Pathways to Breast Cancer

A Case Study for Innovation in Chemical Safety Evaluation

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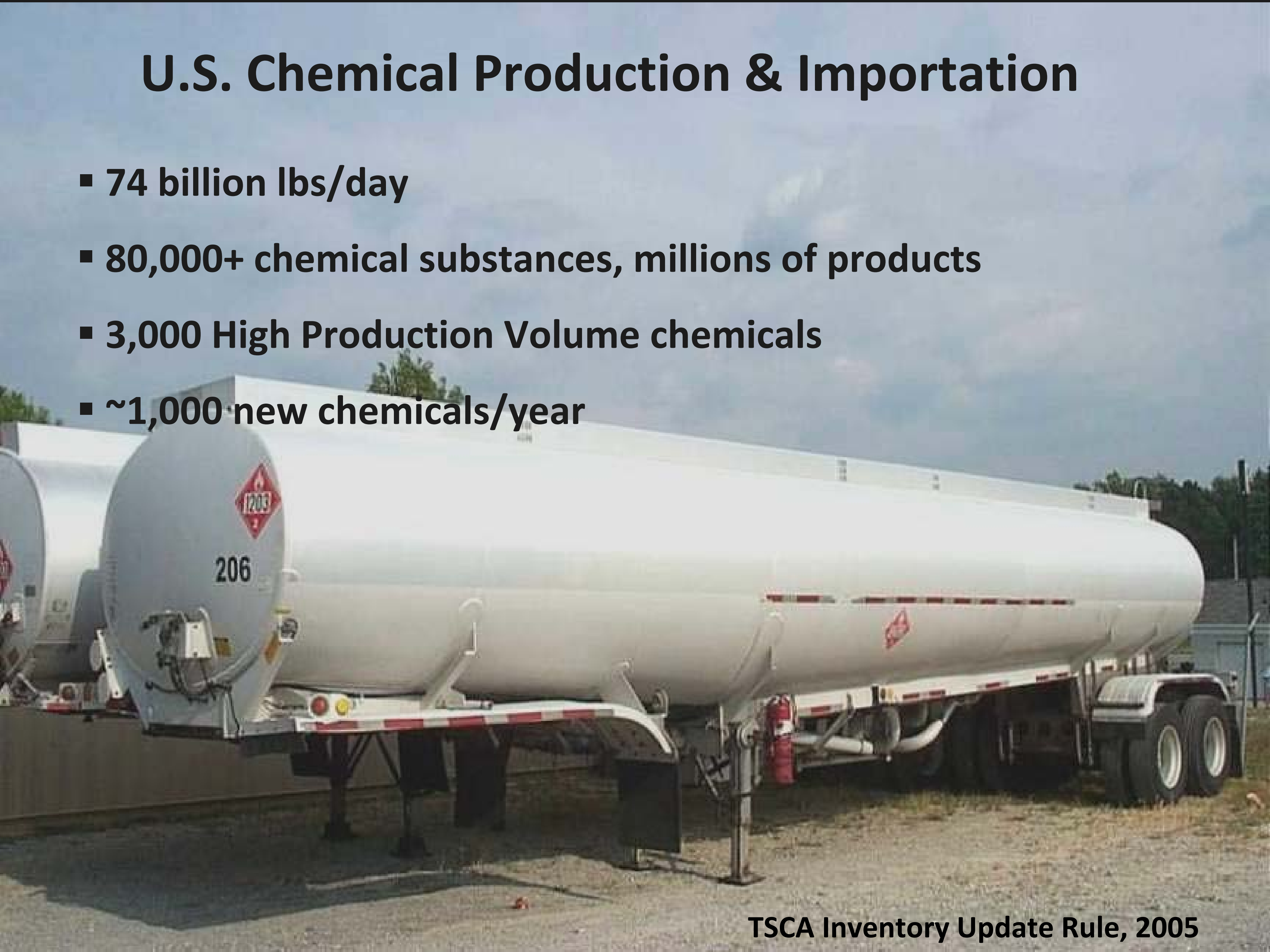
U.S. Chemical Production & Importation

- 74 billion lbs/day
- 80,000+ chemical substances, millions of products
- 3,000 High Production Volume chemicals
- ~1,000 new chemicals/year



TSCA Inventory Update Rule, 2005

Biomonitoring of Chemicals

CDC measured 212 substances in the 2003-04 NHANES cohort

Acrylamide
Acrylamide hemoglobin adducts *
Glycidamide hemoglobin adducts *

Cotinine

N,N-Diethyl-meta-toluamide (DEET)

Environmental Phenols
Benzophenone-3 (2-Hydroxy-4-methoxybenzophenone) *
Bisphenol A (2,2-bis [4-Hydroxyphenyl] propane) *
4-tert-Octylphenol (4-[1,1,3,3-Tetramethylbutyl] phenol) *
Triclosan (2,4,4'-Trichloro-2'-hydroxyphenyl ether) *

Perchlorate *

Pesticides

Fungicides
Pentachlorophenol
ortho-Phenylphenol

Herbicides
Acetochlor mercapturate
Alachlor mercapturate
Atrazine mercapturate
2,4-Dichlorophenoxyacetic acid
Metolachlor mercapturate
2,4,5-Trichlorophenoxyacetic acid

Carbamate Insecticides
Carbofuranphenol
2-Isopropoxyphenol

Organochlorine Pesticides
Aldrin
Dieldrin
Endrin
o,p'-Dichlorodiphenyltrichloroethane
p,p'-Dichlorodiphenyldichloroethene (DDE)
p,p'-Dichlorodiphenyltrichloroethane (DDT)
Heptachlor epoxide
Hexachlorobenzene
beta-Hexachlorocyclohexane
gamma-Hexachlorocyclohexane (Lindane)
Mirex
trans-Nonachlor
Oxychlordane
2,4,5-Trichlorophenol
2,4,6-Trichlorophenol

Organophosphorus Insecticides: Dialkyl Phosphate Metabolites
Diethyldithiophosphate (DEDTP)
Diethylphosphate (DEP)
Diethylthiophosphate (DETP)
Dimethyldithiophosphate (DMDTP)
Dimethylphosphate (DMP)
Dimethylthiophosphate (DMTP)

Organophosphorous Insecticides: Specific Metabolites
3-Chloro-7-hydroxy-4-methyl-2H-chromen-2-one/ol
2-(Diethylamino)-6-methylpyrimidin-4-ol/one
2-Isopropyl-4-methyl-6-hydroxypyrimidine
Malathion dicarboxylic acid
para-Nitrophenol
3,5,6-Trichloro-2-pyridinol

Pyrethroid Pesticides
cis-3-(2,2-Dibromovinyl)-2,2-dimethylcyclopropane carboxylic acid
cis-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
trans-3-(2,2-Dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid
4-Fluoro-3-phenoxybenzoic acid
3-Phenoxybenzoic acid

Metals
Antimony
Arsenic, Total *
Arsenic (V) acid *
Arsenobetaine *
Arsenocholine *
Arsenous (III) acid *
Dimethylarsinic acid *
Monomethylarsonic acid *
Trimethylarsine oxide *
Barium
Beryllium
Cadmium
Cesium
Cobalt
Lead
Mercury
Molybdenum
Platinum
Thallium
Tungsten
Uranium

Perfluorochemicals
Perfluorobutane sulfonic acid (PFBuS) *
Perfluorodecanoic acid (PFDeA) *
Perfluorododecanoic acid (PFDoA) *
Perfluoroheptanoic acid (PFHpA) *
Perfluorohexane sulfonic acid (PFHxS) *
Perfluorononanoic acid (PFNA) *
Perfluorooctane sulfonamide (PFOSA) *
Perfluorooctane sulfonic acid (PFOS) *
2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid (Et-PFO
2-(N-Methyl-perfluorooctane sulfonamido) acetic acid (Me-PI
Perfluorooctanoic acid (PFOA) *
Perfluoroundecanoic acid (PFUA) *

Phthalates
Mono-benzyl phthalate (MBzP)
Mono-n-butyl phthalate (MnBP)
Mono-(3-carboxypropyl) phthalate (MCPP)
Mono-cyclohexyl phthalate (MCHP)
Mono-ethyl phthalate (MEP)
Mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) *
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)
Mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)
Mono-2-ethylhexyl phthalate (MEHP)
Mono-isobutyl phthalate (MiBP)
Mono-isononyl phthalate (MiNP)
Mono-methyl phthalate (MMP)
Mono-n-octyl phthalate (MOP)

Phytoestrogens
Daidzein
Enterodiol
Enterolactone
Equol
Genistein
O-Desmethylangolensin

Brominated Fire Retardants
2,2',4-Tribromodiphenyl ether (BDE 17) *
2,4,4'-Tribromodiphenyl ether (BDE 28) *
2,2',4,4'-Tetrabromodiphenyl ether (BDE 47) *
2,3',4,4'-Tetrabromodiphenyl ether (BDE 66) *
2,2',3,4,4'-Pentabromodiphenyl ether (BDE 85) *
2,2',4,4',5-Pentabromodiphenyl ether (BDE 99) *
2,2',4,4',6-Pentabromodiphenyl ether (BDE 100) *
2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE 153) *
2,2',4,4',5,6'-Hexabromodiphenyl ether (BDE 154) *
2,2',3,4,4',5',6-Heptabromodiphenyl ether (BDE 183) *
2,2',4,4',5,5'-Hexabromobiphenyl (BB 153) *

Non-Dioxin-Like Polychlorinated Biphenyls
2,4,4'-Trichlorobiphenyl (PCB 28)
2,2',3,5'-Tetrachlorobiphenyl (PCB 44) *
2,2',4,5'-Tetrachlorobiphenyl (PCB 49) *
2,2',5,5'-Tetrachlorobiphenyl (PCB 52)
2,3',4,4'-Tetrachlorobiphenyl (PCB 66)
2,4,4',5-Tetrachlorobiphenyl (PCB 74)
2,2',3,4,5'-Pentachlorobiphenyl (PCB 87)
2,2',4,4',5-Pentachlorobiphenyl (PCB 99)
2,2',4,5,5'-Pentachlorobiphenyl (PCB 101)
2,3,3',4',6-Pentachlorobiphenyl (PCB 110)
2,2',3,3',4,4'-Hexachlorobiphenyl (PCB 128)
2,2',3,4,4',5' and 2,3,3',4,4',6-Hexachlorobiphenyl (PCB 138 & 158)
2,2',3,4',5,5'-Hexachlorobiphenyl (PCB 146)
2,2',3,4',5',6-Hexachlorobiphenyl (PCB 149)
2,2',3,5,5',6-Hexachlorobiphenyl (PCB 151)
2,2',4,4',5,5',-Hexachlorobiphenyl (PCB 153)
2,2',3,3',4,4',5-Heptachlorobiphenyl (PCB 170)
2,2',3,3',4,5,5'-Heptachlorobiphenyl (PCB 172)
2,2',3,3',4,5',6'-Heptachlorobiphenyl (PCB 177)
2,2',3,3',5,5',6-Heptachlorobiphenyl (PCB 178)
2,2',3,4,4',5,5'-Heptachlorobiphenyl (PCB 180)
2,2',3,4,4',5',6-Heptachlorobiphenyl (PCB 183)
2,2',3,4',5,5',6-Heptachlorobiphenyl (PCB 187)
2,2',3,3',4,4',5,5'-Octachlorobiphenyl (PCB 194)
2,2',3,3',4,4',5,6-Octachlorobiphenyl (PCB 195)
2,2',3,3',4,4',5,6' and 2,2',3,4,4',5,5',6-Octachlorobiphenyl (PCB 196 & 203)
2,2',3,3',4,5,5',6-Octachlorobiphenyl (PCB 199)
2,2',3,3',4,4',5,5',6-Nonachlorobiphenyl (PCB 206)
2,2',3,3',4,4',5,5',6,6'-Decachlorobiphenyl (PCB 209) *

Dioxin-Like Chemicals

Polychlorinated Dibenzo-p-dioxins
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin (HpCDD)
1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin (HxCDD)
1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin (HxCDD)
1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin (HxCDD)
1,2,3,4,6,7,8,9-Octachlorodibenzo-p-dioxin (OCDD)
1,2,3,7,8-Pentachlorodibenzo-p-dioxin (PeCDD)
2,3,7,8,-Tetrachlorodibenzo-p-dioxin (TCDD)

Polychlorinated Dibenzofurans
1,2,3,4,6,7,8-Heptachlorodibenzofuran (HpCDF)
1,2,3,4,7,8,9-Heptachlorodibenzofuran (HpCDF)
1,2,3,4,7,8-Hexachlorodibenzofuran (HxCDF)
1,2,3,6,7,8-Hexachlorodibenzofuran (HxCDF)
1,2,3,7,8,9-Hexachlorodibenzofuran (HxCDF)
2,3,4,6,7,8-Hexachlorodibenzofuran (HxCDF)
1,2,3,4,6,7,8,9-Octachlorodibenzofuran (OCDF)
1,2,3,7,8-Pentachlorodibenzofuran (PeCDF)
2,3,4,7,8-Pentachlorodibenzofuran (PeCDF)
2,3,7,8-Tetrachlorodibenzofuran (TCDF)

Coplanar Polychlorinated Biphenyls
3,4,4',5-Tetrachlorobiphenyl (PCB 81)
3,3',4,4',5-Pentachlorobiphenyl (PCB 126)
3,3',4,4',5,5'-Hexachlorobiphenyl (PCB 169)

Mono-ortho-substituted Polychlorinated Biphenyls
2,3,3',4,4'-Pentachlorobiphenyl (PCB 105)
2,3',4,4',5-Pentachlorobiphenyl (PCB 118)
2,3,3',4,4',5-Hexachlorobiphenyl (PCB 156)
2,3,3',4,4',5'-Hexachlorobiphenyl (PCB 157)
2,3',4,4',5,5'-Hexachlorobiphenyl (PCB 167)
2,3,3',4,4',5,5'-Heptachlorobiphenyl (PCB 189)

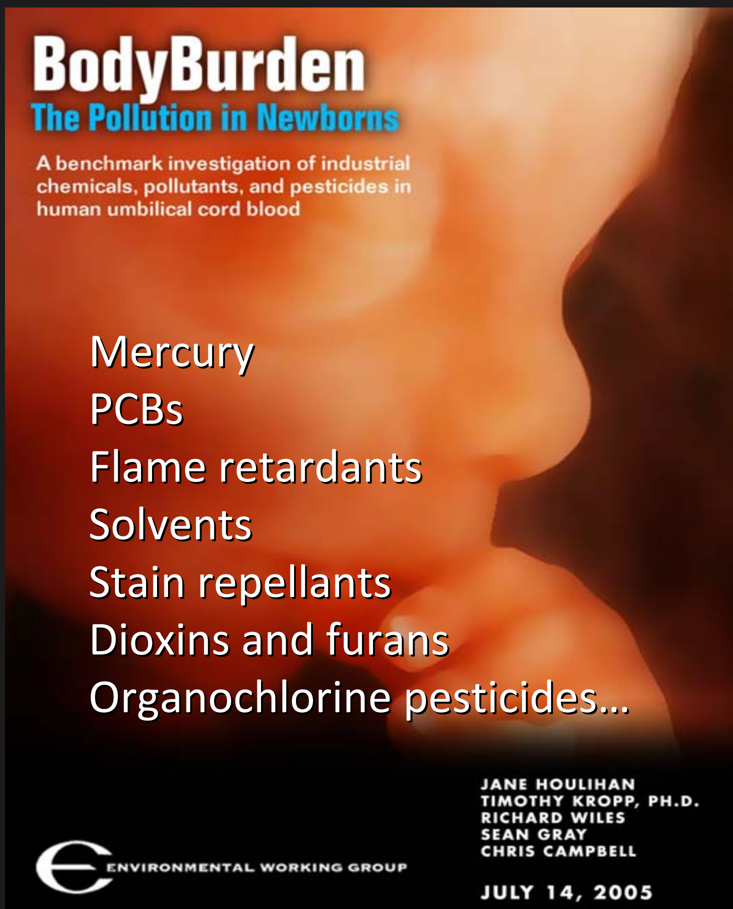
Polycyclic Aromatic Hydrocarbons (PAHs)
2-Hydroxyfluorene
3-Hydroxyfluorene
9-Hydroxyfluorene
1-Hydroxynaphthalene (1-Naphthol)
2-Hydroxynaphthalene (2-Naphthol)
1-Hydroxyphenanthrene
2-Hydroxyphenanthrene
3-Hydroxyphenanthrene
4-Hydroxyphenanthrene
1-Hydroxypyrene

Disinfection By-Products (Trihalomethanes)
Bromodichloromethane *
Dibromochloromethane (Chlorodibromomethane) *
Tribromomethane (Bromoform) *
Trichloromethane (Chloroform) *

Volatile Organic Compounds (VOCs)
Benzene *
Chlorobenzene (Monochlorobenzene) *
1,2-Dibromo-3-chloropropane (DBCP) *
Dibromomethane *
1,2-Dichlorobenzene (ortho-Dichlorobenzene) *
1,3-Dichlorobenzene (meta-Dichlorobenzene) *
1,4-Dichlorobenzene (para-Dichlorobenzene) *
1,1-Dichloroethane *
1,2-Dichloroethane (Ethylene dichloride) *
1,1-Dichloroethene (Vinylidene chloride) *
cis-1,2-Dichloroethene *
trans-1,2-Dichloroethene *
Dichloromethane (Methylene chloride) *
1,2-Dichloropropane *
2,5-Dimethylfuran (DMF) *
Ethylbenzene *
Hexachloroethane *
Methyl tert-butyl ether (MTBE) *
Nitrobenze *
Styrene *
1,1,2,2-Tetrachloroethane *
Tetrachloroethene (Perchloroethylene) *
Tetrachloromethane (Carbon tetrachloride) *
Toluene *
1,1,1-Trichloroethane (Methyl chloroform) *
1,1,2-Trichloroethane *
Trichloroethene (Trichloroethylene, TCE) *
meta- and para-Xylene *
ortho-Xylene *

CDC, Fourth National Report on Human Exposure to Environmental Chemicals, 2009

Biomonitoring of Chemicals & Pollutants:
Umbilical Cord Blood and Breast Milk



Mercury
PCBs
Flame retardants
Solvents
Stain repellants
Dioxins and furans
Organochlorine pesticides…

PBDE Levels in Breast Milk, Sweden

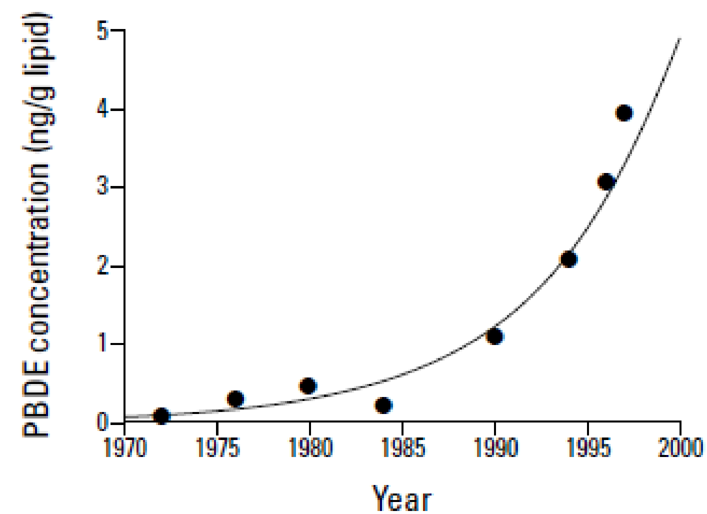


Figure 5. Time trend of the sum concentrations of 8 PBDE congeners in pooled mother's milk samples from Swedish mothers living in the Stockholm region. Data from Norén and Meironyté (*51*).

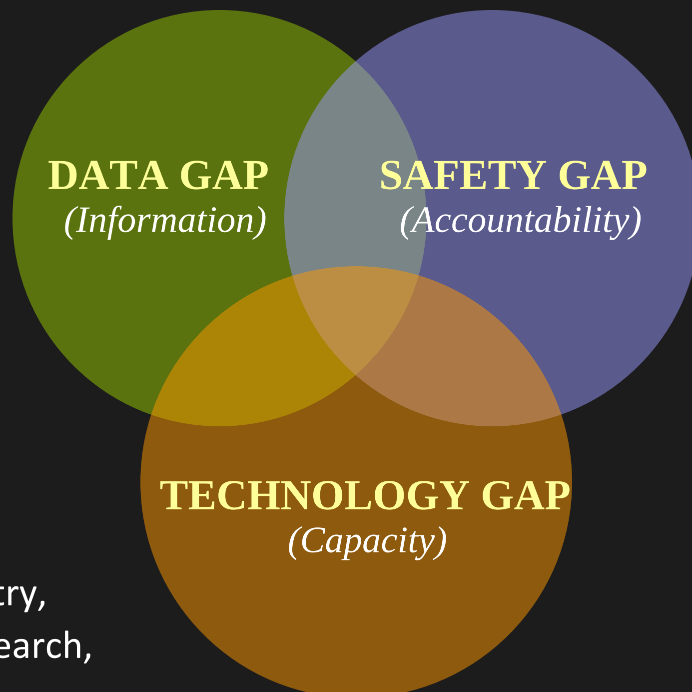
Darnerud et al. *Environ Health Persp,* 107 (supp1), March, 2001.

The Toxic Substances Control Act (TSCA)

A Legacy of Three Policy Gaps

62,000 chemicals grandfathered;
90 day review for new chemicals;
Health data absent in 85% of new chemical notices

5 chemicals/classes formally regulated under TSCA since 1976



Minimal investment by industry, government, academia in research, development, and education.

Wilson and Schwarzman, *Environmental Health Perspectives*, 117:8, August, 2009.

Context: New Chemicals Policy in the U.S.

Federal Toxic Substances Control Act reform

- House and Senate versions, 2010
- Will require chemical testing

California EPA Green Chemistry Initiative

- Ingredient Disclosure (SB 928 pending)
- Create an Online Toxics Clearinghouse (SB 509)
- Accelerate the Quest for Safer Products (AB 1879)

Other U.S. State Policies

- Regulation of specific product categories
- Identify and prioritize chemicals of concern
- Eliminate categories of hazards (e.g., known carcinogens)

European Union Affecting Global Change

Cosmetics Directive (2004)

WEEE: Waste in Electrical and Electronic Equipment (2005)

RoHS: Restriction on Hazardous Substances (2006)

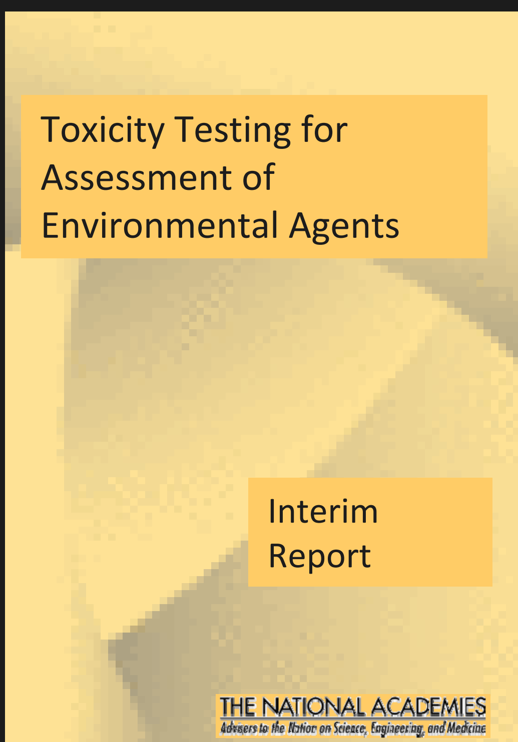
REACH: Registration, Evaluation, Authorization, and Restriction of Chemicals (2007)

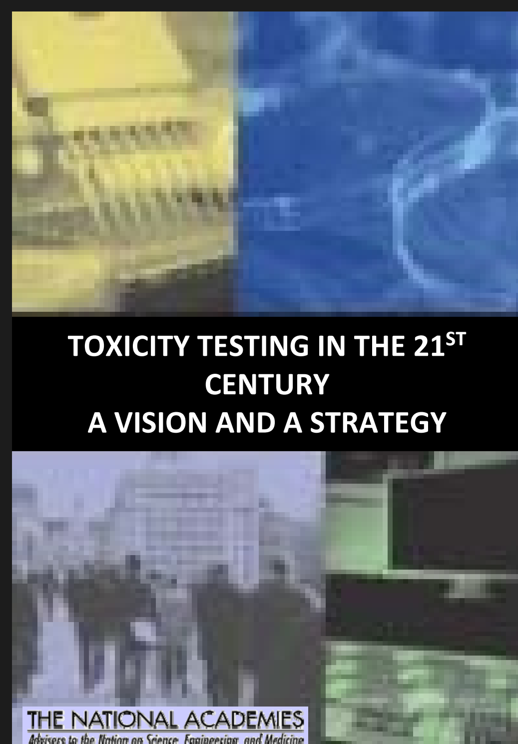
Context: Information Needs

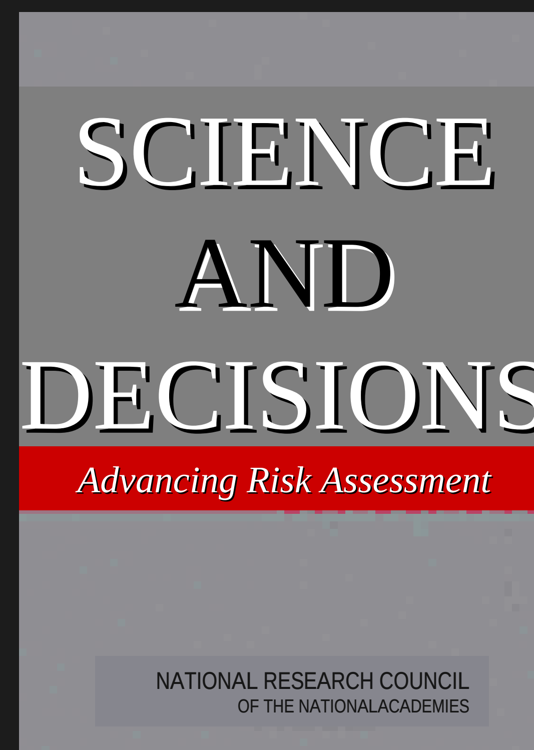
Methods for using existing data and current test methods in chemical decision-making.

New tools for:

- Understanding biological pathways
- Toxicity testing methods
- Application of science in decisions





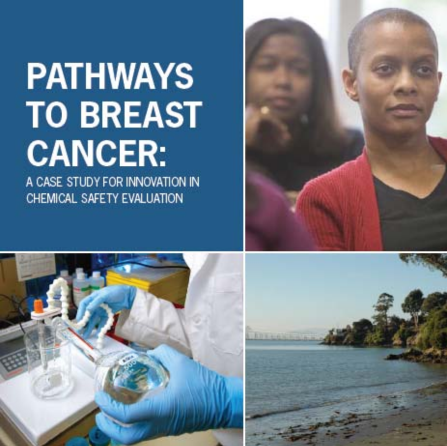


Chemical Testing Capacity

1-3/yr | 10's/yr | 100's/yr | 10,000's/day | 100,000's/day

High Throughput &
Molecular mechanisms

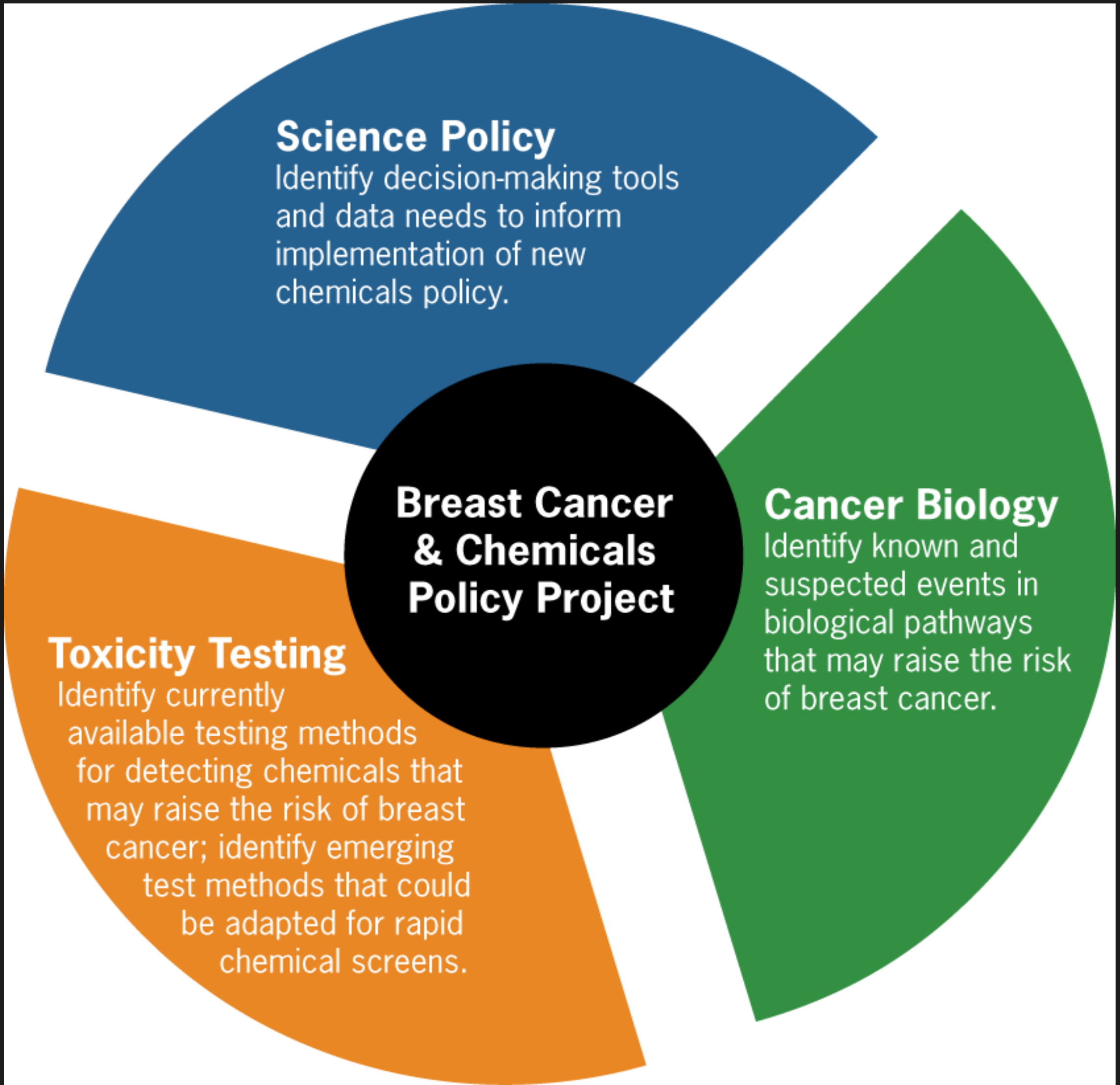
Source: National Research Council, *Toxicity Testing in the 21st Century*, 2007



Why Focus on Breast Cancer?

- Most common invasive cancer and a leading cause of cancer death in women.
- Affects one in eight U.S. women
- Most breast cancer is not caused by inherited genes
- Increasing recognition that environmental exposures contribute to the development of disease
- Over 200 chemicals have been associated with mammary cancer in laboratory animals.
- Most standard toxicity testing methods do not regularly evaluate potential chemical effects on the breast

Breast Cancer & Chemicals Policy Project Structure



Breast Cancer & Chemicals Policy Project

Core Question

As new chemicals policies develop toxicity testing requirements, what body of toxicity data– obtained using *existing methods*– could best identify chemicals that may increase the risk of breast cancer?

Expert Panel

- **Susan Braun, MA** Commonweal
- **Vincent James Cogliano, PhD** WHO International Agency for Research on Cancer
- **Shanaz Dairkee *, PhD** California Pacific Medical Center Research Institute
- **Suzanne Fenton, PhD** National Institute of Environmental Health Sciences
- **William H. Goodson III, MD** California Pacific Medical Center Research Institute
- **Joe Guth *, PhD, JD** Science and Environmental Health Network
- **Dale Johnson, PharmD, PhD** University California Berkeley & Emiliem
- **Jean Latimer, PhD** School of Medicine University of Pittsburgh
- **Ron Melnick, PhD** National Institute of Environmental Health Sciences
- **Rachel Morello-Frosch, PhD, MPH** University of California Berkeley
- **Ruthann A. Rudel, MS** Silent Spring Institute
- **Gina Solomon*, MD, MPH** University of California San Francisco & Natural Resources Defense Council
- **Carlos Sonnenschein, MD** Tufts University School of Medicine
- **Lauren Zeise*, PhD** Cal/EPA Office of Environmental Health Hazard Assessment

Breast Cancer & Chemicals Policy Project Goals

1. **Develop an approach for identifying chemicals** that may contribute to the development or progression of breast cancer;
2. **Identify research needs** and recommend improvements to existing test methods; and
3. **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.

Steps of the Breast Cancer and Chemicals Policy Project

An interdisciplinary panel with expertise in breast cancer biology, toxicology, epidemiology, risk assessment, chemicals policy, community advocacy met to:

Identify toxicity "endpoints": alterations to biological processes resulting in an increased risk of breast cancer.

Identify toxicity testing methods capable of screening chemicals for their impact on biological processes relevant to breast cancer.

Propose a "Hazard Identification Approach," consisting of prioritization and testing for altered mammary gland development, endocrine disruption, and carcinogenesis in general.

Conduct a "virtual" pilot test to validate the proposed Hazard Identification Approach by investigating how several well-studied chemicals would "perform" if tested.

Step 1. Identify Events in Biological Processes Associated with Breast Cancer

Premises:

In identifying chemicals likely to increase the risk of breast cancer, we should investigate chemicals that:

- Are associated with general carcinogenic mechanisms
- Increase estrogenic or other proliferative effects on breast tissue by any mechanism (e.g. altered hormone metabolism, early puberty)
- Interfere with development of the mammary gland

The impact of such substances is determined by two kinds of vulnerabilities:

- Population susceptibility factors (e.g. genetic polymorphisms, obesity, other exposures, occupation)
- Timing of exposure (developmental stage)

Step 1. Events in Biological Processes Associated with Breast Cancer

Cellular & Molecular Events

- Alterations in hormone levels, metabolism or receptors
- Changes in gene transcription & translation
- Cell cycle changes
- Peptide hormones (growth hormones)
- Genotoxicity
- Oxidative stress
- Immune modulation
- Limitless replication potential
- Evasion of apoptosis
- Self-sufficiency in growth

Tissue Changes

- Breast density
- Tissue invasion
- Sustained angiogenesis
- TEB proliferation
- Altered mammary gland development
- Ductal hyperplasia
- Atypical hyperplasia

Susceptibility Factors

- Obesity
- Early onset of breast development
- Alterations in cyclicity
- Genetic polymorphisms in metabolizing enzymes
- Duration of lifetime estrogen exposure

Step 2: Identify test methods (Sample 1)

	Detectable Events Affecting Breast Cancer Risk					
	Molecular Mechanisms			**Phenotypic Indicators**		
Model System	Gene Expression	Genotoxicity	Steroid Hormones	Pathological Markers	TEB Proliferation	Carcinoma
In Silico						
In Vitro						
In Vivo						
Epidemiological						

http://coeh.berkeley.edu/greenchemistry/cbcrpdocs/matrix.pdf

Step 2: Identify Test Methods (Sample 2)

	Detectable Events Affecting Breast Cancer Risk					
	Susceptibility Factors			Biological Programs		
Model System	Altered Cyclicity	Metabolic Factors	Estrogen Exposure	Immune Modulation	Oxidative Stress	Apoptosis Evasion
In Silico						
In Vitro						
In Vivo						
Epidemiological						etc...

http://coeh.berkeley.edu/greenchemistry/cbcrpdocs/matrix.pdf

Step 3. Hazard Identification Approach:
Chemical Prioritization

Chemical Prioritization

Chemicals, their metabolites and degradation products, should be prioritized for testing based on the following parameters:

Hazard indicators

including structural similarities to other mammary gland carcinogens, or indicators that a chemical or its possible metabolite have endocrine activity, alter breast development or gene expression, or create genetic mutations.

Exposure potential

predicted by physical-chemical properties that indicate potential for bioaccumulation, persistence in the environment, or result in exposure to breast tissue. Also those identified by biomonitoring, environmental monitoring, or other proxy measures such as high production volume or dispersive use in consumer products or workplaces. Exposure potential should be assessed across the entire human life-cycle, and the product lifecycle from manufacturing through disposal.

Step 3. Hazard Identification Approach:

Rapid Screening Methods

Hazard Identification Approach

Rapid (in vitro) screening

Genotoxicity

Mutagenicity (e.g., Ames or equivalent)

Chromosome aberrations (e.g., OECD TG 473)

Micronuclei formation (e.g., OECD TG 487)

DNA strand breaks (e.g., COMET assay)

Cell cycle changes

Cell division (e.g., ^{3}H thymidine proliferation assay)

Altered apoptosis (e.g., TUNNEL assay)

Endocrine disruption

Activation or inhibition of:

Estrogen-mediated transcription (e.g., E-screen)

Androgen-mediated transcription (e.g., A-screen)

Enzymes specific to synthesis or metabolism of estrogen, androgen or progesterone (e.g., aromatase activity assay)

Step 3. Hazard Identification Approach:
in vivo studies

Hazard Identification Approach

Animal studies (in vivo): development and maturation

Genotoxicity in breast epithelial cells

Mutagenicity

Chromosome aberrations

Micronuclei formation

DNA strand breaks

Precursor changes, biomarkers and induction of mammary gland tumors

Modification of existing long-term cancer bioassays* redesigned to evaluate mammary gland endpoints, and:

include whole mounts of mammary tissue

include in utero exposures

assess effects over the whole lifespan

use an animal strain appropriate to the exposure and the endpoint

Cell cycle changes in breast epithelial cells

Cell proliferation

Decreased apoptosis

Endocrine disruption

Estrogenic activity (e.g., Uterotrophic assay)

Androgenic activity (e.g., Hershberger assay)

Developmental changes in female and male mammary gland tissue (e.g. TEB formation, ductal branching, ER and AR levels)

Reproductive changes in males and females (e.g., AGD, nipple retention, altered cyclicity, pubertal timing)

Altered circulating hormone levels (e.g. steroid or peptide hormones)

Breast Cancer & Chemicals Policy Recommendations

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

1. Chemicals should be tested now for possible impact on breast cancer risk and include the following endpoints:

   - Genotoxicity
   - Cell cycle changes
   - Endocrine disruption (e.g., estrogenicity)
   - Altered mammary gland development

Breast Cancer & Chemicals Policy Recommendations

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

2. To accurately evaluate the potential of a chemical to raise the risk of breast cancer, toxicity tests must be designed and conducted to include considerations of

   – *timing of exposure* and

   – *underlying susceptibility factors.*

Breast Cancer & Chemicals Policy Recommendations

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

3. Research needs:

- Further elucidation of biological pathways
- Adaptation of current testing methods to be more relevant to breast cancer
- Development and validation of new toxicity tests – HTS screening

Tests on the Horizon

Panel recommended an approach, not specific tests

- The field of toxicity testing is rapidly evolving
- Best practices can evolve with emerging tests

High throughput screens are under development

- Promise of testing thousands of chemicals
- Potential to address metabolic differences by testing many possible metabolites

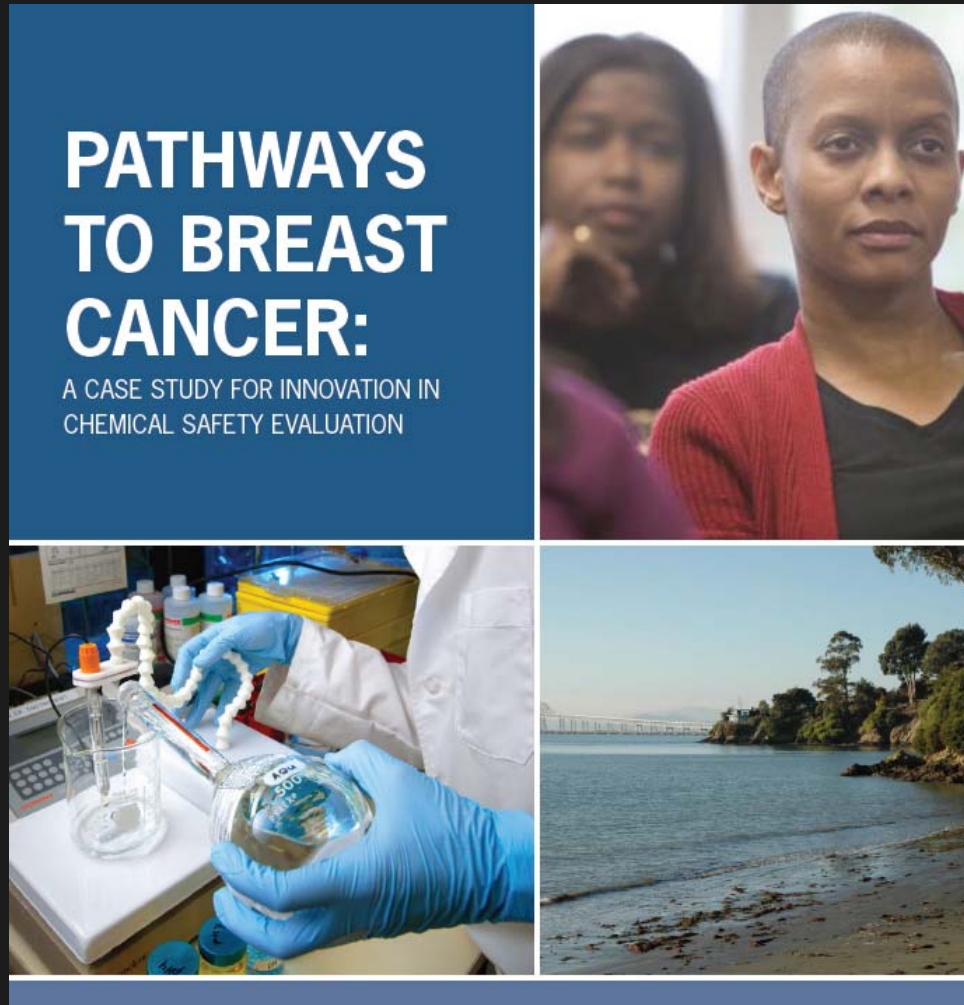
Medium throughput screens using human breast tissue

- Methods currently applied in research could be adapted for toxicity testing to replace some animal studies (e.g., for mammary gland development effects)

Breast Cancer & Chemicals Policy Recommendations

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

4. Process used by Panel could be applied to other disease endpoints to develop a comprehensive approach to identify chemicals that pose a risk to human health.



Final report: http://coeh.berkeley.edu/greenchemistry/cbcrp.htm

Next steps

- **Scientific publications**
  - “Virtual” pilot screen of chemical compounds
  - Utility of *in silico* (QSAR) methods in evaluating mammary carcinogens (SOT abstract, 2010)
  - Science policy commentary
  - Need for improved toxicity testing to encorporate mammary gland endpoints