

# Protecting Children from Harmful Chemicals

An Effective Approach to Toxic Chemicals Reform



*“It is simply not possible with all the animals in the world to go through chemicals in the blind way we have at the present time, and reach credible conclusions about the hazards to human health.”*

**-Dr. Joshua Lederberg, Nobel Laureate in Medicine**

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## Protecting Children from Harmful Chemicals

Chemicals are regulated based on their potential for causing toxic effects; therefore, whether, how, and when toxicity testing is conducted is an essential cornerstone to any chemical safety legislation, and we need to ensure it is laid down correctly.

Revision of the Toxic Substances Control Act must incorporate scientific approaches to information collection based on human-relevant testing methods, developed with modern biological understanding, as outlined in the National Academy of Sciences report *Toxicity Testing in the 21st Century: A Vision and Strategy*.

These recommendations encompass core principles that would ensure an efficient toxicity testing process now, and lay the foundation for a more protective, human-relevant, and humane toxicity-testing paradigm in the near future.

### Effective Regulations Start with Modern Science

The current legislation 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 calls for TSCA reform. We must, however, also be sure to reform the science that underlies these regulations—namely, the way in which toxicity testing is conducted. Done right, TSCA reform can leave the United States with a strong program of chemical assessment and management consistent with the National Academy of Sciences recent landmark report detailing a vision and strategy for toxicity testing in the 21st Century (NRC, 2007). Pursued unwisely, TSCA reform could be the latest in a string of disastrous and ineffective chemical regulation programs that wastes time, money, and hundreds of thousands of animals while leaving human health and the environment unprotected.<sup>1</sup> This report focuses on a critical aspect of this reform: updating the science behind toxicity data used to make regulatory decisions.

Under TSCA, the marketing, sale, and distribution of a chemical do not require prior safety testing. One of the major issues driving TSCA reform is the desire to reverse this process and shift the burden of proof for safe use to the manufacturer prior to marketing. While this is a desirable goal, it presents a significant logistical and scientific challenge. Not only will safety testing be required for all chemicals under development, but a back-log of tens of thousands of chemicals will also require testing. To review all of the chemicals in the TSCA Inventory 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 1,000 pre-manufacture notices<sup>2</sup> each year.

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<sup>1</sup> See, for example, the June 17, 1999, proceeding of the Hearing Before the Subcommittee on Energy and the Environment of the House Committee on Science (106th Congress, Serial No. 106-18) on the EPA's High Production Volume (HPV) Chemical Testing Program at which the authors' organizations, PETA and PCRM, testified.

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

## The Existing Toxicity Testing Paradigm Is in Urgent Need of Overhaul

The current toxicity testing paradigm used by the Environmental Protection Agency (EPA) and other regulatory agencies is largely based on experiments on animals, particularly rodents, and uses methods that were developed as long ago as the 1930's and 1940's. These tests are time-consuming, expensive, and use thousands of animals. For example, a single two-generation reproductive toxicity study takes a minimum of two years, \$380,000, and 2,600 rats to perform. Generation of data for all of the existing chemicals using current toxicology tests is not feasible within a reasonable time-frame (it is more likely to take several decades); there are simply not enough laboratories in the world to conduct all the testing required. In addition, the current testing paradigm has a poor record in predicting effects in humans (Knight and Bailey 2006a & b; Ennever and Lave 2003) and an even poorer record in leading to actual regulation of dangerous chemicals (PETA 2006).

Many scientific and practical factors contribute to the poor predictivity and performance of animal testing including that, in order to see an effect, animals are usually given extremely high doses of chemicals, and results are often complicated by side-effects from the large doses. In addition, results from non-human animals are often misleading due to biochemical and metabolic differences between humans and other animals. Consequently, regulators are challenged to determine the real relevance of test results to humans—and this uncertainty leads to more testing and further delays in taking regulatory action.

Toxicity assessment needs are increasingly outpacing the capacity of toxicity testing laboratories. Animal experiments take anywhere from months to years and tens of thousands to millions of dollars to perform. It is simply not possible to test all the chemicals, ingredients, products, mixtures, and environmental contaminants to which humans are exposed using animal-based methods—the time, money, and laboratory space do not exist.

In light of these concerns, the EPA realized that the current toxicity testing paradigm is in urgent need of overhaul and contracted the National Academy of Sciences' National Research Council to assess the current system and recommend actions to improve it. The NRC Committee on Toxicity Testing and Assessment of Environmental Agents (NRC Committee)<sup>3</sup> found that the current system is not predictive or practical—in terms of time, cost, animals, or testing needs—and 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 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*<sup>4</sup> cell and tissue assays instead of whole-animal tests for hazard assessment and regulatory decision-making.

Such a biology-based approach could also address currently intractable problems such as 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 concentrations (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, which in turn leads to increased protections for people and the environment.

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<sup>3</sup> 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.

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

<sup>5</sup> Memorandum of Understanding on High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings between the US DHHS NIH NIEHS/NTP and the US DHHS NIH NHGRI NCGS and the US EPA ORD. Signed 30 January 2008. Available at: <http://www.epa.gov/comptox/articles/files/ntpnccgcepamou.pdf>. Accessed 12 December 2008.

## The Foundation for a Paradigm Shift Is Underway

While much of the necessary technology is in use today (Anderson 2009), accomplishing the NRC vision in a timely fashion will take a concerted effort and an influx of resources. Spurred in part by the NRC report, work is underway at several different government agencies and private research centers to create the knowledge base necessary. Work underway at the National Institutes of Health's Chemical Genomics Center (NCGC), the National Toxicology Program, and the EPA's Office of Research and Development (ToxCast Program) has been formalized into a working partnership to share funds and resources.<sup>5</sup> 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 chemicals, to create clusters of chemicals with similar mechanisms of action, and to prioritize chemicals for immediate investigation or regulation.<sup>6</sup>

Currently, these methods are being used to prioritize chemicals for further study or as a first "tier" in order to characterize the potential mechanisms of action of test chemicals—as has been done at Harvard with 50 different nanomaterials (Shaw et al. 2008). *In vivo* testing need not be conducted on those agents that do not show the potential to perturb a toxicity pathway and initiate the chain of events leading to an apical<sup>7</sup> effect. These analyses are also being used to elucidate the major pathways by which environmental agents cause toxic effects. A refined suite of assays that detect perturbations of these pathways will form the basis of the new toxicity-testing paradigm.

Stakeholders from various backgrounds, including industry, government, and non-governmental organizations (NGOs), have formed partnerships to conduct research projects and other activities with the aim of making toxicity testing more efficient and reducing animal use, mainly through the use of tiered (Becker et al. 2007; Sullivan et al. 2007) or integrated (Hoffmann et al. 2008) testing strategies. For example, in November 2007, the EPA, through the Organisation for Economic Co-operation and Development (OECD), hosted a workshop on Integrated Approaches to Testing and Assessment, which sought to establish recommendations on how to use nontraditional test data, data from similar chemicals, *in vitro* data, and simulation data from QSAR modeling<sup>8</sup> to prioritize and characterize the hazards of pesticides and industrial chemicals.<sup>9</sup>

A workshop sponsored by the International Life Sciences Institute Health and Environmental Sciences Institute in 2002 to streamline the testing process for pesticides (Carmichael et al. 2006) resulted in a series of publications outlining a comprehensive, tiered approach that integrates key studies with existing knowledge on the chemistry, toxicology, and actual human exposure scenarios of a chemical. Complicated or lengthy animal studies are only conducted if triggered by results of initial studies (Doe et al. 2006). When implemented, such a tiered approach will reduce the number of animals killed per registered pesticide by 2,500 or more (Cooper et al. 2006). The EPA's Office of Pesticide Programs and the OECD are both currently working to implement these recommendations.<sup>10</sup>

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<sup>6</sup> This 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, R et al. 2008. Characterization of diversity in toxicity mechanism using *in vitro* cytotoxicity assays in quantitative high throughput screening. *Chem Res Toxicol* 21:659-667.

<sup>7</sup> In this context, an apical effect is a toxic effect that is the final, visible result of a chemical exposure, such as a tumor, lesion, or neurological symptom. Current animal tests look for apical endpoints, but the NRC vision would shift this emphasis to the identification of chemical-mediated precursor events, such as gene induction or cytokine regulation, that will eventually result in a toxic effect. The NRC vision calls these events perturbations.

<sup>8</sup> Structure-Activity Relationship, or SAR, modeling refers to computer models built to correlate chemical structure to some resulting activity, such as receptor binding. Quantitative SAR, or QSAR, does this quantitatively.

<sup>9</sup> [http://www.epa.gov/NHEERL/ontheroad/washington\\_dc.html#6](http://www.epa.gov/NHEERL/ontheroad/washington_dc.html#6)

<sup>10</sup> See <http://www.epa.gov/pesticides/ppdc/testing/index.html>

Some simple strategies for increasing the efficiency of testing programs, and thereby reducing the number of animals killed, were put into the EPA's High Production Volume Challenge program in 1999 as a result of input from animal protection organizations. During the program, the EPA and NGOs codified further principles that minimized the testing conducted (Sandusky et al. 2006). The major principles include: (1) combining protocols that assess the same endpoints; (2) identifying chemical clusters that allow extrapolation of results from related chemicals; (3) eliminating testing requirements for classes of chemicals with known toxicity (e.g. acids, corrosives); (4) identifying chemicals for which certain testing is not feasible (e.g. highly reactive or insoluble materials); and (5) applying of weight-of-evidence approaches.

The clustering approach will make the biggest impact in reducing the overall lack of knowledge about existing chemicals that currently exists. Chemicals with similar properties, structures, or modes of action can be grouped together, and toxicity information about one or more chemicals can be extrapolated to other chemicals in that cluster. Along with the use of Quantitative Structure Activity Relationship (QSAR) models, this approach is being promoted by European scientists in order to successfully administer the REACH legislation (see below) (van Leeuwen et al 2009).

Outside the United States, the development of alternatives has progressed at a quicker pace, primarily due to legislative deadlines set by the European Union Cosmetics Directive and the impending European Registration, Evaluation, Authorization and Restriction of Chemical Substances (REACH) legislation (EC 2006). Amendments to the Cosmetics directives prohibit the use of animals for cosmetics testing beginning in 2009 (EC 2003). Consequently *in vitro* methods have been developed for most of the required endpoints for cosmetics. REACH is an overarching program that will require the toxicity characterization of all chemicals manufactured or sold in the European Union. The amount of testing a chemical undergoes is proportional to its annual production or import amount. Because of the sheer magnitude of this program, as it will be with any revision of TSCA that contains the pre-emptive elements of REACH, it is physically impossible to carry out complete batteries of animal tests for every chemical; therefore, REACH incorporates several alternative strategies for risk assessment. In addition to the incorporation of nonanimal 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

To facilitate regulatory application of these new methods, the European Union has funded a facility whose sole purpose is the validation of alternative methods, the European Center for the Validation of Alternative Methods (ECVAM). ECVAM receives approximately 25 million € per year from the E.U. Directorate General on Research (ICCVAM 2006). ECVAM is a division of the EC's Joint Research Council's Institute for Health and Consumer Protection (IHCP) and is housed in IHCP facilities in Ispra, Italy. It has 60 staff members, roughly half of whom work directly in laboratories. ECVAM is currently involved in the evaluation of 170 methods (Hartung 2007).

There is no equivalent effort in the United States. The only entity dealing with the validation of alternative methods in the United States is a voluntary committee, the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). ICCVAM does not receive major funding, lacks a scientific staff or facilities, and has been repeatedly documented as obstructing the implementation of nonanimal testing methods (Gaul 2008, PETA 2007). The European Commission also funds directives for special applications of alternative methods to specific areas of toxicity. These are interdisciplinary projects involving the government, academia, and industry, with focused goals. For example the ACuteTox and ReProTect projects are developing nonanimal methods for acute toxicity and reproductive toxicity, respectively.

## Any Effective Revision of TSCA Must Include This Paradigm Shift

The strategies outlined above all lead to a decreased reliance on animal testing and collectively help move toxicity testing into the future. However, as the NRC report describes, a bird's-eye-view is needed to create a comprehensive program, coupled with a substantial commitment of resources, along with the support of lawmakers, regulators, industry, environmental groups, and the general public. Interpretive tools and policy mechanisms to deal with new kinds of hazard data are required and must be developed along with the science. All of this requires the support and investment of all stakeholders and Congress.

The fact that implementation of this science-based approach will take some time and effort should not be used as a rationale to postpone its development. Is it worth the effort to achieve? Why not just go ahead with the approach we have been using since we need protection now? Enacting legislation based on the current approach to toxicity testing will only maintain the status quo, leading to the expenditure of vast resources and years of testing new and existing chemicals that will continue to generate data of dubious value for protecting humans or the environment. If long-term protection of human and environmental health is the goal, then the NRC approach is the only option.

### Recommendations for TSCA Reform

For any legislative reform of TSCA to be effective in generating data that could be used for the protection of human health or the environment in general, or any vulnerable sub-population in particular, that legislation would have to include the paradigm shift described in the NRC report. For example, application of the technology outlined in the NRC report will also allow for the assessment of low-doses and mixtures (Anderson 2009), which is not currently possible under the existing paradigm. During the development of this paradigm, concrete steps can also be taken to minimize animal testing over current approaches. Outlined below are some specific principles with these two goals in mind.

#### Mandate the release and use of existing data

1. Require public availability of all existing information on TSCA Inventory chemicals, as well as information from any other chemical testing programs (e.g., the High Production Volume Challenge Program, the Voluntary Children's Chemical Evaluation Program, various NTP programs such as the Center for the Evaluation of Risks to Human Reproduction, and the Rodent Carcinogenicity Bioassay program).
2. Mandate relevant data-sharing among companies (with fair compensation). This is a stipulation of the REACH legislation, and new legislation should be consistent with REACH where appropriate.
3. Require coordination between the U.S. EPA and the regulatory agencies of other regions (e.g. Health Canada, which is currently reviewing the safety of 23,000 chemicals on its Domestic Substance List; the EU's REACH program, which aims to generate a wide array of toxicity data for approximately 30,000 chemicals; the Danish EPA's database of QSAR evaluations of toxicity for approximately 47,000 chemicals).
4. These data should be collected in a comprehensive, publicly available database prior to the initiation of any further testing.

#### Explicitly incorporate the toxicity-testing paradigm outlined by the NRC

1. Expressly prohibit the duplication of animal studies or further testing on animals if another scientifically satisfactory method is reasonably and practicably available and stipulate manufacturer and regulator education on available alternatives. New legislation should also embrace the REACH maxim of animal testing as a last resort for the collection of hazard data.
2. As in REACH, encourage grouping of similar chemicals into scientifically appropriate clusters to enable data gaps to be filled by read-across and to limit new testing to representative chemicals.

3. As in REACH, require that companies form consortia for the purposes of data sharing and the coordination of any new testing.
4. A significant amount of funding should be stipulated for alternative methods development, translation, and evaluation. An estimate of the investment required to achieve the NRC vision in 10–15 years is \$100–\$200 million per year, much of which is already being invested by relevant industry and the U.S. and European governments, albeit in a non-coordinated fashion (NRC 2007; Rowan 2008; Collins et al. 2008). Revised TSCA legislation should therefore stipulate a minimum of \$15 million per year additional to be invested in alternative methods development.
5. The revised TSCA should provide for a public review process before new animal testing takes place.

### Incorporate integrated testing strategies

1. Hazard data should be collected as part of a chemical-specific strategy that takes into account physiochemical properties, existing *in vitro*, *in vivo*, and *in silico* data, and real or potential exposure information for each chemical—a minimum list of initial tests or hazard data to be generated should not be prescribed in legislation. This is consistent with national and international chemical policies that emphasize integrated toxicology.
2. Chemical testing should be performed in a stepwise manner, starting with shorter-term nonanimal tests, and reassessing results according to a decision strategy approach before moving on to the next step.
3. The EPA should be given flexibility to determine quantitative risk estimates, toxic effects and/or endpoints of concern, and necessary evaluations should be conducted on a case-by-case basis. Hazard and risk assessments should be made based on any relevant data using a weight-of-evidence approach; hence, specific references to animal-based risk measures (BMD1, LD50, etc) should be removed. This would also allow for greater test method flexibility and allow for new approaches as they become available.
4. Proving “Reasonable certainty of no harm” for industrial chemicals—most of which are much less toxic than pesticides—is scientifically unsupported and practically infeasible. Attempting to reach this standard would require an enormous use of animals and resources that simply don’t exist. Suggested alternative language: “weight of evidence suggests that the chemical poses no significant risk to human health (or the environment) under reasonably anticipated conditions of use.”

## Summary and Conclusion

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. Reform of TSCA should not only modernize policy, but modernize the science that supports that policy. The approach mentioned above, and described in detail in the NRC report, will

“produce more relevant data on which to base risk management decisions about chemical hazards and greatly expand the numbers of chemicals that can be tested. These improvements can fulfill the vision of better protecting people from the risks posed by chemicals in our environment” (Krewski 2008).

This approach has only benefits: an increased ability to regulate unsafe chemicals, resulting in improved human and environmental health, and a decreased reliance on the use of animals in the process of safety testing. Many of the necessary tools already exist, and the NRC has provided a roadmap for achieving the rest of what remains to be accomplished in order to create an effective and protective toxicity program. The time to move forward is now.

Please visit [www.reformtoxicitytesting.org](http://www.reformtoxicitytesting.org) to learn more.

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