So Many Chemicals...So Little Time

Stem cell research and environmental health
Converging Forces

Need to increase pace of Toxicity Testing

Increasing chronic diseases

Increase in chemicals

Biomonitoring

More science about links between chemicals and adverse health outcomes
  • Developmental windows
  • Cumulative exposures
  • Effects at environmentally relevant and lower doses

Increasing public concern
Increasing Burden of chronic disease

- **Children**
  - Asthma
  - Autism/ADHD
  - Certain childhood cancers
  - Obesity

- **Adults**
  - Reproductive difficulty
    - Fecundity
    - Declining male sperm count/testosterone
  - Certain cancers
  - Obesity
• Prevalence of chronic conditions among children and youth increased from 1988 to 2006
  – Obesity, asthma, other physical conditions, and behavior/learning problems
    • 51.5% of 8- through 14-year-olds at one point in the 6-year study period reported a chronic condition compared with 27.8% in cohort 1
U.S. Chemical Production

Chemical production has increased **23.5-fold** between 1947 and 2007.

**Production (100 = 2002 production)**

- Year 1945: 10
- Year 1955: 20
- Year 1965: 30
- Year 1975: 40
- Year 1985: 50
- Year 1995: 60
- Year 2005: 120

*Federal Reserve G.17*
By 2006 …

Vast majority of chemicals in commerce have entered the marketplace without comprehensive and standardized information on their reproductive or other chronic toxicities.
March 13, 2005

WHAT’S IN YOU

Michele Hammond gives Rowan, 20 months, a bath before bedtime. The family leads a typical life for the Bay Area, but tests of their hair, blood and urine found metals, PCBs, plasticizers and — in Rowan — some of the highest fire retardant levels ever measured.

In a pioneering study, we tested a Bay Area family for a suite of chemical pollutants. The results stunned even scientists.

Reporting by staff writer Douglas Fischer, Staff photos by Nick Lammers
## Environmental contaminants that can affect the endocrine system

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Percent of US population with measurable levels*</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phthalates (7 kinds)</td>
<td>50 – 97%</td>
<td>Flooring, wall covering, medical devices, food wrap, personal care products, lacquers</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>93%</td>
<td>Polycarbonate plastic, food can lining dental sealant</td>
</tr>
<tr>
<td>Perfluorinated Chemicals (PFCs) 4 types</td>
<td>98%</td>
<td>Nonstick cookware, stain resistant fabrics, food packaging, dental products</td>
</tr>
<tr>
<td>Parabens (4 kinds)</td>
<td>36-99%</td>
<td>Personal care products, food</td>
</tr>
<tr>
<td>PCBs</td>
<td>83% (with at least one congener)</td>
<td>Banned in 1977 – persistent through food</td>
</tr>
</tbody>
</table>

*Representative US sample from NHANES/CDC generally from 2003/2004, PCBs for women ages 16-39
Timing Matters
Timing Matters

Preconception, prenatal and childhood exposures can have a lifetime of health consequences

Exposures to adverse insults during critical windows of development can permanently reprogram normal physiologic responses, and thus give rise to disorders later in life

Chemicals at Birth

• Chemicals cross the placenta
  – Study of 10 African American, Hispanic and Asian Babies found all babies had
    – lead, mercury, perfluorinated chemicals, polybrominated diphenyl ethers, polychlorinated naphthalenes, PCBs, dioxins
  
• Most had Bisphenol A, perchlorate, and polycyclic musks

“Numerous environmental contaminants can cross the placental barrier; to a disturbing extent, babies are born “pre-polluted.” “

President’s Cancer Panel 2008-09

EWG http://www.ewg.org/minoritycordblood/home
Evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on … thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis.

Diamanti-Kandarakis E et al. 2009
“The Panel was particularly concerned to find that the true burden of environmentally induced cancer has been grossly underestimated.”
Typical skin care product

- INGREDIENTS: WATER, CYCLOPENTASILOXANE, ZINC OXIDE, CYCLOMETHICONE, DIMETHICONE, ETHYLHEXYL METHOXYCINNAMATE, PEG-10 DIMETHICONE, BUTYLENE GLYCOL, DICAPRYLYL CARBONATE, GLYCERIN, TITANIUM DIOXIDE (CI 77891), TRIBEHENIN, SODIUM CHLORIDE, METHYL METHACRYLATE CROSPOLYMER, DISTEARDIMONIUM HECTORITE, DIMETHICONE/VINYLMETHICONE CROSSPOLYMER, POLYGLYCERYL-2 DIISOSTEARETATE, C30-45 ALKYLMETHICONE, C30-45 OLEFIN, PEG/PPG-19/19 DIMETHICONE, METHICONE, CHLORPHENESIN, FRAGRANCE (PARFUM), IRON OXIDES (CI 77492), METHYL PARaben, TRIETHOXYPRYLYLSILANE, IRON OXIDES (CI 77491), IRON OXIDES (CI 77499), PROPYPARaben, TALC, CAMELLIA SINENSIS LEAF EXTRACT, ECHINACEA ANGUSTIFOLIA EXTRACT, HERBASOME CENTELLA ASIATICA, MIMOSA PUDICA LEAF EXTRACT, ORIGANUM MAJORANA LEAF EXTRACT, SILICA, BHT, ACETYL GLUCOSAMINE, ASCORBYL TETRAISOPEMLTATE

www.lipglossate.com

Found in over 90% of Americans
No current NTP study
? Health effects?
…EPA has been aggressive in getting BP to scale back its use of the dispersants, whose long-term effects are unknown. The chemicals are used to break up oil spilled into water.
More knowledge needed

- "At this time, neither industry nor government confirm the safety of existing or new chemicals prior to their sale and use"

- "The Toxic Substances Control Act of 1976 (TSCA) may be the most egregious example of ineffective regulation of environmental contaminants"
• GAO’s High Risk recommendations for high attention focus areas for the government - 2 new ones in 2009

  1) Transforming EPA’s Processes for Assessing and Controlling Toxic Chemicals. EPA does not have sufficient chemical assessment information to

  2) Modernizing the Outdated U.S. Financial Regulatory System.
EPA unveils plan to review 6 controversial chemicals, reform US toxics policy.

By Jane Kay  Environmental Health News  30 September 2009

Saying that the public is “understandably anxious and confused” about chemicals in their bodies and in their environment, President Obama’s top environmental official announced on Tuesday a new push to transform the way the nation regulates industrial compounds.

U.S. Environmental Protection Agency Administrator Lisa Jackson called the workings of a 1976 law “inordinately cumbersome and time-consuming.” She said the administration will promote a new chemical law in Congress in the coming months.

In the meantime, Jackson said, the EPA will begin to analyze and regulate six high-profile chemicals that have raised concerns. Included are bisphenol A, found in hard, clear polycarbonate bottles, and phthalates, which are used in vinyl and cosmetics.

more...

- Chemicals should be reviewed against risk-based safety standards based on sound science and protective of human health and the environment
- Manufacturers should provide EPA with the necessary information to conclude that new and existing chemicals are safe and do not endanger public health or the environment
And in California

GREEN CHEMISTRY:
Cornerstone to a Sustainable California

Press Release

09/29/2008  GAAS:680:08  FOR IMMEDIATE RELEASE  PrintVersion | ShareThis

Governor Schwarzenegger Signs Groundbreaking Legislation Implementing First-in-the-Nation Green Chemistry Program

California reached another environmental milestone today with Governor Arnold Schwarzenegger’s signing of AB 1879 by Assemblymember Mike Feuer (D-Los Angeles) and SB 509 by Senator Joe Simitian (D-Palo Alto), moving our state on the path toward a comprehensive green chemistry program to reduce or eliminate
Chemical Policy Reform

• Current laws in the US recognized as inadequate to test chemicals in use or introduced into the market

• Lautenberg/Waxman have introduced bills to overhaul current TSCA
  – New testing will be included
Challenges to Toxicity Testing

- Focus on overt endpoints in human and animal studies – costly and time consuming
- Extrapolating from animal studies
- Extrapolating from high dose animal studies to lower, everyday human exposures
- Accounting for variability in the human population
  - Genetic
  - Lifestage (e.g. earlylife susceptibility)
  - Disease status
Transforming Environmental Health Protection

Francis S. Collins,¹ George M. Gray,² John R. Bucher³

<table>
<thead>
<tr>
<th>Human experience</th>
<th>Standard rodent toxicological tests</th>
<th>Alternative animal models</th>
<th>Biochemical- and cell-based in vitro assays</th>
</tr>
</thead>
<tbody>
<tr>
<td>1–3 studies/year</td>
<td>10–100/year</td>
<td>100–10,000/year</td>
<td>&gt;10,000/day</td>
</tr>
</tbody>
</table>

Computational toxicology

Critical toxicity pathways

High throughput

Immediate human relevance
Published Genome-Wide Associations through 3/2010, 779 published GWA at $p \leq 5 \times 10^{-8}$ for 148 traits

NHGRI GWA Catalog
www.genome.gov/GWAStudies
• Need to revolutionize toxicity testing to meet design criteria
Design Criteria: Toxicity Testing of Environmental Agents

- Brodest coverage of chemicals, end points, life stages
- Fewest animals; least suffering for those used
- Lowest cost; least time
- Detailed mode of action and dose response information for human health risk assessment
The Future

• “Toxicity testing …is poised to take advantage of the revolutions in biology and biotechnology. Advances in toxicogenomics, bioinformatics, systems biology, epigenetics, and computational toxicology could transform toxicity testing from a system based on whole animal testing to one founded primarily on in vitro methods that evaluate changes in biologic processes using cells, cell lines, or cellular components, preferably of human origin.”

• Toxicity Testing in the 21st Century
Upstream biological perturbations and downstream effects
Adverse Effect (USEPA)

A *biochemical change*, functional impairment, or pathologic lesion that affects the performance of the whole organism, *or reduces an organism's ability to respond* to an additional environmental challenge.
Stem Cells and Environmental Health

- Human Relevance
- Early Life Susceptibility
- Ability to identify different mechanisms/targets
- Incorporate into high through put
FIGURE 3-7 Risk assessment components. End product is development of one or more indicators of risk, such as a reference dose or concentration.
Evaluating the evidence base – Hazard Identification

• Decisions and evidence
  – Pharmaceuticals must show efficacy and safety prior to use
  – Manufactured chemicals must show evidence of harm before removing/regulating
    • Often little to no information
    • Intentional dosing human studies for adverse effects unethical
    • People are already exposed

Decisions must be made in a timely manner to prevent ongoing harmful exposures
Conclusion

- Sufficient information linking upstream and downstream event for some perturbation classes (e.g. thyroid hormone disruption, anti-androgens)
Dose-response

“Threshold determinations should not be made in isolation inasmuch as other chemical exposures and biologic factors that influence the same adverse effect can modify the dose response relationship and therefore should be considered.”

National Academy of Sciences, 2009
Conclusion - Background can increase effects of chemical exposures

- Background
  - Biological
  - Exposure

- Vulnerability, e.g., from
  - Life stage
  - Genetics
  - Health disease status

Source: Woodruff et al. 2008
A chemical’s risk is determined by:

- Background exposures
- Biological susceptibility
- Exposure level to the chemical
Stem Cells and Decision Making

- Human Relevance
- Early Life Susceptibility
- Ability to identify different mechanisms/targets and use in high throughput
- Need to evaluate the outputs within the context of improved approaches to risk assessment
  - Linking early biological perturbations to overt effects
  - Consider background
    - Exposures
    - Susceptibility/variability
UCSF Program on Reproductive Health and the Environment

Mission
To create a healthier environment for human reproduction and development through advancing scientific inquiry, clinical care, and health policies that prevent exposures to harmful chemicals in our environment.

Department of Obstetrics, Gynecology and Reproductive Sciences/Center of Excellence in Women’s Health
“I’d rather be vaguely right than precisely wrong”

John Maynard Keynes
## Examples of changes in reproductive conditions

<table>
<thead>
<tr>
<th>Reproductive Diseases/Disorders</th>
<th>Increase</th>
<th>Period</th>
<th>Location</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testicular cancer</td>
<td>1– 6%</td>
<td>1953 - 1999</td>
<td>Europe</td>
<td>[20]</td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>1973 - 2003</td>
<td>USA</td>
<td>[21]</td>
</tr>
<tr>
<td>Certain childhood cancers</td>
<td>20 – 24%</td>
<td>1976 - 2005</td>
<td>USA</td>
<td>[22]</td>
</tr>
<tr>
<td>Autism</td>
<td>700–800%</td>
<td>1990 - 2006</td>
<td>California</td>
<td>[23]</td>
</tr>
<tr>
<td>Attention Deficit Hyperactivity Disorder</td>
<td>3% per year</td>
<td>1997 - 2006</td>
<td>USA</td>
<td>[24]</td>
</tr>
<tr>
<td>Birth defects:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>300%</td>
<td>1978 - 2005</td>
<td>California</td>
<td>[26]</td>
</tr>
<tr>
<td>Congenital hypothyroidism</td>
<td>138%</td>
<td>1987 - 2003</td>
<td>New York</td>
<td>[27]</td>
</tr>
</tbody>
</table>

### Reproductive Function

<table>
<thead>
<tr>
<th>Reproductive Function</th>
<th>Time</th>
<th>Location</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported difficulty conceiving and maintaining pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All ages</td>
<td>60% more women</td>
<td>1982; 2002</td>
<td>USA</td>
</tr>
<tr>
<td>&lt;25 years old</td>
<td>200% more women</td>
<td>1982; 2002</td>
<td>USA</td>
</tr>
<tr>
<td>Prematurity</td>
<td>2.9% shorter gestation</td>
<td>1992 - 2002</td>
<td>USA</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>19-36%</td>
<td>1968-2002</td>
<td>Norway</td>
</tr>
<tr>
<td>Gestational Diabetes</td>
<td>122%</td>
<td>1989-2004</td>
<td>USA</td>
</tr>
<tr>
<td>Premature puberty:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at onset of breast development</td>
<td>1 – 2 years younger</td>
<td>1940 - 1994</td>
<td>USA, Denmark</td>
</tr>
<tr>
<td>Age at onset of menstruation</td>
<td>2.5 – 4 months younger</td>
<td>1940 - 1994</td>
<td>USA</td>
</tr>
<tr>
<td>Sperm count</td>
<td>~1% decline per year</td>
<td>1931 - 1994</td>
<td>Western countries</td>
</tr>
<tr>
<td>Serum testosterone</td>
<td>1% decline per year</td>
<td>1987 - 2004</td>
<td>Boston, USA</td>
</tr>
</tbody>
</table>

Woodruff, Schwartz, Giudice JECH (in press)