

Information Needs in Green Chemistry & Chemicals Policy



Meg Schwarzman, MD, MPH
GETA – NorCal SETAC
November 16, 2010

Berkeley Center for Green Chemistry
Center for Occupational and Environmental Health
University of California, Berkeley



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



Federal Policy Governing Chemicals & Pollutants

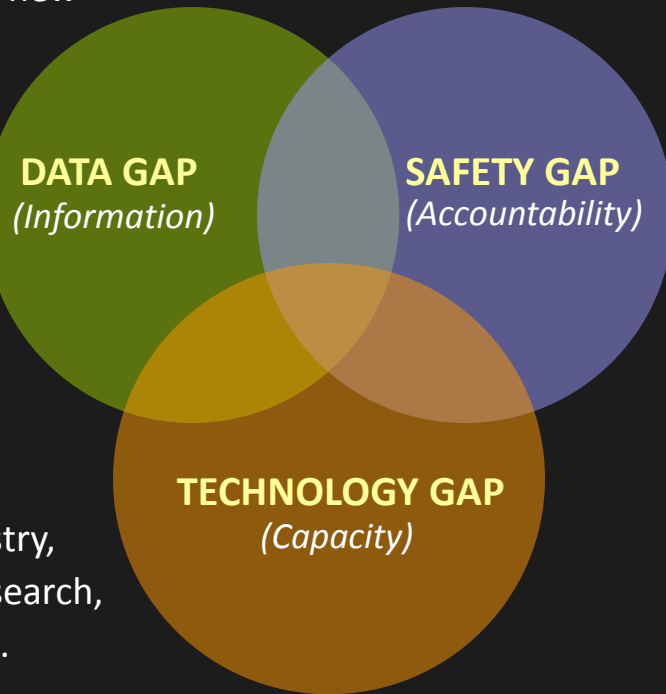
• Toxic Substances Control Act	83,000
<hr/>	
• Clean Water Act (CWA)	148
• Resource Conservation and Recovery Act	502
• Clean Air Act (CAA)	189
• Occupational Safety and Health Act	453
• Emergency Planning and Community Right-to-Know (EPCRA):	600
– Toxics Release Inventory (TRI)	
<hr/>	
Total 1,134 (with overlap)	



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



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

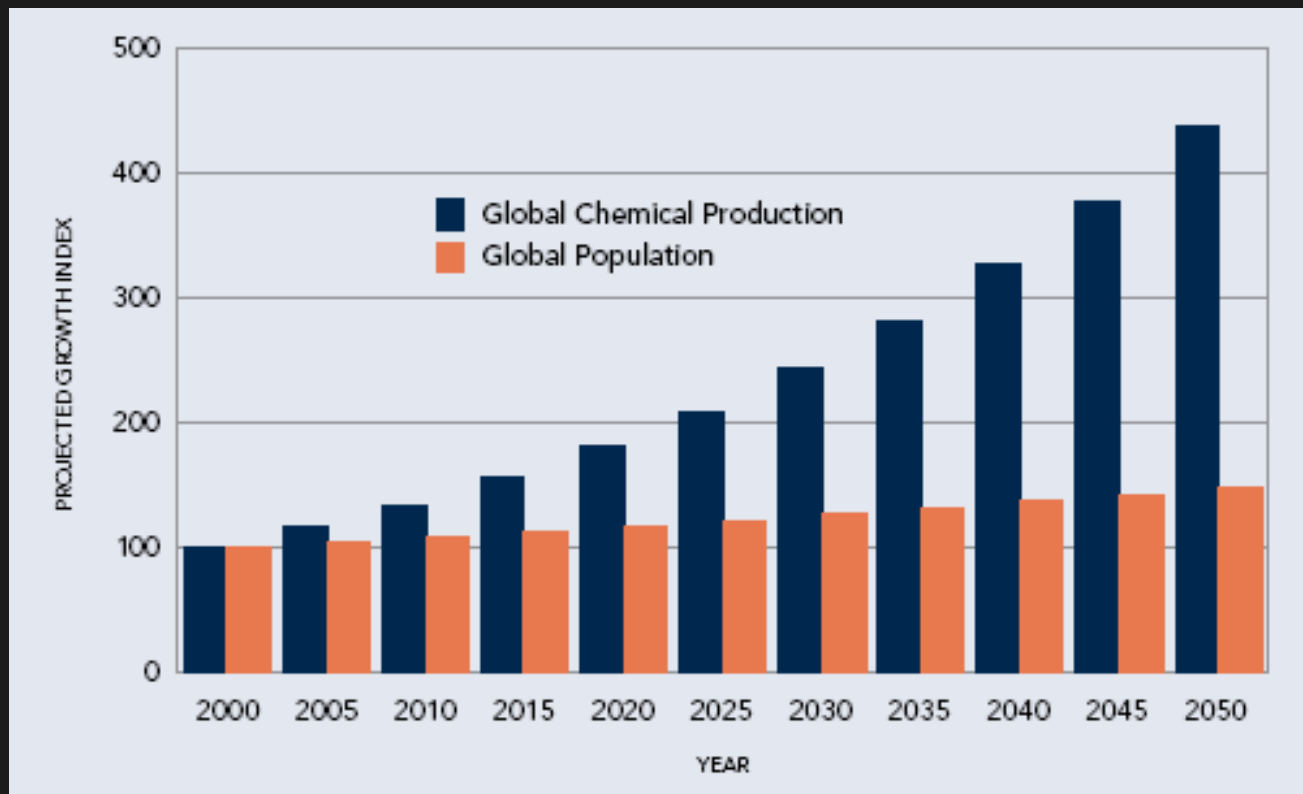
EPA must provide “substantial evidence” of
unreasonable risk to health/environment,
AND
benefits of regulation outweigh cost to
industry or lost social value of a product,
AND
EPA has chosen the least burdensome
solution.

5 chemicals/classes formally regulated
under TSCA since 1976

Global Chemical Production

Growing 3% per year

Doubling every 25 years



Hazardous waste



50% of substances at hazardous waste sites are carcinogens and/or teratogens

61 of 85 of CA largest hazardous waste sites leaking into groundwater.

94% of those pose “a major threat to human health or the environment.”

Cleaning up existing sites in California: 400 years at current rate.

600 new sites will be needed in the U.S. each month (US EPA)







426,000 cell phones retired each day in the U.S.



Photo: Kate Davison, Greenpeace



Photo: DanWatch

E-waste Recycling and Disposal: Africa and China



Biomonitoring of Chemicals

2009

Fourth National Report on Human Exposure to Environmental Chemicals

CDC measured 212 substances
in the 2003-04 NHANES cohort

Acrylamide

Acrylamide hemoglobin adducts *

Glycidamide hemoglobin adducts *

Cotinine

N,N-Diethyl-methacrylamide (DEET)

Environmental Phenols

Benzophenone-3 (2-Hydroxy-4-methoxybenzophenone) *

Bisphenol A (2,2-bis[4-Hydroxyphenyl] propane) *

4-tert-Octylphenyl [4-[1,1,3,3-Tetramethylbutyl] phenol] *

Triclosan (2,4,4'-Trichloro-2-hydroxybiphenyl ether) *

Perchlorate *

Pesticides

Pungicides

Pentachlorophenol

ortho-Pentachlorophenol

Herbicides

Azoxychlor mercaptate

Alachlor mercaptate

Azinphos mercaptate

2,4-Dichlorophenoxyacetic acid

Metolachlor mercaptate

2,4,5-Trichlorophenoxyacetic acid

Carbamate Insecticides

Carbofuranophenol

2-Isopropoxyphenol

Organochlorine Pesticides

Aldrin

Dieldrin

Endrin

o,p'-Dichlorodiphenyltrichloroethane

p,p'-Dichlorodiphenyldichloroethane (DDE)

p,p'-Dichlorodiphenyltrichloroethane (DDT)

Heptachlor epoxide

Hexachlorobenzene

beta-Hexachlorocyclohexane

gamma-Hexachlorocyclohexane (Lindane)

Mirex

trans-Nonachlor

Oxychlorane

2,4,5-Trichlorophenol

2,4,6-Trichlorophenol

Organophosphorus Insecticides: Dialkyl Phosphate Metabolites

Diethylthiophosphate (DETP)

Diethylthiophosphate (DETP)

Diethylthiophosphate (DETP)

Diethylthiophosphate (DETP)

Dimethylthiophosphate (DMOTP)

Dimethylthiophosphate (DMP)

Dimethylthiophosphate (DMTP)

Organophosphorus Insecticides: Specific Metabolites

2-Chloro-7-hydroxy-8-methyl-2H-chromen-2-one/ol

2-[(Diethylamino)-6-methylpyrimidin-4-yl]one

2-Isopropyl-4-methyl-5-hydroxypyrimidine

Metolachlor dicarboxylic acid

para-Nitrophenol

3,5,6-Trichloro-2-pyridinol

Phenol Metabolites

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

2,3,4,5-Tetrachlorophenyl 2,2-dimethylcyclopropane carboxylic acid

Metals

Antimony

Arsenic, Total *

Arsenic (V) acid *

Arsenobutane *

Arsenocholine *

Arsenous (III) acid *

Dimethylarsinic acid *

Monomethylarsinic acid *

Trimethylarsine oxide *

Barium

Beryllium

Cadmium

Cesium

Cobalt

Lead

Mercury

Molybdenum

Platinum

Thallium

Tungsten

Uranium

Perfluorinated Chemicals

Perfluorobutane sulfonic acid (PFBS) *

Perfluorodecanoic acid (PFDA) *

Perfluorododecanoic acid (PFDDA) *

Perfluorooctanoic acid (PFOS) *

Perfluorooctane sulfonic acid (PFOS) *

Perfluorononanoic acid (PFNA) *

Perfluorooctane sulfonamide (PFOSA) *

Perfluorooctane sulfonic acid (PFOS) *

2-Ethyl-perfluorooctane sulfonamide) acetic acid (Et-PFO)

2-(N-Perfluorooctane sulfonamido) acetic acid (Me-PFO)

Perfluorooctanoic acid (PFOA) *

Perfluoroundecanoic acid (PFUA) *

Phthalates

Mono-benzyl phthalate (MBzP)

Mono-n-butyl phthalate (MBzP)

Mono-2-carboxyphenyl phthalate (MCPP)

Mono-cyclohexyl phthalate (MCPP)

Mono-ethyl phthalate (MEP)

Mono-ethyl phthalate (MEP)

Mono-2-ethyl-5-carboxyphenyl phthalate (MECPP) *

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Mono-2-ethyl-5-hydroxyphenyl phthalate (MEHP)

Phthalates

Diethyl

Endrinol

Enterolactone

Equol

Gestodene

O-Desmethyldangolensin

Phthalates

2,2,4,4-Tetrabromodiphenyl ether (BDE 17) *

2,2,4,4-Tetrabromodiphenyl ether (BDE 28) *

2,2,4,4-Tetrabromodiphenyl ether (BDE 47) *

2,2,4,4-Tetrabromodiphenyl ether (BDE 66) *

2,2,3,4,4-Pentabromodiphenyl ether (BDE 85) *

2,2,4,4,5-Pentabromodiphenyl ether (BDE 99) *

2,2,4,4,5-Pentabromodiphenyl ether (BDE 100) *

2,2,4,4,5,5-Hexabromodiphenyl ether (BDE 153) *

2,2,4,4,5,5-Hexabromodiphenyl ether (BDE 154) *

2,2,3,4,4,5,5-Heptabromodiphenyl ether (BDE 183) *

2,2,4,4,5,5-Hexabromodiphenyl ether (BDE 153) *

2,2,4,4,5,5-Hexabromodiphenyl ether (BDE 153) *

2,2,4,4,5,5-Hexabromodiphenyl ether (BDE 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 103)

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)

2,3,3,5,5',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 173)

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',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

2,2',3,3',4,4',5,6,6'-Decachlorobiphenyl (PCB 209) *

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

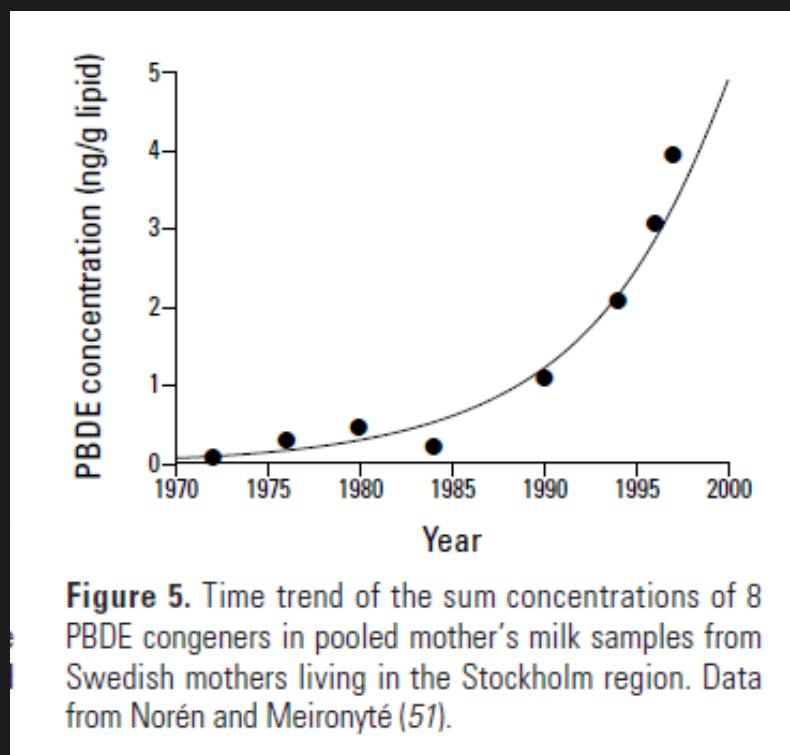
Disinfection By-Products (Trihalomethanes)

Bromodichloromethane *

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



PBDE Levels in Breast Milk, Sweden



Prevention Through Green Chemistry?



The design of chemical products and processes that are safer for health and ecosystems.

1. Make safer products
2. Use less-toxic feedstocks and processes
3. Design for cradle-to-cradle use
4. Account for energy efficiency



European Union Affecting Global Change

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

- Requires registration of all chemicals sold in EU > 1 ton/yr/producer
- Increasing data requirements based on volume in commerce
- Designates some chemicals as Substances of Very High Concern (SVHCs)
- Can require use-by use authorization for a subset of SVHCs
- Establishes “no data, no market” paradigm
- Shifts burden of proof of safety to manufacturers for chemicals of highest concern

35 Chemicals Bills in California, 2005-2006



AB 121 (Vargas)	AB 908 (Chu)	SB 419 (Simitian)
AB 263 (Chan)	AB 912 (Ridley-Thomas)	SB 432 (Simitian)
AB 289 (Chan)	AB 966 (Saldana)	SB 484 (Migden)
AB 319 (Chan)	AB 985 (Dunn)	SB 490 (Lowenthal)
AB 342 (Baca)	AB 990 (Lieber)	SB 600 (Ortiz)
AB 597 (Montanez)	AB 1125 (Pavley)	SB 838 (Escutia)
AB 623 (Aanistad)	AB 1337 (Ruskin)	SB 849 (Escutia)
AB 639 (Aghazarian)	AB 1342 (Assem ESTM)	SB 982 (Sen EQ comm)
AB 752 (Karnette)	AB 1344 (Assem ESTM)	SB 989 (Sen EQ comm.)
AB 815 (Lieber)	AB 1354 (Baca)	SB 1067 (Kehoe)
AB 816 (Lieber)	AB 1415 (Pavley)	SB 1070 (Kehoe)
AB 848 (Berg)	AB 1681 (Pavley)	

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)



New Chemicals Policy in California

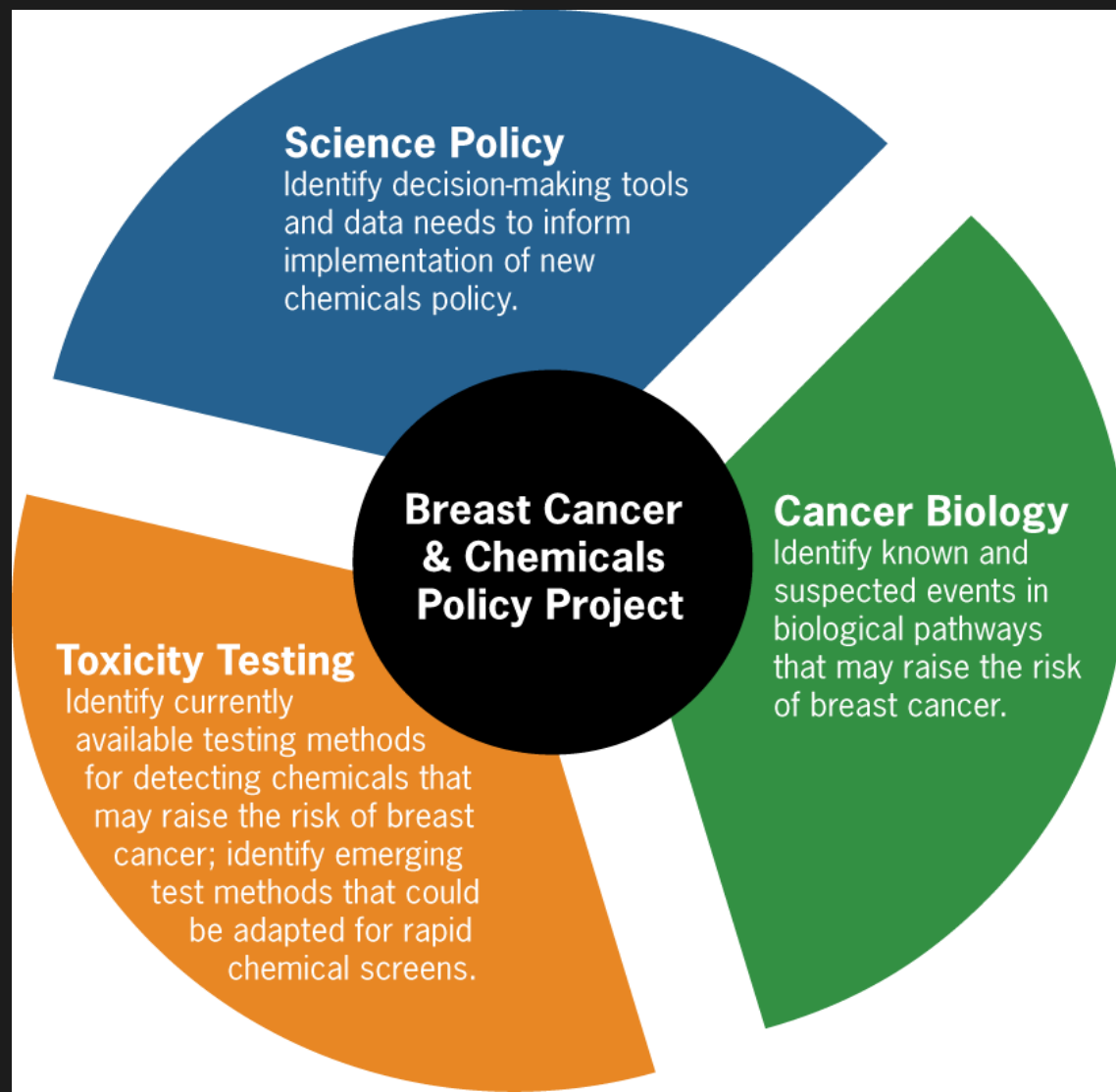
Accelerate the Quest for Safer alternatives

Systematic process for:

- Evaluating chemicals of concern in consumer products
 - Identifying safer alternatives
 - Stimulating investment in CA's product development sector
-
1. Generate list of Chemicals of Concern (CoC)
 2. Identify products containing CoCs
 3. Create a list of Priority Products based on exposure potential
 4. Perform an alternatives analysis (AA) using a lifecycle approach
 5. Complete requirements of a regulatory response



Breast Cancer & Chemicals Policy Project





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?



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.



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



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. 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)

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

<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
<i>In Silico</i>						
<i>In Vitro</i>						
<i>In Vivo</i>						
<i>Epidemiological</i>						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., ^3H 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 inform breast cancer prevention efforts by identifying chemicals that may raise the risk of breast cancer.

1. Chemical testing relevant to breast cancer should include the following endpoints:
 - *Genotoxicity*
 - *Cell cycle changes*
 - *Endocrine disruption (e.g., estrogenicity)*
 - *Altered mammary gland development*
2. Design and conduct toxicity tests to consider:
 - *Timing of exposure*
 - *Underlying susceptibility factors*



Breast Cancer & Chemicals Policy Recommendations



3. Research needs:

- Further elucidate biological pathways
- Adapt current methods to increase relevance for breast cancer
- Develop and validate new toxicity tests – HTS screening methods

4. Apply a similar process to other disease endpoints to develop a comprehensive approach to identifying chemicals of concern.



Breast Cancer & Chemicals Policy Recommendations



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 evaluate many possible metabolites

Medium throughput screens using human breast tissue

- Research methods could be adapted for toxicity testing to replace some animal studies (e.g., for mammary gland development effects)



PATHWAYS TO BREAST CANCER:

A CASE STUDY FOR INNOVATION IN
CHEMICAL SAFETY EVALUATION



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

