PATHWAYS TO BREAST CANCER:

A CASE STUDY FOR INNOVATION IN CHEMICAL SAFETY EVALUATION

A report of the Breast Cancer and Chemicals Policy Project, produced by the University of California, Berkeley and the Natural Resources Defense Council, with funding from the California Breast Cancer Research Program, University of California Office of the President

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Authors

Megan Schwarzman, MD, MPH
Sarah Janssen, MD, PhD, MPH

Contributors

Ruthann Rudel, MS
Lauren Zeise, PhD
Joseph Guth, PhD, JD
Gina Solomon, MD, MPH
Dale Johnson, PharmD, PhD
Shanaz Dairkee, PhD
Rachel Morello-Frosch, PhD
Suzanne Fenton, PhD
Ron Melnick, PhD
Jean Latimer, PhD
Vincent James Cogliano, PhD

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Executive Summary

Breast cancer, the most common invasive cancer in women, is hypothesized to be linked to industrial chemical exposure through the environment and the use of consumer products. A major challenge in understanding the extent to which chemicals contribute to breast cancer is a lack of toxicity information—a data gap—for tens of thousands of commonly used chemicals. Through its Green Chemistry Initiative, California is attempting to address this data gap by seeking ways to develop toxicity information for chemicals used in consumer products. A bill recently introduced in the U.S. Congress to reform the decades-old Toxic Substances Control Act (TSCA) calls for the generation and disclosure of information on the toxicity of industrial chemicals. Generating the data to inform these programs will require new, more efficient approaches to produce reliable information on the hazards posed by the tens of thousands of chemicals already in commerce.

To investigate how such efforts could help identify chemicals that may raise the risk of breast cancer, the California Breast Cancer Research Program[1] designed and funded the Breast Cancer and Chemicals Policy (BCCP) project.[2] The goals of the BCCP project were three-fold:

- **Develop an approach for identifying chemicals** that may contribute to the development or progression of breast cancer,
- **Identify research needs** and recommend improvements to existing test methods, and
- **Pilot a model process** that can be applied to other disease endpoints, enabling the ultimate aim of producing a comprehensive approach for identifying hazardous chemicals.

Drawing on the fields of cancer biology, toxicology, medicine, epidemiology, public health, and public policy (*Figure 1*), a multidisciplinary expert panel (Panel) reviewed existing methods for chemical toxicity testing and developed a testing scheme, called the Hazard Identification Approach. This approach provides a methodology for the identification of substances that could elevate breast cancer risk.

The Panel's analysis followed the lead of major new initiatives in chemical hazard evaluation that seek to shift emphasis from decades-old whole animal testing protocols to more efficient *in vitro* mechanism-based chemical screening.[3, 4, 5, 6, 7]

The Panel used a four step process to achieve the stated goals. Working from current epidemiologic and laboratory evidence, the Panel first identified changes in biological processes associated with the development or progression of breast cancer. Second, they identified existing toxicity testing methods that detect these changes. Third, the Panel designed a testing scheme, calling it the Hazard Identification Approach, for identifying chemicals that may raise the risk of breast cancer. The panel also recommended ways of prioritizing the types of chemicals that would undergo testing. The fourth step was to conduct a virtual pilot test of the recommended Hazard Identification Approach. Following is a description of each step.

1. Identification of biological processes associated with breast cancer

The Panel determined toxicity endpoints: alterations to biological processes associated with the development, progression, or susceptibility to breast cancer. These toxicity endpoints were divided into three categories (Figure 6):

- Cellular and molecular mechanisms, (e.g., activity at hormone receptors),
- Tissue changes (e.g., altered mammary gland development), and
- Susceptibility factors (e.g., early puberty).

Within each category, the Panel identified distinct biological endpoints that could be evaluated in a toxicity test.

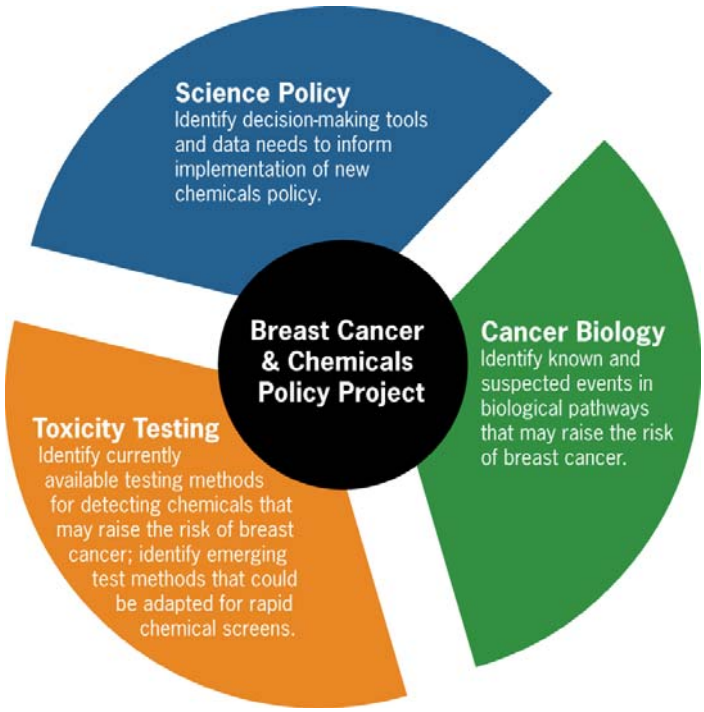

Figure 1. **Framework of the Breast Cancer and Chemicals Policy Project.** The Breast Cancer and Chemicals Policy Project was conducted by a multidisciplinary panel consisting of experts in toxicology, cell and mammalian biology, medicine, epidemiology, endocrine disruption, environmental justice, science policy and breast cancer advocacy. The Panel developed a method for identifying, prioritizing, and testing chemicals that may raise the risk of breast cancer.

2. Identification of toxicity testing assays for evaluating chemicals

The Panel identified examples of computational (*in silico*),[*] *in vitro, in vivo,* and epidemiological methods for evaluating a chemical's ability to alter biological processes relevant to breast cancer. Validated assays were catalogued, as were those that could be validated in the near future (based on their current use in laboratory

[*] Computational toxicology, is described by U.S. EPA (U.S. EPA, 2003) as "the application of mathematical and computer models to predict the effect of an environmental agent and elucidate the cascade of events that result in an adverse response."

research), and those that are emerging from high throughput toxicity testing methods.[†]

3a. Propose methods for setting priorities
As tens of thousands of largely untested chemicals are considered for toxicity testing, substances should be prioritized based on preliminary indicators of hazard (e.g., potential estrogenic activity). Additionally, substances to which people are likely to be exposed, which have physical or chemical properties of concern (such as persistence or bioaccumulative potential), or which have been flagged by computational methods—should be prioritized for evaluation of any potential harmful human health effects, not only breast cancer.

3b. Designing an overall Hazard Identification Approach
The Panel designed a testing scheme for identifying chemicals that may raise the risk of breast cancer. This testing scheme is the Panels' Hazard Identification Approach (Figure 7), which recommends testing chemicals for their potential to increase breast cancer risk through any of the following mechanisms:

- Mechanisms associated with carcinogenesis in general, including cell cycle changes and genotoxicity,
- Mechanisms associated with endocrine disruption, and
- Altered development and maturation of the mammary gland.

4. *Pilot testing the Hazard Identification Approach*
The panel conducted a virtual validation of the proposed Hazard Identification Approach—a pilot test of 20 substances for which sufficient animal or human data exist to characterize their links to breast cancer. This pilot test consisted of a literature review, searching for results of toxicity tests from the Panel's Hazard Identification Approach. The findings of this pilot test will be published separately in a peer-reviewed publication.

Recommendations of the Breast Cancer and Chemicals Policy Project

Based upon their expert consensus and preliminary assessment, the Panel recommends the following approach to toxicity testing to increase its relevance to breast cancer:

1. Chemicals used in industrial processes or found in the environment, consumer products, or workplaces must be tested for their possible impact on breast cancer risk. Testing should identify alterations in biological processes relevant to breast cancer, including:

- Cell cycle changes,
- Genotoxicity,
- Endocrine disruption (estrogenicity and other hormonal effects), and
- Mechanisms associated with altered mammary gland development or maturation.

2. To accurately evaluate the potential of a chemical to raise the risk of breast cancer, toxicity tests must be designed and conducted with the understanding that effects vary depending on *timing of exposure* and *underlying susceptibility factors.* To account for this, toxicity tests need to:

- Assess the impact of chemical exposure during a variety of life stages, including gestation, puberty, pregnancy, and post-menopause; and
- Account for increased susceptibility due to genetic variation, underlying disease, or exposure to other chemicals and environmental stressors.

[†] A National Academy of Sciences committee (NAS/NRC 2007) defined high-throughput testing as "efficiently designed experiments that can be automated and rapidly performed to measure the effect of substances on a biologic process of interest. These assays can evaluate hundreds to many thousands of chemicals over a wide concentration range to identify chemical actions on gene, pathway, and cell function."

3. New research is needed to improve the scientific tools available to identify chemicals that contribute to breast cancer risk. This includes:

- Further investigation of the biological processes that, when altered, increase the risk of breast cancer;
- Development and validation of new toxicity testing methods, including high-throughput screening, to detect chemicals that alter relevant biological processes;
- Adaptation of current toxicity testing methods to more specifically address mechanisms relevant to breast cancer; and
- Interdisciplinary efforts to link current knowledge of breast cancer etiology with the design and implementation of chemical toxicity tests.

4. A similar process as that used by the Panel should be used to develop testing methods specific to other diseases. In practice, a comprehensive approach to identifying chemicals that may pose a human health hazard is necessary to generate information for regulatory agencies as well as chemical producers and end users.

Conclusions

Chemical toxicity testing—and the public policies that require it—can be critical tools in breast cancer prevention, providing a practical basis for reducing potentially harmful exposures.[8] [9] The Hazard Identification Approach developed by the Panel can guide the development of toxicity testing specific to breast cancer. Information generated by implementing the Hazard Identification Approach could a) increase the relevance of chemical assessments for public health; b) provide a scientific basis for identifying and prioritizing chemicals that may increase breast cancer risk; and c) generate data to support use of less toxic alternatives.

More comprehensive and efficient detection of chemicals linked to breast cancer will require both ongoing research into the biological basis of breast cancer and development of new toxicity testing methods, particularly the development of *in vitro* chemical screening techniques and high-throughput methods.

Meanwhile, it is essential that practical approaches to identifying potential breast carcinogens are implemented now, to begin addressing the backlog of untested chemicals and inform the development of new chemicals policies. These approaches should include use of currently available methods (e.g. tests for estrogen-like effects or genotoxicity), as well as the adaptation of existing tests to include endpoints relevant to breast cancer. For example, the OECD extended-one generation assay currently used in international toxicity testing guidelines could easily be modified to include an evaluation of changes to mammary gland development after chemical exposure. [10]

Chemical toxicity testing—and the public policies that require it—can be critical tools in breast cancer prevention, providing a practical basis for reducing potentially harmful exposures

When fully developed, the Hazard Identification Approach recommended by the Panel has the potential to generate toxicity information useful to consumers, workers, product manufacturers, chemical producers, and policy makers. Applied to large numbers of chemicals, this could greatly improve our ability to focus the lengthiest and most expensive tests on chemicals with the highest potential for increasing the risk of breast cancer or other diseases. Ultimately, this should lead to the ability to identify and use the least toxic chemical alternatives.

BCCP Participants

Project Leaders:

Sarah Janssen, MD, PhD, MPH (Co-Director)
Senior Scientist, Natural Resources Defense Council
Assistant Clinical Professor
Occupational & Environmental Medicine
UC San Francisco, CA

Megan Schwarzman, MD, MPH (PI and Co-Director)
Center for Occupational and Environmental Health,
UC Berkeley; and Clinical Instructor, Family and
Community Medicine
UC San Francisco, CA

Panel Members:

Susan Braun, MA
Executive Director, Commonweal
Bolinas, CA

Vincent James Cogliano, PhD
Head, IARC Monographs Programme
International Agency for Research on Cancer
World Health Organization
Lyon, France

***Shanaz Dairkee, PhD**
California Pacific Medical Center Research Institute
San Francisco, CA

Suzanne Fenton, PhD
Reproductive Endocrinologist
Cellular and Molecular Pathology Branch
National Toxicology Program, NIEHS
Durham, NC

William H. Goodson, III, MD
Senior Clinical Research Scientist
California Pacific Medical Center Research Institute
San Francisco, CA

***Joe Guth, PhD, JD**
Legal Director
Science and Environmental Health Network
Albany, CA

Dale Johnson, PharmD, PhD
Adjunct Professor, Nutritional Science & Toxicology
College of Natural Resources
UC Berkeley, CA
President & CEO, Emiliem

** Member of the Core Advisory Panel Group*

Jean Latimer, PhD
UPCI Hillman Cancer Center
School of Medicine
University of Pittsburgh, PA

Ron Melnick, PhD
Retired Associate
Environmental Toxicology Program
National Institute of Environmental Health Sciences
Research Triangle Park, NC

Rachel Morello-Frosch, PhD, MPH
Associate Professor
Environmental Science, Policy and Management
Division of Society and Environment
College of Natural Resources
UC Berkeley, CA

Ruthann A. Rudel, MS
Director of Research
Senior Scientist, Toxicology and Risk Assessment
Silent Spring Institute
Newton, MA

***Gina Solomon, MD, MPH**
Senior Scientist, Natural Resources Defense Council
Associate Clinical Professor
Occupational and Environmental Medicine and
Internal Medicine
UC San Francisco, CA

Carlos Sonnenschein, MD
Professor
Department of Anatomy and Cellular Biology
Tufts University School of Medicine
Boston, MA

***Lauren Zeise, PhD**
Chief, Reproductive and Cancer Hazard Assessment
Office of Environmental Health Hazard Assessment
California EPA, Oakland, CA

Funding Agency:
California Breast Cancer Research Program
UC Office of the President, Oakland, CA

Marion H.E. Kavanaugh-Lynch, MD, MPH, Director
Catherine Thomsen, MPH, Project Lead, Special
Research Initiatives

Administrative Staff: Suzanne Llewellyn, MEd

References

[1] California Breast Cancer Research Program, Special Research Initiatives. http://www.cbcrp.org/sri/

[2] Breast Cancer and Chemicals Policy project website: http://coeh.berkeley.edu/greenchemistry/cbcrp.htm

[3] National Academy of Sciences/National Research Council "Toxicity Testing in the 21st Century: A Vision and Strategy." NAS/NRC Committee on Toxicity Testing and Assessment of Environmental Agents. National Academies Press, Washington D.C. 2007.

[4] Collins F, Gray G, Bucher J. "Toxicology. Transforming environmental health protection." Science. 2008. 319(5865):906-907.

[5] U.S. Environmental Protection Agency, National Center for Computational Toxicology, ToxCast http://www.epa.gov/ncct/toxcast/ , accessed June, 2010. And Judson RS. et al. "In vitro screening of environmental chemicals for targeted testing prioritization: the ToxCast project." Environ Health Perspect. 2010. 118(4):485-92.

[6] U.S. Environmental Protection Agency U. S EPA, (2003) A Framework for Computational Toxicology Research Program in ORD. Draft Report EPA/600/R-03/065. Office of Research and Development, U.S. EPA. July 2003.

[7] National Toxicology Program's High Throughput Screening (HTS) Initiative. Available: http://ntp.niehs.nih.gov/?objectid=05F80E15-F1F6-975E-77DDEDBDF3B941CD, accessed June 2010.

[8] Rudel RA, Attfield KR, Schifano JN, Brody JG. "Chemicals causing mammary gland tumors in animals signal new directions for epidemiology, chemicals testing, and risk assessment for breast cancer prevention." Cancer 2007. 109(12):2635-66.

[9] President's Cancer Panel 2008-2009 Annual Report. "Reducing Environmental Cancer Risk: What We Can Do Now." Published April 2010, Available at: http://deainfo.nci.nih.gov/advisory/pcp/pcp.htm

[10] Spielmann H. and Vogel R. "The extended 1-generation study (OECD 415), as a replacement of the mammalian 2-generation study (OECD 416)."Alternatives to Animal Testing and Experimentation (AATEX). 2007. 14(Special Issue): 795-798. Available: http://altweb.jhsph.edu/wc6/paper795.pdf