

# Reproductive Health & the Environment: What Does the Current Research Tell Us?

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Advocacy through Education:

Women's Reproductive Health &

The Environment in Los Angeles County

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# Acknowledgment

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- ❑ The Iris Cantor-UCLA Women's Health Education & Resource Center
  - ❑ Los Angeles County Department of Public Health Office of Women's Health
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***E Pluribus Unum***



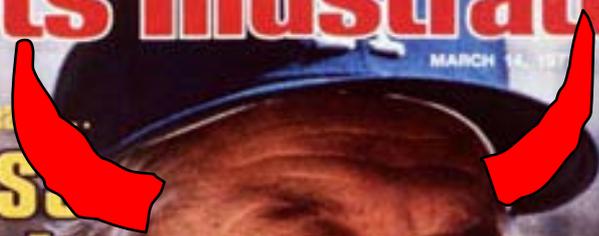
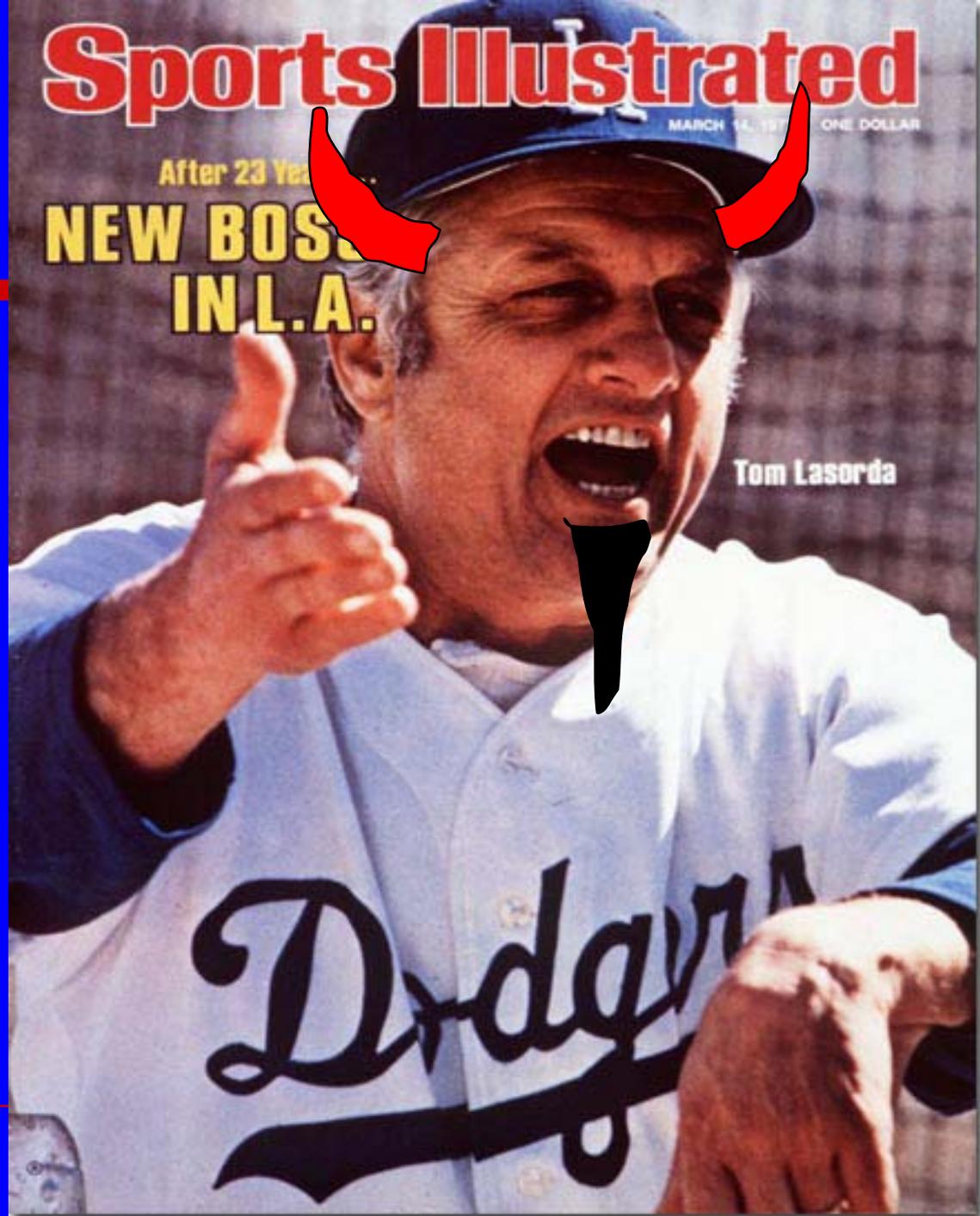


# Sports Illustrated

MARCH 14, 1977 ONE DOLLAR

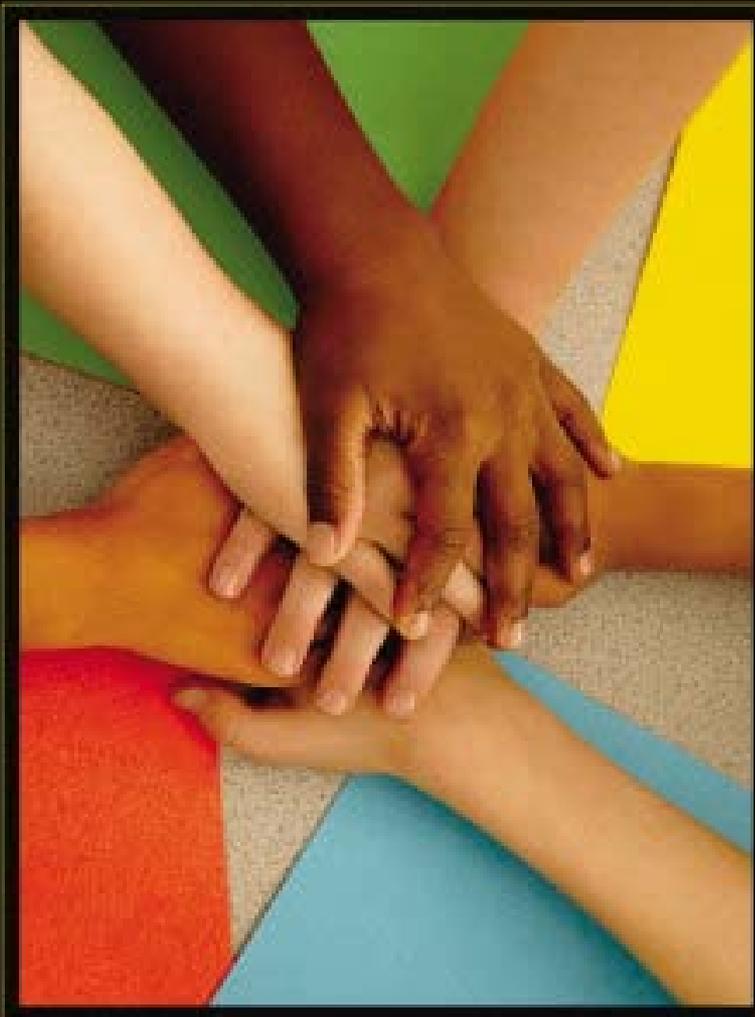
After 23 Years  
**NEW BOS.  
IN L.A.**

Tom Lasorda









# DIVERSITY

*Diversity is the one true thing we all have in common. Celebrate it everyday.*







***“Just Like Every Other Kid in LA”***

**What a pediatrician said about Sasha’s asthma**



# Reproductive Health & the Environment

# Early Puberty

- ❑ Age of puberty onset has declined in developed nations
- ❑ Early puberty is associated with depression, sexual victimization, substance abuse, & adult breast cancer
- ❑ Early puberty has been linked to PCBs, PBBs, cigarette smoke, & organochlorine pesticide exposure in the womb or in early life
- ❑ Growing body of evidence linking early puberty to cumulative exposures to estrogen-like substances e.g. phthalates, BPA, DES, & some phytoestrogens
- ❑ Cumulative estrogenic exposures can promote early puberty by accelerating maturation of hormonal axis or by acting directly on development of ovaries and breasts

Woodruff et al Fert Steril 2008;89:e1-20; Howdeshell et al Nature 1999;401:763-4; Windham et al Am J Epidem 2004;159:862-71; Ouyang et al Occup Environ Med 2005;62:878-4; Guillette et al Environ Health Perspect 2006;114:471-5; Krstevska et al Hum Reprod 2001;16:1020-6; Vasiliu et al Hum Reprod 2004;19:1506-12; Colon et al Environ Health Perspect 2000;1008:895-900; Brown et al Environ Health Perspect 1995;103:708-13; Freni-Titulaer et al Am J Dis Child 1986;140:1263-7; Hannon et al Arch Environ Contam Toxicol 1987;16:255-62; Denham et al Pediatrics 2005;115:e127-34; Blanck et al Epidemiology 2000;11:641-7; Crain et al Fert Steril 2008;90:911-40



# Impaired Fertility & Infertility

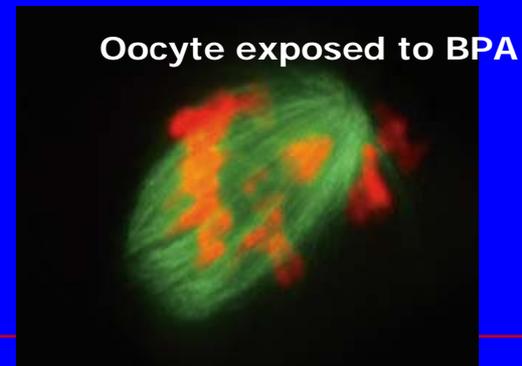
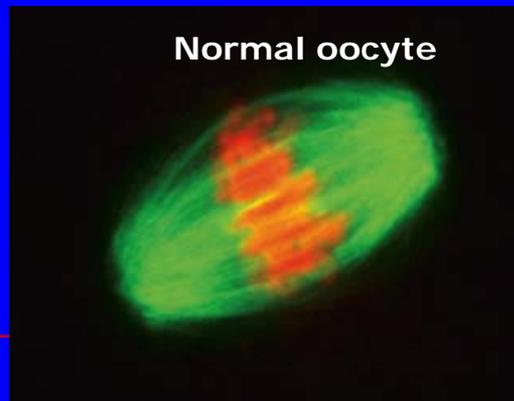
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- ❑ Endocrine disruptors such as BPA, cigarette smoke, DDT, DES, PCBs have been linked to impaired fertility
- ❑ Male factor infertility
- ❑ Female factor infertility by disrupting ovarian & uterine development and functions

Woodruff et al Fert Steril 2008;89:e1-20; Sugiura-Ogasawara Hum Reprod 2005;20:2325-2329; Hruska et al Clin Obstet Gynecol 2000;43:821-9; Younglai et al Hum Reprod Update 2005;11:43-57; Cohn et al Lancet 2003;361:2205-6; Venners et al AAm J Epidemiol 2005;162:709-16; Longnecker et al Environ Res 2005;97:127-33; Perez et al Fert Steril 2005;84:1649-56; Sharara Fert Steril 1998;70:613-22; Miller et al Toxicol Appl Pharmacol 2004;198:111-31; Toft Reprod Toxicol 2004;19:5-26; Crain et al Fert Steril 2008;90:911-40

# Aneuploidy

- ❑ A condition in which a cell has extra or missing copies of specific chromosomes (e.g. Trisomy 21)
- ❑ Exposure to BPA in the womb or as adult can lead to production of eggs & embryos with abnormal number of chromosomes
- ❑ Prenatal exposure leads to altered synapsis & recombination during meiosis
- ❑ Adult exposure leads to altered spindle formation & chromosomal alignment during meiosis





# Polycystic Ovarian Syndrome (PCOS)

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- ❑ PCOS characterized by hyperandrogenism, anovulation or oligoovulation, and polycystic ovaries
- ❑ Women with PCOS found to have higher levels of BPA
- ❑ PCOS has been linked to excessive androgen exposure in the womb



# Endometriosis

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- ❑ **Animal studies have linked endometriosis to adult exposures to DDT, methoxychlor, dioxin, PCBs**
- ❑ **Human studies have linked endometriosis to adult exposures to dioxin, phthalates, PCBs**
- ❑ **Organochlorines can interfere with hormonal regulation (e.g. reduced PR expression) & immune function to promote endometriosis**
- ❑ **In utero exposures are also associated with endometriosis**
  - **DES daughters have 80% higher risk of developing endometriosis**
  - **Prenatal exposure to dioxin shown to promote endometriosis in mice**



# Fibroids

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- ❑ **Animal studies have linked uterine fibroids to DES, BPA and some organochlorine pesticides**
- ❑ **DES exposure during sensitive periods of development turns on estrogen sensitive genes**
- ❑ **DES daughters have twofold increased risk of fibroids**
- ❑ **In utero or neonatal exposures to BPA, at levels to which women are currently exposed, also increase the risk of fibroids in adult mice**
- ❑ **In vitro studies show DES and organochlorines induce proliferation of fibroid cells**

# Spontaneous Abortion

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- ❑ Spontaneous abortion can be caused by aneuploidy, uterine anomalies, & endocrine or immune disruption
  
- ❑ May also be caused by poor implantation
  - Early gestation exposure to BPA causes poor placentation
  - Early gestation exposure to methoxychlor reduces proliferation & induces apoptosis
  - Early gestation exposure to synthetic estrogen induces trophoblast degeneration
  
- ❑ Poor implantation has also been implicated in preeclampsia, IUGR and preterm birth

# Preterm Birth

<b>Air pollution</b>	<b>Positive findings for sulfur dioxide &amp; particulates</b> ; inconsistent findings for carbon monoxide, nitrous oxides, ozone
<b>Water pollution</b>	No association with THM or other chlorination disinfection by-products
<b>Agricultural chemicals</b>	Inconsistent findings; <b>DDT associated with preterm birth OR 2.5-3.1</b>
<b>Polychlorinated biphenyls</b>	Inconsistent findings for PCBs
<b>Dioxins</b>	Inconsistent findings for TCDD
<b>Environmental tobacco smoke</b>	<b>Passive smoking consistently associated with preterm birth OR 1.2-2.4</b>
<b>Metals &amp; metalloids</b>	<b>Lead consistently associated with preterm birth</b> ; Inconsistent findings for aluminum, cadmium, arsenic

# Breast Cancer

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- ❑ Mammary gland tumors have been linked to more than 200 chemicals, including BPA, cigarette smoke, DES, & pesticides DDT and atrazine
- ❑ DES daughters have increased risk of breast cancer
- ❑ In utero exposure to BPA is associated with increased density of mammary gland tissue, a risk factor for breast cancer, which is not manifested until after puberty
- ❑ In human studies, no link was found between adult exposure to DDT, but among women who were exposed to high levels of DDT under the age of 14, there was a fivefold increased risk of breast cancer

# Summary

<b>Early puberty</b>	BPA, cigarette smoke, organochlorine pesticides (e.g. DDT/DDE), DES, PBBs, PCBs, phthalates, some phytoestrogen
<b>Impaired fertility or infertility</b>	BPA, cigarette smoke, DDT, DES, PCBs
<b>Aneuploidy</b>	BPA
<b>Menstrual irregularities</b>	BPA & some phytoestrogens, DDT, other pesticides, DES, dioxins, PCBs
<b>Polycystic ovarian syndrome (PCOS)</b>	BPA
<b>Uterine fibroids</b>	DES, BPA, some organochlorine pesticides
<b>Spontaneous abortion</b>	BPA, DES, DDT/DDE, methoxychlor
<b>Preterm Birth</b>	Sulfer dioxide, particulates, DDT, lead
<b>Endometriosis</b>	Organochlorines such as DDT, methoxychlor, dioxin, PCBs, phthalates, DES
<b>Breast cancer</b>	BPA, cigarette smoke, DES, pesticides DDT & atrazine



# Male Reproductive Health & the Environment

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- ❑ Cryptorchidism, hypospadias, testicular germ cell cancer, infertility are on the rise
- ❑ Testicular dysgenesis syndrome may have a common fetal origin due to “abnormal testis development”
- ❑ In utero exposure to DBP reduces Sertoli cells
- ❑ Adult exposure to phthalates, PCBs, heavy metals, DBCP, pesticides linked to decreased sperm quality

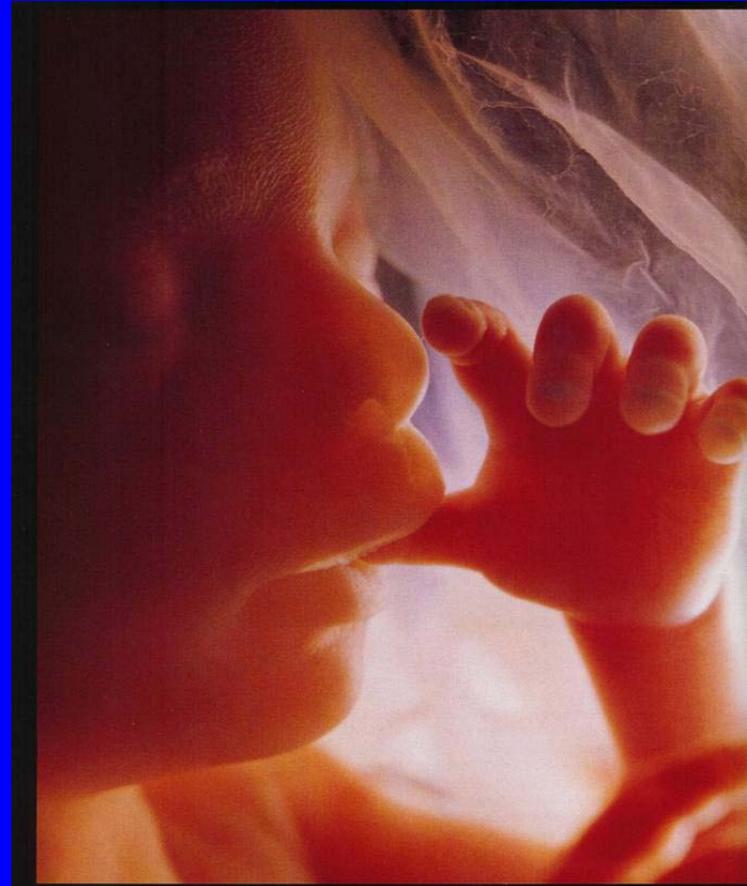
# No "Safe" Dose

- ❑ Very low levels of BPA can harm reproductive health in female mice and their offspring
- ❑ Mice exposed to extremely low levels of DES in the womb grew to be extremely obese in adulthood, whereas mice exposed to higher levels of DES actually lost weight



# Timing Matters

- **Programming:** The process whereby a stimulus or insult, at a sensitive or 'critical' period, has lasting or lifelong impact on health or function.
- **Critical or sensitive windows of susceptibility:** Time-sensitive interval when exposures to a stimulus or insult can disrupt or interfere with the physiology of a cell, tissue, or organ

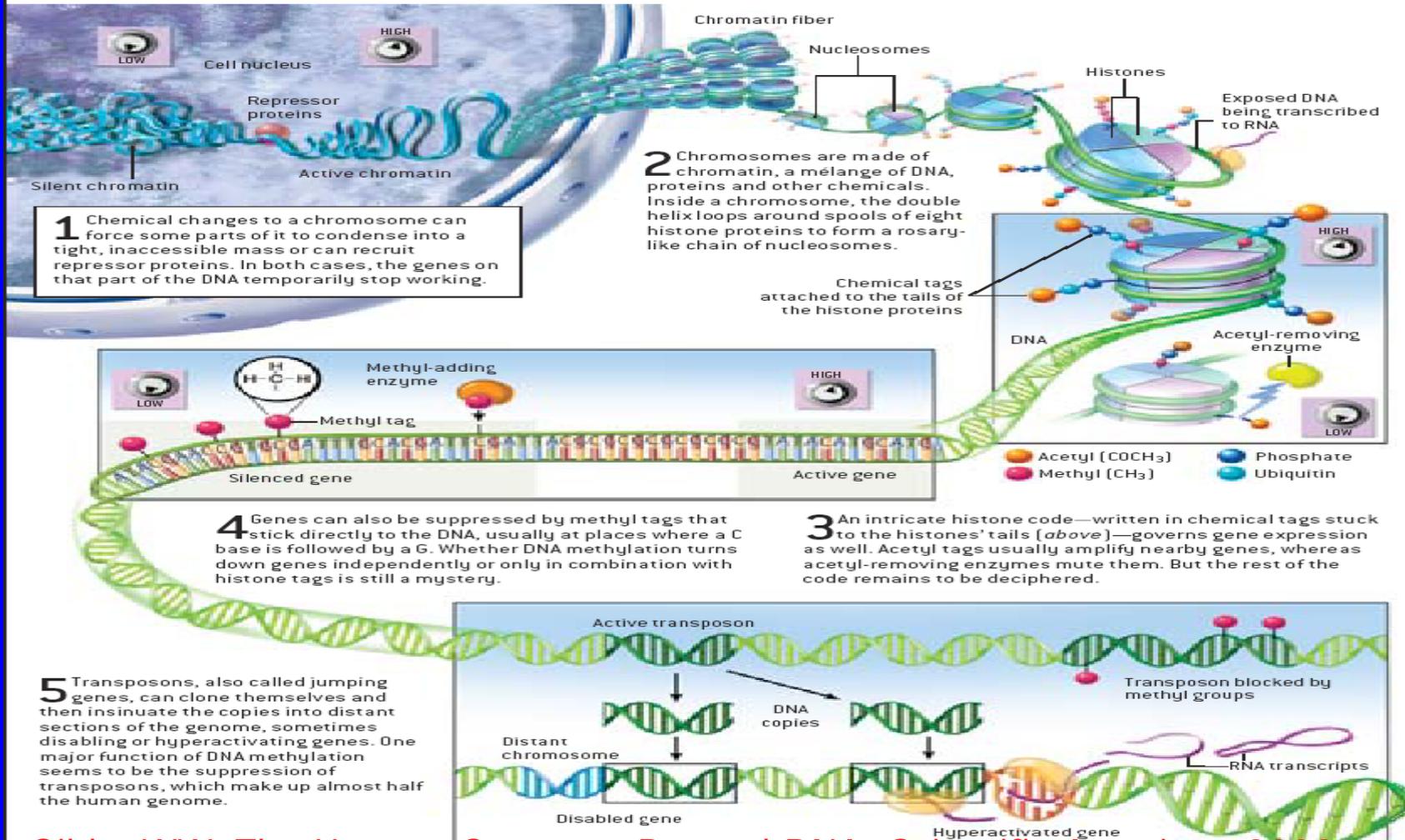


# Epigenetics

## VOLUME CONTROLS FOR GENES

THE DNA SEQUENCE is not the only code stored in the chromosomes. So-called epigenetic phenomena of several kinds can act like volume knobs to amplify or mute the effect of genes. Epigenetic information is encoded as chemical attachments to

the DNA or to the histone proteins that control its shape within the chromosomes. Among their many functions, the epigenetic volume controls muffle parasitic genetic elements, called transposons, that riddle the genome.





# Epigenetics

## *Same Genome, Different Epigenome*

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R.A. Waterland, R.A. Jirtle, "Transposable elements: targets for early nutritional effects on epigenetic gene regulation," *Mol Cell Biol*, 23:5293-300, 2003. Reprinted in the New Scientist 2004

# Prevention Begins Before Conception: Dioxins

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- ❑ Endocrine disruptor
- ❑ Developmental neurotoxicant & immunotoxicant
- ❑ Bioaccumulate in animal fat
  - Long half life: 7 years
  - Crosses the placenta easily
- ❑ Prevention
  - Low animal fat diet for children & young women
  - Quit feeding animal fat to animals

# Research Priorities

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- ❑ Human and animal studies that are longitudinal, including prenatal exposures
- ❑ Incorporate semen analysis into CDC's NHANES study
- ❑ Biomarker collection & banking should be incorporated into epidemiological study designs
- ❑ Development of biomarkers of exposure and preclinical indicators of disease & better biomarkers of human fertility
- ❑ Strategies to address regulatory obstacles (e.g. HIPPA)
- ❑ Increased funding for emerging areas of research: epigenetics, fetal programming and transgenerational effects, low-dose effects, nontraditional dose-response curves, crosstalk among endocrine systems and receptors
- ❑ Develop systems to identify new emerging contaminants
- ❑ Enhanced collaborations among researchers and between researchers and granting agencies

# Southern California Environmental Health Sciences Center

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- ❑ Collaboration between UCLA & USC
  - ❑ Established in 1996 to promote environmental health research in Southern California
  - ❑ Center studies have included improved approaches for assessing exposure to automobile exhaust, toxicologic assessment of toxic air contaminants, and the measurement of particles of all sizes.
  - ❑ In one major study, Center investigators are studying 6,000 children living in Southern California who breathe some of the most polluted air in the United States.
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# National Children's Study

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- ❑ Longitudinal study – from before birth to 21 years of age
  - ❑ Cohort of 100,000 children from 100 Study Locations
  - ❑ Study how children's genes and their environments interact to affect their health and development
  - ❑ In Los Angeles,
    - 4,000 children
    - 56 neighborhoods
    - 67 birth hospitals
    - Followed for 21+ years
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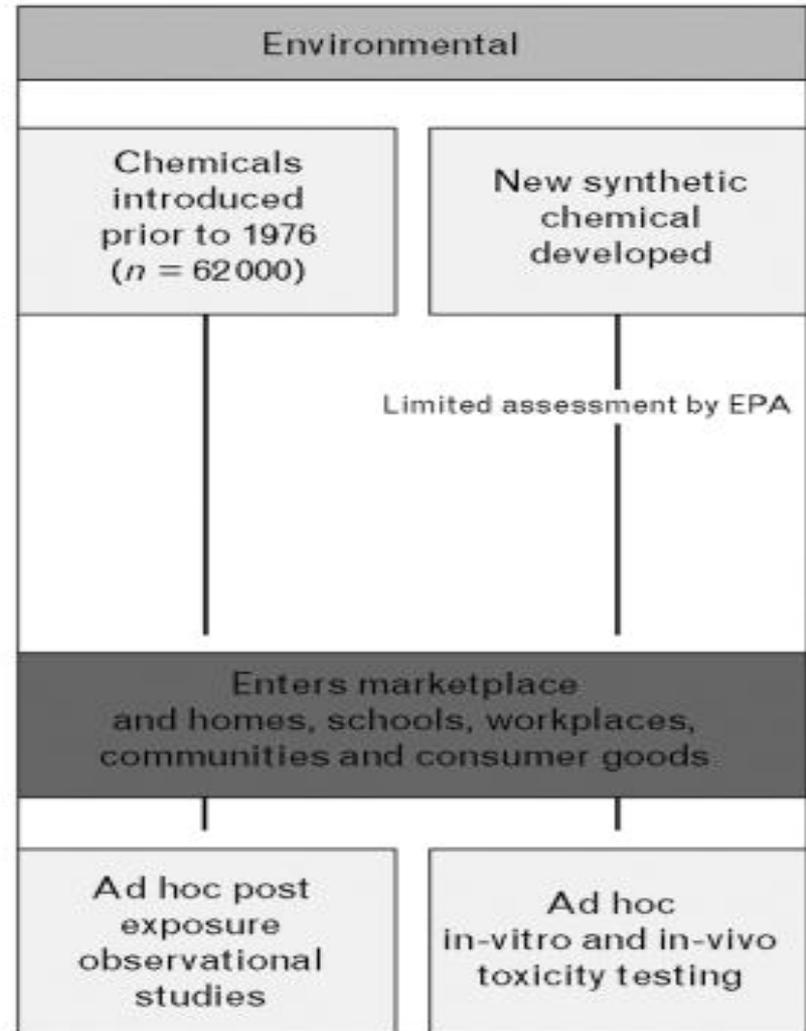
# Policy

Reproductive environmental health.

Sutton, Patrice; Giudice, Linda; Woodruff, Tracey

Current Opinion in Obstetrics & Gynecology. 22(6):517-524, December 2010.

DOI: 10.1097/GCO.0b013e3283404e59



# Policy

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- **2007: REACH**
    - **European Community Regulation on chemicals and their safe use (EC 1907/2006)**
  
  - **2009: Essential Principles for Reform of Chemicals Management Legislation**
    - **US EPA to help inform legislative efforts to reauthorize and strengthen the effectiveness of chemical regulations**
-

"Now that *you're* here,  
the word of the Lorax seems perfectly clear.

**UNLESS** someone like you  
Cares a whole awful lot,  
Nothing is going to get better.  
It's not.

"SO...

Catch!" calls the Once-ler.  
He lets something fall.

"It's a Truffula Seed.

It's the last one of all!

You're in charge of the last of the Truffula Seeds.

And Truffula Trees are what everyone needs.

Plant a new Truffula. Treat it with care.

Give it clean water. And feed it fresh air.

Grow a forest. Protect it from axes that hack.

Then the Lorax  
And all of his friends  
May come back."