toxicity testing, and dose-response and extrapolation modeling informed by population-based data and human exposure information (NRC 2007). The report calls for the development of a suite of human-based 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,

[3] The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals, March 2009 (http://www.epa.gov/spc/toxicitytesting/docs/toxtest_strategy_032309.pdf)

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 A Transformation in Chemical Safety Assessment is Underway

While the 2007 NRC report outlines a way forward that will take time to fully achieve, currently available methods and technologies can be applied to the prioritization of chemicals today (Andersen 2009). EPA Office of Research and Development is implementing the ToxCast Program that uses automated assays (called "high-throughput screening assays") to evaluate potential effects of chemicals on living cells and tissues.[4] According to EPA, "These innovative methods have the potential to limit the number of required laboratory animal-based toxicity tests while quickly and efficiently screening large numbers of chemicals." EPA, along with NIH's National Chemical Genomics Center (NCGC) and the Food and Drug Administration are collaborating on Tox21 to use a collection of automated assays to "screen thousands of chemicals for potential toxicity, using screening data to predict the potential toxicity of chemicals and developing a cost-effective approach for prioritizing the thousands of chemicals that need toxicity testing."[5] The FDA has partnered with the Defense Advanced Research Projects Agency to provide $70 million in funding to develop human-based "organs-on-a-chip" that can be used to study chemical effects on organs and multi-organ systems.[6] The sponsored work at the Wyss Institute at Harvard in Cambridge, MA, is proceeding much faster than

[4] http://www.epa.gov/ncct/toxcast/
[5] http://epa.gov/ncct/Tox21/
[6] http://www.darpa.mil/Our_Work/DSO/Programs/Microphysiological_Systems.aspx

expected; they have developed functional lung and intestine micro-tissues and are working on several other organ types.[7]

EPA is developing methods to interpret the data to both prioritize chemicals and to profile each chemical with respect to its potential to cause toxicity (Sipes et al., 2013; Wambaugh et al., 2013; Wetmore et al, 2013). Currently this screening information is intended to be used to target further testing; however, it has the potential to identify the most potentially harmful chemicals and greatly improve the efficiency of their safety characterization (Cote et al., 2014).

These new technologies are elements of a predictive approach that involves combinations of several of these tools in an "integrated testing strategy" that, through combinatorial testing, provides toxicity information that can be used in making safety decisions about chemicals (Bradbury et al., 2004; Cooper et al., 2006; Becker et al., 2007). Used in isolation, these tools provide only part of the total picture. To increase confidence in the application of these tools in integrated strategies, the concept of biological pathways is critical. The 2007 NRC report mentioned above used this understanding to propose that toxicity can be more efficiently and accurately evaluated by probing networks of key biological pathways for their response to chemical disturbances (NRC, 2007). A normal pathway becomes what the NRC authors refer to as a "toxicity pathway" when it has been perturbed or disrupted to the point where it can no longer correct itself (also known as an "adverse outcome pathway;"Ankley et al., 2010). Information obtained using the tools described above can be used to test steps along the pathway to predict toxicity of a chemical. The pathway concept is relatively new, and most pathways are not yet well characterized. In addition, there are not yet non-animal tests for many steps in the pathways and therefore, in the near term, information requirements for chemical safety may

[7] http://wyss.harvard.edu/viewpage/100/biomimetic-microsystems; Keynote talk at ASCCT 2013 Annual meeting.

involve animal testing. However, as the pathways become more well described, and assays developed to query critical steps in the pathways, reliance on animal testing will be reduced and eventually eliminated.

Many regulatory bodies around the world, including the US EPA, the European Commission's Joint Research Centre, and the Organization for Economic Coordination and Development (OECD), are developing pathways, guidance on harmonizing pathway development and documentation, and large complex databases to store the pathways and the relational information necessary to use the pathways for predicting toxicity (OECD, 2013).[8]

III. Relevant Principles from Existing Chemicals Legislation

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) have drafted 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

[8] http://www.epa.gov/ord/priorities/docs/aop-wiki.pdf; http://ihcp.jrc.ec.europa.eu/our_activities/alt-animal-testing-safety-assessment-chemicals/improved_safety_assessment_chemicals/adverse-outcome-pathways-aop

- 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

Incorporating these strategies into legislation to update TSCA 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.

IV. 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 non-testing approaches (e.g. predictive computer programs), high-throughput and other non-animal tests 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. Incentives should be provided to get companies to share data where appropriate, in order to prevent duplicative testing on the same chemical or category of chemicals.

V. 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. Updated 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 chemicals 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.

VI. Some Input Related to Section 4, S.1009, the Chemical Safety Improvement Act of 2013

On review of the Senate bill, there are provisions within S. 1009 that reduce animal testing and lead to more efficient assessment by the EPA, beginning with Section 2: Findings, Policy and Intent that states that EPA "should minimize the use of animal testing through the use of scientifically reliable and relevant test methods, where appropriate."

Section 4: Chemical Assessment Framework; Prioritization Screening; Testing, includes a flexible framework that for athorough evaluation of all existing data is essential for designing an effective chemical assessment; it allows EPA to not only understand what is known, but to design a clear path to obtain the information that it needs to make a determination. This approach recognizes that not all chemicals are the same and assessments need to be tailored to the chemical and to the Agency's needs. Importantly, this approach also allows a rapid identification of chemicals that are a high priority for assessment.

The framework outlined in Section 4 also emphasizes the need to collect and interpret mechanistic information – characterization of the mechanism of action of a chemical is fundamental to being able to make better predictions about its potential biological activities – and this is critical to improving risk assessment of all chemicals, but particularly of new chemicals.

In describing the conditions for developing new test data, Section 4 also includes options to minimize animal testing, including requiring an evaluation of all existing information before considering any new vertebrate testing, encouraging the use of scientifically reliable and relevant

alternative methods, and the use of a structured evaluation framework to focus testing where it is needed.

Section 4(i), "Reduction of Animal-based Testing," reinforces the use of integrated and tiered assessment strategies and the use of methods that replace or reduce the use of animals. It also provides for the development and use of non-animal methods by requiring EPA to develop a strategic plan for implementation that includes the development of pathway-based systems, computational and high-throughput tools. Finally, it authorizes the agency to fund and carry out research for development and translation of these tools. There is also a detailed provision in this section for waiving animal testing in certain circumstances.

V. Summary and Conclusion

As the NRC and EPA[9] both state, advances in computational and cellular technologies will allow more predictive and protective toxicological assessments of chemicals than animal testing. 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 varying interpretation, and as a consequence of these factors, cannot 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

[9] The U.S. Environmental Protection Agency's Strategic Plan for Evaluating the Toxicity of Chemicals, March 2009 (http://www.epa.gov/spc/toxicitytesting/docs/toxtest_strategy_032309.pdf).

unmanageable bottlenecks that would further stymie environmental protections.

While the language in Section 4 of S1009 falls short of implementing an overarching policy of animal testing as a last resort, we believe that it presents an improvement over the existing of the Toxic Substances Control Act by providing increased authority for EPA to request and use information to protect human and environmental health, while minimizing animal use by focusing testing where it is needed. In addition, by supporting new pathway and systems biology tools, these provisions also allow EPA to better implement its current shift from an imperial, animal-testing based assessment process, toward a more predictive process built on thorough understanding of chemistry and biology.

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