Environmental Contaminants and Reproductive Health

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Chemicals and Reproductive effects

- High exposures and reproductive health outcomes well known
- What about now?

Case Study: Dibromochloropropane (DBCP)

- DBCP - pesticide widely used in the U.S. to treat citrus, grapes, peaches, pineapples, soybeans, and tomatoes
- 1961 - testicular atrophy due to DBCP documented in three rodent species
- 1977 - small group of agricultural workers became aware that none had fathered children
- Investigation of sentinel worker cohort found profound and in many cases permanent effects on spermatogenesis due to exposure to DBCP
- 1985 DBCP was banned from all food crops in the U.S., its export was not

Disclosure

No financial conflicts of interest
Some Reproductive Effects Are Well Known

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Can Increase the Risk of…</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco smoke</td>
<td>Miscarriage</td>
</tr>
<tr>
<td></td>
<td>Infertility</td>
</tr>
<tr>
<td></td>
<td>Preterm delivery</td>
</tr>
<tr>
<td>Heavy alcohol use</td>
<td>Fetal alcohol syndrome</td>
</tr>
<tr>
<td></td>
<td>Mental retardation</td>
</tr>
<tr>
<td>Heavy metals (lead, mercury)</td>
<td>Miscarriage</td>
</tr>
<tr>
<td>Toluene (e.g., in paint thinner, solvents)</td>
<td>Fetal solvent syndrome</td>
</tr>
<tr>
<td>DBCP (pesticide)</td>
<td>Low sperm count</td>
</tr>
<tr>
<td></td>
<td>Other male reproductive effects</td>
</tr>
</tbody>
</table>


Since DBCP … Advances in Reproductive Health Science

- More evidence on link between environmental chemicals at higher levels and adverse reproductive and developmental health outcomes

- Can no longer assume that “low-level” environmental exposures are benign
  - For example: neurological, reproductive and developmental health outcomes

Our Reproductive Capacity Is Under Strain

Scientific indicators of declining reproductive function and increasing rates of reproductive illnesses since the mid-20th century

- Difficulty conceiving & maintaining pregnancy

- Rates testicular cancer

- Sperm counts

The percent of women with impaired fecundity has increased

<table>
<thead>
<tr>
<th>Age</th>
<th>1982</th>
<th>1988</th>
<th>1995</th>
<th>2002</th>
<th>% change from '82-'02</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-24</td>
<td>4.3</td>
<td>4.8</td>
<td>6.1</td>
<td>8.3</td>
<td>+90%</td>
</tr>
<tr>
<td>25-34</td>
<td>10.0</td>
<td>9.6</td>
<td>11.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>12.1</td>
<td>10.6</td>
<td>12.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td>8.4</td>
<td>8.2</td>
<td>10.2</td>
<td>11.8</td>
<td>+40%</td>
</tr>
</tbody>
</table>

Swann, Hertz-Picciotto. Family Planning Persp 1999;31:156-157

- One out of eight babies is born prematurely
- Rate has increased 36% since the early 1980s

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

What’s Changing?
Environmental Contaminants, What are they?

By 2006 ...

Vast majority of chemicals in commerce have entered the marketplace without comprehensive and standardized information on their reproductive or other chronic toxicities.
**What Is Reproductive Environmental Health?**

- Exposure to environmental contaminants (metals and synthetic chemicals)
- During critical and sensitive windows of development
- Health effects across the life course and generations to come

**Streams of Evidence for Toxicity Assessment**

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>New pharmaceutical developed</td>
<td>Chemicals introduced prior to 1976 (N=0,000)</td>
</tr>
<tr>
<td>in vitro &amp; in vivo toxicity testing</td>
<td>New synthetic chemical developed</td>
</tr>
<tr>
<td>Human experimental studies (Randomized Control Trials)</td>
<td></td>
</tr>
<tr>
<td>Pest exposure observational studies</td>
<td></td>
</tr>
</tbody>
</table>

In general, ... there is concordance of developmental effects between animals and humans and that humans are as sensitive or more sensitive than the most sensitive animal species. NAS 2000 Scientific Frontiers in Dev Tox and Risk Ass.
Evaluating the evidence base

- **Decisions and evidence**
  - Pharmaceuticals must show efficacy and safety prior to use
    - Requires extensive animal and human data
  - Manufactured chemicals need to show evidence of harm before removing/regulating
    - No specific toxicity testing required
      - Except for pesticides
    - Human studies are mostly byproduct of already exposed populations
    - Ethical issues with intentional dosing studies
  - Decisions must be made in a timely manner to prevent ongoing harmful exposures

### Agents Which Cause Developmental Toxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Earliest Date Reported</th>
<th>Species Studied in Earliest Report</th>
<th>Other Species Studied</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>alcohol(ism)</td>
<td>1919</td>
<td>Rat</td>
<td>Guinea pig, chicken, human, mouse</td>
<td>(Ahilt, 1919)</td>
</tr>
<tr>
<td>amphetamine</td>
<td>1950</td>
<td>Mouse &amp; Rat</td>
<td>Chicken, human</td>
<td>(Tiersch and Phillips, 1950)</td>
</tr>
<tr>
<td>cigarette smoking</td>
<td>1940</td>
<td>Rabbit</td>
<td>human, rat</td>
<td>(Shenker, 1941)</td>
</tr>
<tr>
<td>diethylstilbestrol</td>
<td>1940</td>
<td>Rat</td>
<td>human, mouse</td>
<td>(Graene et al., 1940)</td>
</tr>
<tr>
<td>heroin/morphine</td>
<td>1969</td>
<td>Hamster</td>
<td>rat, human, rabbit</td>
<td>(Geber and Schramm, 1969)</td>
</tr>
<tr>
<td>ionizing radiation</td>
<td>1960</td>
<td>Mouse</td>
<td>hamster, human, rat, rabbit</td>
<td>(Russell, 1950)</td>
</tr>
<tr>
<td>methylmercury</td>
<td>1965</td>
<td>Human</td>
<td>rat, rat, mouse</td>
<td>(Matsumoto et al., 1965)</td>
</tr>
<tr>
<td>polybrominated biphenyls</td>
<td>1969</td>
<td>Human</td>
<td>Rat</td>
<td>(Taki et al., 1969)</td>
</tr>
<tr>
<td>steroidal hormones</td>
<td>1943</td>
<td>Monkey</td>
<td>hamster, human, mouse, rat, rabbit</td>
<td>(van Wagenen and Hamilton, 1943)</td>
</tr>
<tr>
<td>thalidomide</td>
<td>1961</td>
<td>Human</td>
<td>mouse, monkey, rabbit</td>
<td>(Lenz, 1961; McBride, 1961)</td>
</tr>
</tbody>
</table>

1984 Kimmel, NCTR Technical Report for Experiment No. 6015

References are given only for the earliest report(s) indicated in parentheses.

Limitations of Human Evidence

- **Human**
  - Measurement of exposure often limited
  - Increase “risk” from environmental contaminant exposure often small
    - Many risks in range of 2 fold increase
    - Exposure misclassification can hide true associations
    - But exposure ubiquitous – so still a public health problem
      - Example – particulate matter air pollution
      - Increases risk of respiratory and cardiovascular morbidity and mortality
    - RR mortality ~ 1.06 for estimating benefits in the United States
      > 184,000 lives “saved” per year

**SCIENCE CHANGERS**
**Timing Matters**

**Developmental Basis of Adult Disease**
- Human evidence from study of WW II Dutch famine
- Prenatal under-nutrition affected health in adulthood
- Timing of nutritional insult determined organ system affected
  - Exposure in:
    - Early gestation: three-fold increase in coronary heart disease, more obesity
    - Mid-gestation: increase in obstructive airways disease
    - Late gestation: impaired glucose tolerance


**Child Development and Windows of Susceptibility**
- Blastocyst
- Embryo
- Fetus
- Infant
- Child
- Adolescent

Proper reproductive development orchestrated by hormones

- Periconception
- Prenatal
- Postnatal
- Childhood

Environmental Chemical Exposure

Immediate & Long Term Consequences


**Oakland Tribune**

March 13, 2005

WHAT’S IN YOU
Health Impacts of “Everyday” Toxic Environmental Exposures

Studies show the levels of chemicals an average person is exposed to can perturb biological processes:

Endocrine Disrupting Chemicals: Chemicals which can alter or interfere with natural hormone levels in the body

Contaminants in US pregnant women*

<table>
<thead>
<tr>
<th>Contaminant</th>
<th>Percent of US population with measurable levels*</th>
<th>Some evidence can disrupt endocrine system?</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phthalates (4 kinds)</td>
<td>80 – 100%</td>
<td>Yes</td>
<td>Flooring, wall covering, medical devices, food wrap, personal care products, lacquers</td>
</tr>
<tr>
<td>Bisphenol A</td>
<td>92%</td>
<td>Yes</td>
<td>Polycarbonate plastic, food can lining, dental sealant</td>
</tr>
<tr>
<td>Polyfluoroalkyl Chemicals (PFOS) (4 kinds)</td>
<td>91-99%</td>
<td>Yes</td>
<td>Nonstick cookware, stain resistant fabrics, food packaging, dental products</td>
</tr>
<tr>
<td>Parabens (4 kinds)</td>
<td>36-99%</td>
<td>Yes</td>
<td>Personal care products, food</td>
</tr>
<tr>
<td>Benzophenone-3</td>
<td>100%</td>
<td>Yes</td>
<td>Sunscreen, food packaging</td>
</tr>
<tr>
<td>PCBs (many)</td>
<td>100% (with at least one congener)</td>
<td>Yes</td>
<td>Banned in 1977 – persistent through food</td>
</tr>
</tbody>
</table>

Cumulative Exposures Matter

- Exposures to multiple chemicals can have an additive effect
- Risks of chemicals should be considered together that act on the same common adverse outcome

Prenatal Exposures and Adverse Pregnancy Outcomes

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October 21, 2009
Environmental Tobacco Smoke

• A known risk factor for
  – Low birthweight and decreases in birthweight
  – Preterm birth

Figure 3.2 ETS and Risk of Low Birth Weight

*California Environmental Protection Agency. 2005. Identification of Environmental Tobacco Smoke as a Toxic Air Contaminant.

LBW & Preterm

• Likely role for air pollution (Slama EHP, 2008)

• Effects are small but exposure ubiquitous and high in certain areas
  – For LBW ~ 30 grams reduction in BW for 10 ug/m3 increase in particulate matter air pollution in CA
    • ETS (20-30 grams) (Windham et al. 1999)

• Variable critical window

Ambient Environment: Air

• Traffic
• Industrial Sources
• Power Plants
• Farming
• Forest Fires
• Second hand smoke (Environmental tobacco smoke)

Personal Environment

• Pesticide use
  – In home pesticide use suggested effects on birth weight (Whyatt et al. 2004 EHP)

• PFOS (Perfluorooctanesulfonic Acid)
  – Primarily from animal studies, and small number human study
  – Effects observed on gestational growth

• Persistent compounds
  – Organochlorines (DDT/PCBs)
    • Some evidence on gestational growth and preterm delivery
**Congenital anomalies and Occupational Exposures**

- **Solvents**
  - Structurally diverse, can dissolve other organic substances
    - Glycol ethers, Benzene, toluene, xylene, trichloroethylene, perchloroethylene
    - Occupations: Factories, lab techs, printing, painting, chemists, cleaning
  - Meta-analysis retrospective studies (5 studies, 7,036 patients) (McMartin Am J Ind Med 1998)
    - OR for major malformations 1.64 (CI 1.16–2.30)
  - Prospective study (n=125) (Khattak et al. JAMA 1999)
    - OR for major malformations 13.0 (1.8-99.5)

**Exposures during prenatal development and other effects**

**Prenatal exposures and neurodevelopmental outcomes**

- Developing brain vulnerable to environmental contaminants
  - Cognitive impairments, behavioral deficits
- Environmental conti...
Future reproductive effects

Phthalates found in

- Medical devices
- Toys
- Air Fresheners
- Food Wrap
- Personal care products (perfumes, lotions, cosmetics, hair spray)
- Flooring, wall coverings, lacquers, varnishes, and wood finishes and coatings

Dibutyl phthalate, Dethylhexyl phthalate, Dimethyl phthalate, Butyl benzyl phthalate

Why Do Chemicals in People Matter?

50-97% of people have Phthalates in their bodies

- Flooring, wall covering, medical devices, food wrap, personal care products, lacquers
- Animal studies show increases deformities in penis and testicles and lower testosterone from prenatal exposures
- Phthalates in pregnant women associated with decrease in anogenital distance – a marker for feminization

* Howes et al. 2007 ToxSci, Swan et al. 2005 EHP
**Strength of the Evidence**

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.


**Patient Counseling: Focus on Windows of Susceptibility**

- For male and female adolescents
- For male and female patients who experience unintended pregnancy
- For women and men during pregnancy planning
- For pregnant women
- For male and female patients with newborns and children

**“So What Do I Do?”**

- Science for environmental exposures and reproductive health is:
  - Primarily based on animal studies
  - Warrants guidance to limit/avoid exposure
- Approach patients on case-by-case basis
- Exposure is unavoidable, but specific changes can make a difference

**Environmental Health History Should Be Routine**

**The Environmental Health History**

<table>
<thead>
<tr>
<th>HOW? Incorporate into reproductive health history</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHEN? Vulnerable Stages:</td>
</tr>
<tr>
<td>Early childhood</td>
</tr>
<tr>
<td>Puberty</td>
</tr>
<tr>
<td>Adolescence</td>
</tr>
<tr>
<td>Preconception planning (men &amp; women)</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

| WHY? Identify and reduce or eliminate potentially harmful exposures |

Guide patients in making decisions

*Expert Medical Advisory Committee on Environmental Impacts on Reproductive Health.*
Actions can reduce exposure

• 23 children monitored for metabolites before/after organic diet
• Levels of urinary metabolites for chlorpyrifos and malathion reduced to non-detectable
• Again elevated on re-introduction of conventional diet

5 Areas of Focus

• Prevent Exposure At Home
  – Example – don’t smoke, eat organic when possible

• Prevent Exposure At Work
  – Example – know what is in your workplace and talk with your healthcare provider

• Prevent Exposure In Your Community
  – Example – drive less, do not burn trash

• Become A Smart Consumer
  – Example – consumer guides can help you buy less toxic products

• Make The Government Work For You
  – Example – the government should know you care

FASTEP - Reproductive Environmental Health Toolkit

• Clinical guidance based on AAP Endorsed PSR Pediatric Environmental Toolkit® and other authoritative sources
• Co-branded by FASTEP Alliance partners
• Disseminating with PSR Pediatric Environmental Toolkit®, Centers for Excellence in Women’s Health, Magee Women’s Hospital, and other partners
• Concrete advice on how women can avoid harmful chemicals

www.prhe.ucsf/prhe

We Can’t Shop Our Way out the Problem
**Actions can reduce exposures**

![Graph showing lead levels in gasoline over time](image)

- **Blood Lead Levels**
- **Lead in Gasoline**

**Program on Reproductive Health and the Environment**

**Mission**

- To create a healthier environment for human reproduction and development by advancing scientific inquiry, clinical care, and health policies that prevent exposures to harmful chemicals in our environment
  - Targeted research
  - Expanding clinical practice
  - Advancing science-based policy solutions

**We expect to know about drugs before they go to market, why not chemicals?**

- Pharmaceuticals must have data to show **efficacy** and **safety** prior to use
- Do manufactured chemicals have to have data on **safety** before use?

**NO**

[Source: fda.gov/about/history/ and Pomper, G.M., Ordinary Heroes and American Democracy]

- Except for pesticide active ingredients