Environmental Contaminants in Our Drinking Water, Breast Milk and Our Babies. How Worried Should We Be?

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1Clinical Professor Neonatology Indiana University School of Medicine
2USGS NAWQA National Data Manager

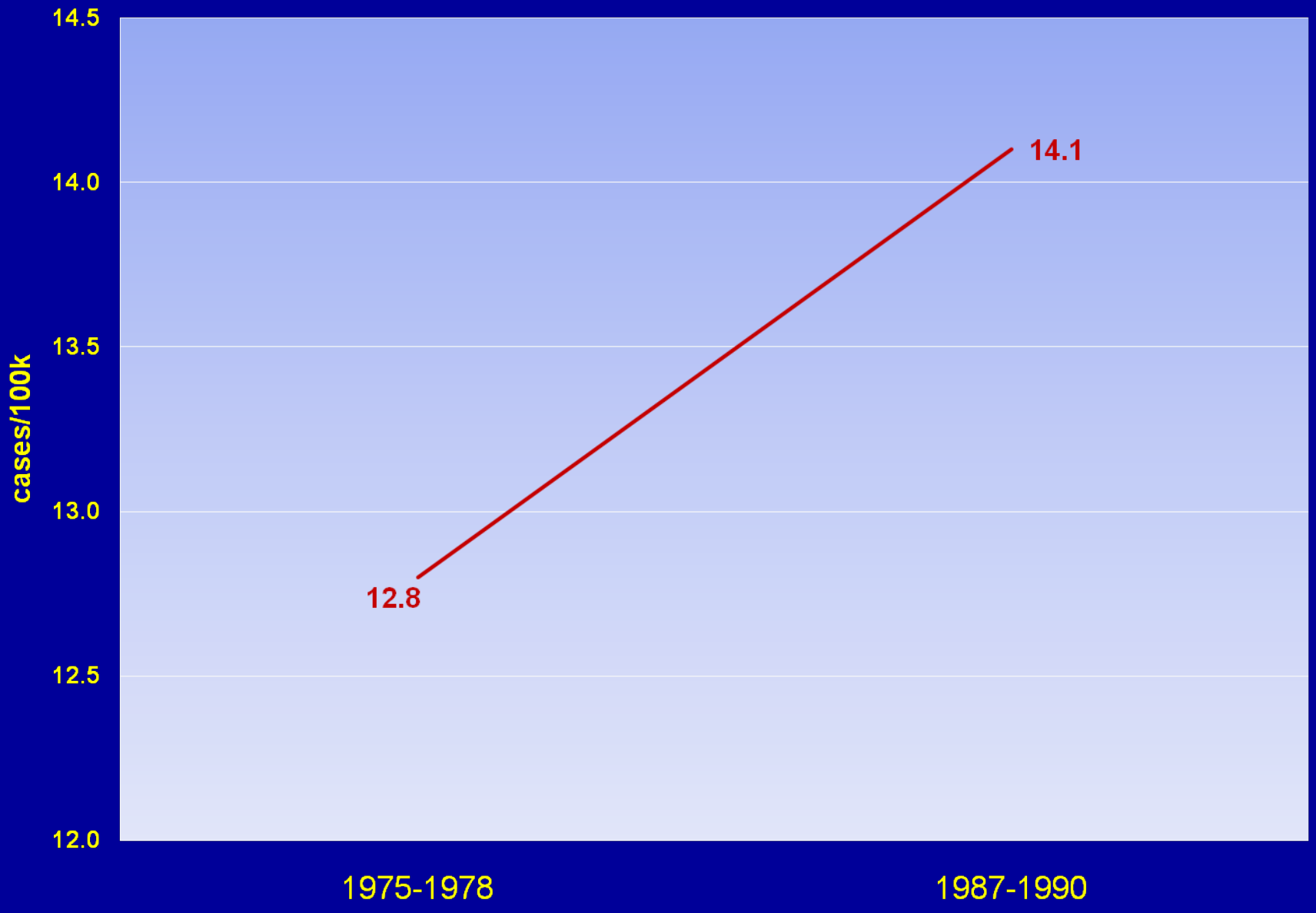
How Healthy Are We?

- Cure rates are up for most cancers.
- Cholesterol and tobacco use; declining.
- More premature babies are being saved.
- More birth defects are being repaired.
- Decision to incision and door to cath times are down.
- There is now a cancer center, heart center or Infertility and High Risk Pregnancy Center near you.
- BUT……..

AUTISM	**10X**	increase early 80's-1996
MALE BIRTH DEFECTS	**2X**	increase hypospadias, 1970-1993
CHILDHOOD ASTHMA	**2X**	increase 1982-1993
ACUTE LYMPHOCYTIC LEUKEMIA	**62%**	increase in children, 1973-1999
CHILDHOOD BRAIN CANCER	**40%**	increase 1973-1994
PRETERM BIRTH	**23%**	increase mid 80's-2002
INFERTILITY	**5-10%**	of couples
BIRTH DEFECTS	**3-5%**	of all babies
SPERM COUNTS	**1%**	decrease yearly 1934-1996

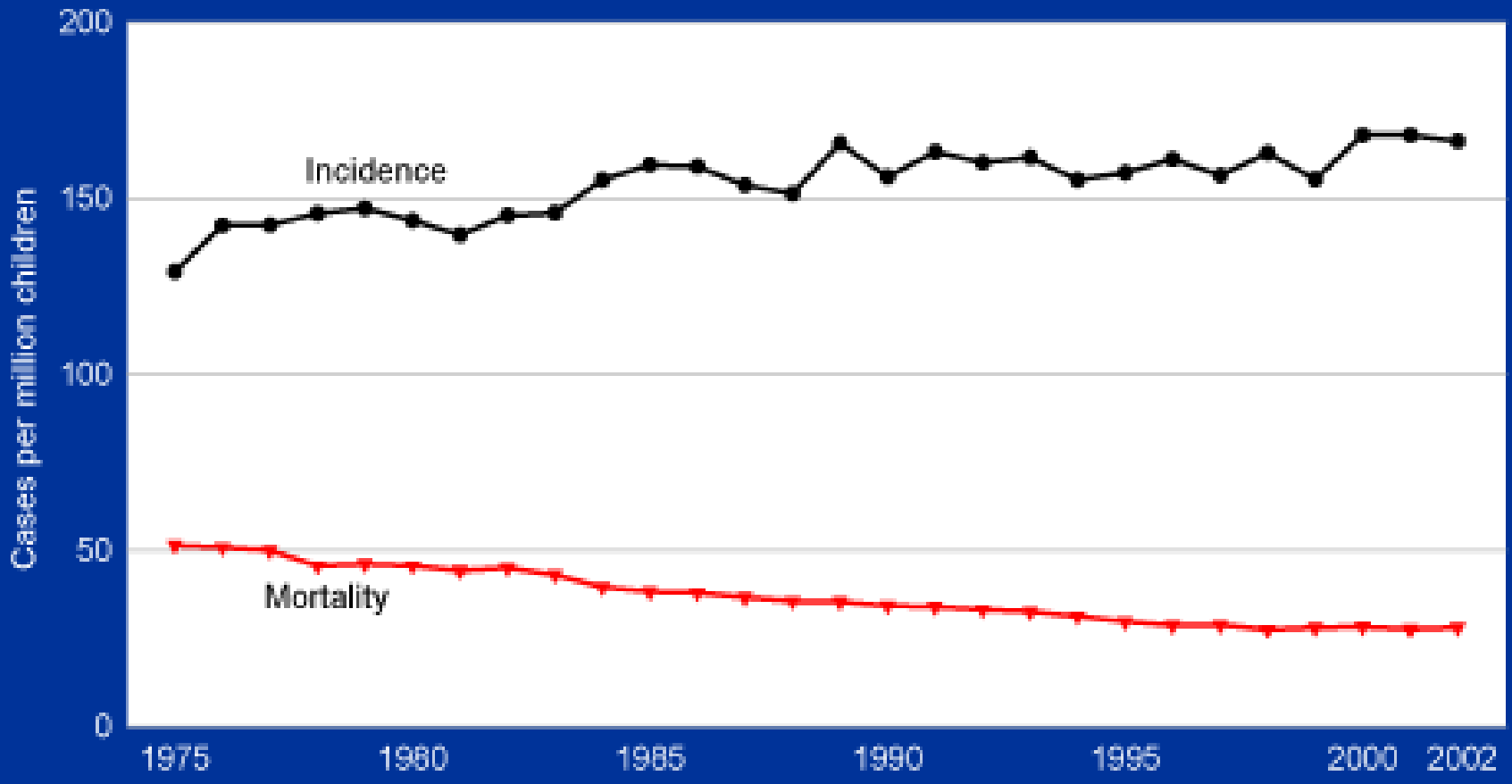
Children's Health Report Card 2007

Childhood Cancer Rates



Environmental Health Perspectives Volume 103, Supplement 6, September 1995

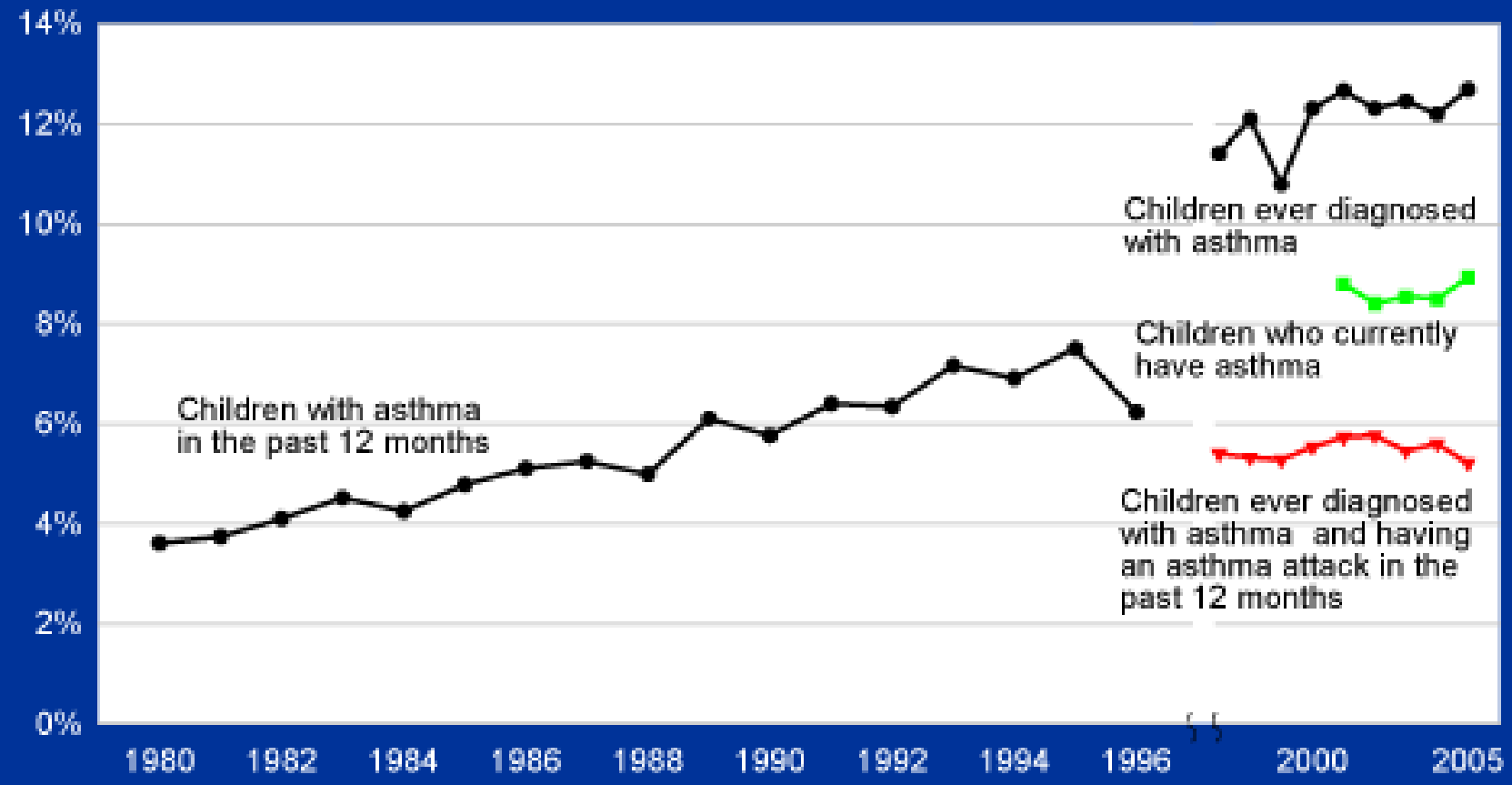
Cancer incidence and mortality for children under 20



SOURCE: U.S. EPA. America's Children and the Environment. www.epa.gov/envirohealth/children

DATA: National Cancer Institute, Surveillance, Epidemiology and End Results Program

Percentage of children with asthma



SOURCE: U.S. EPA. America's Children and the Environment. www.epa.gov/envirohealth/children

DATA: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health Interview Survey

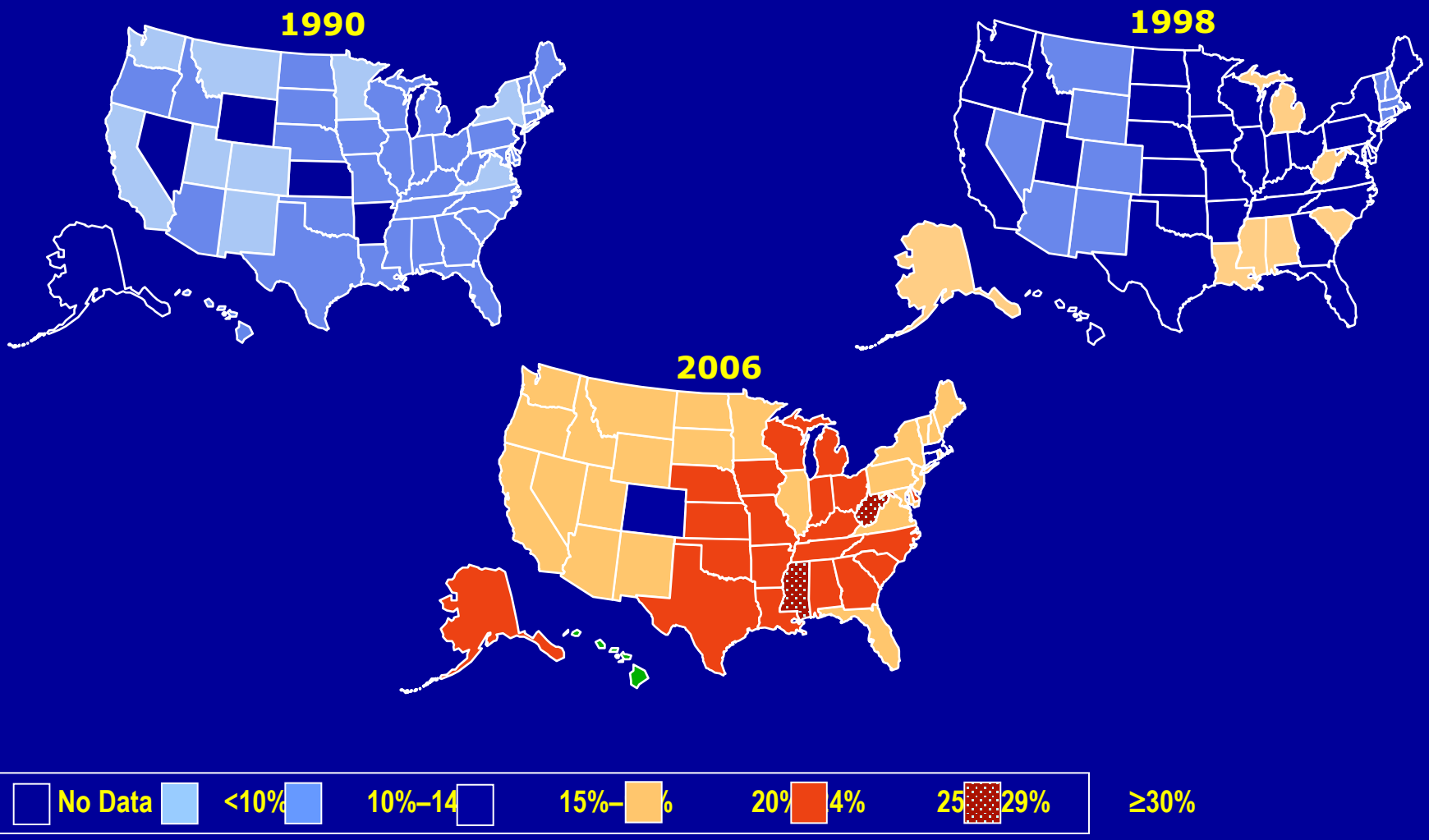
Note: The survey questions for asthma changed in 1997; data before 1997 cannot be directly compared to data in 1997 and later.

Other Diseases On the Rise

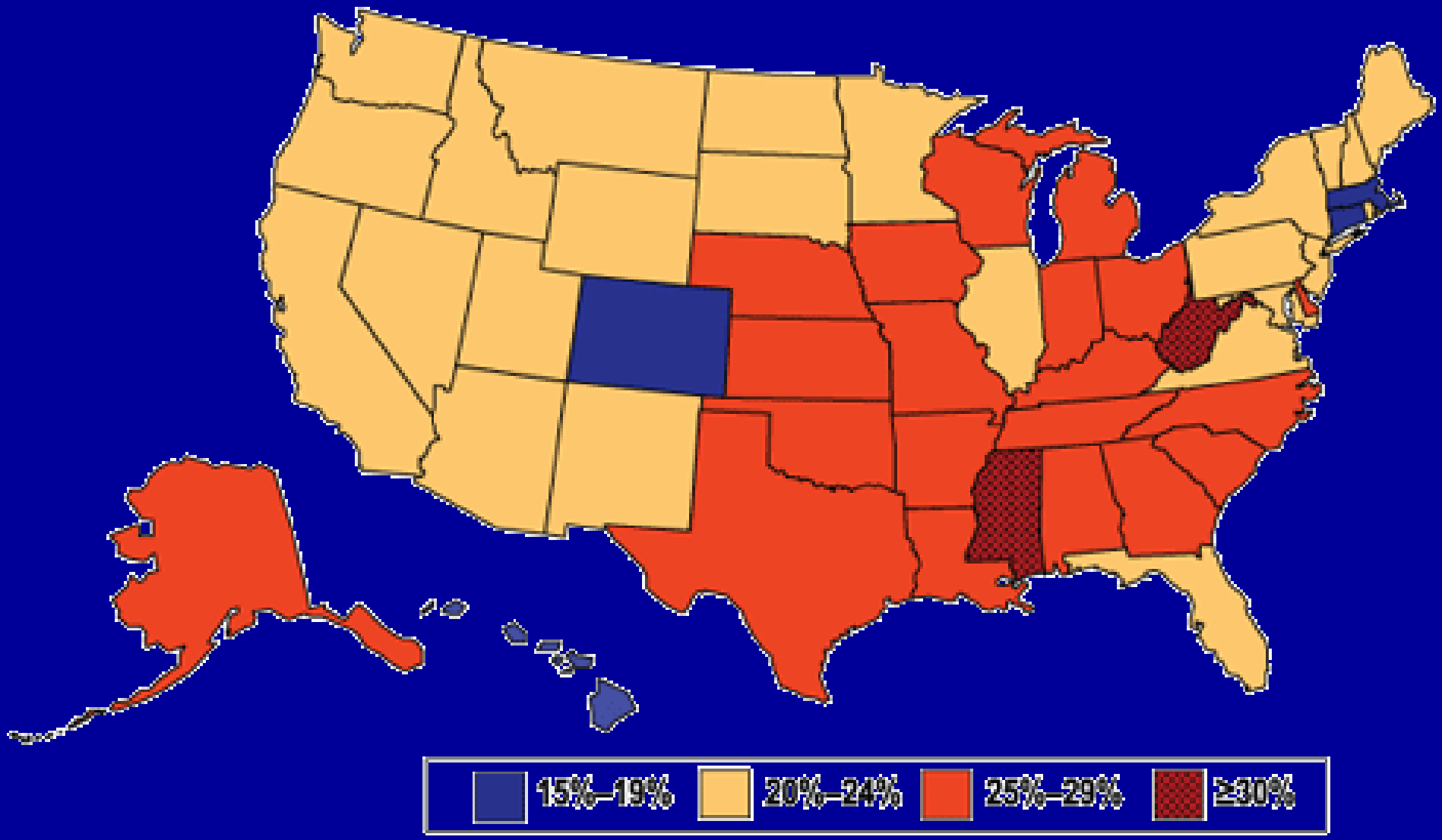
- Obesity
- ADHD and learning disabilities
- Major Depression
- Premature menarche

Obesity Trends* Among U.S. Adults
BRFSS, 1990, 1998, 2006

(*BMI ≥30, or about 30 lbs. overweight for 5'4" person)

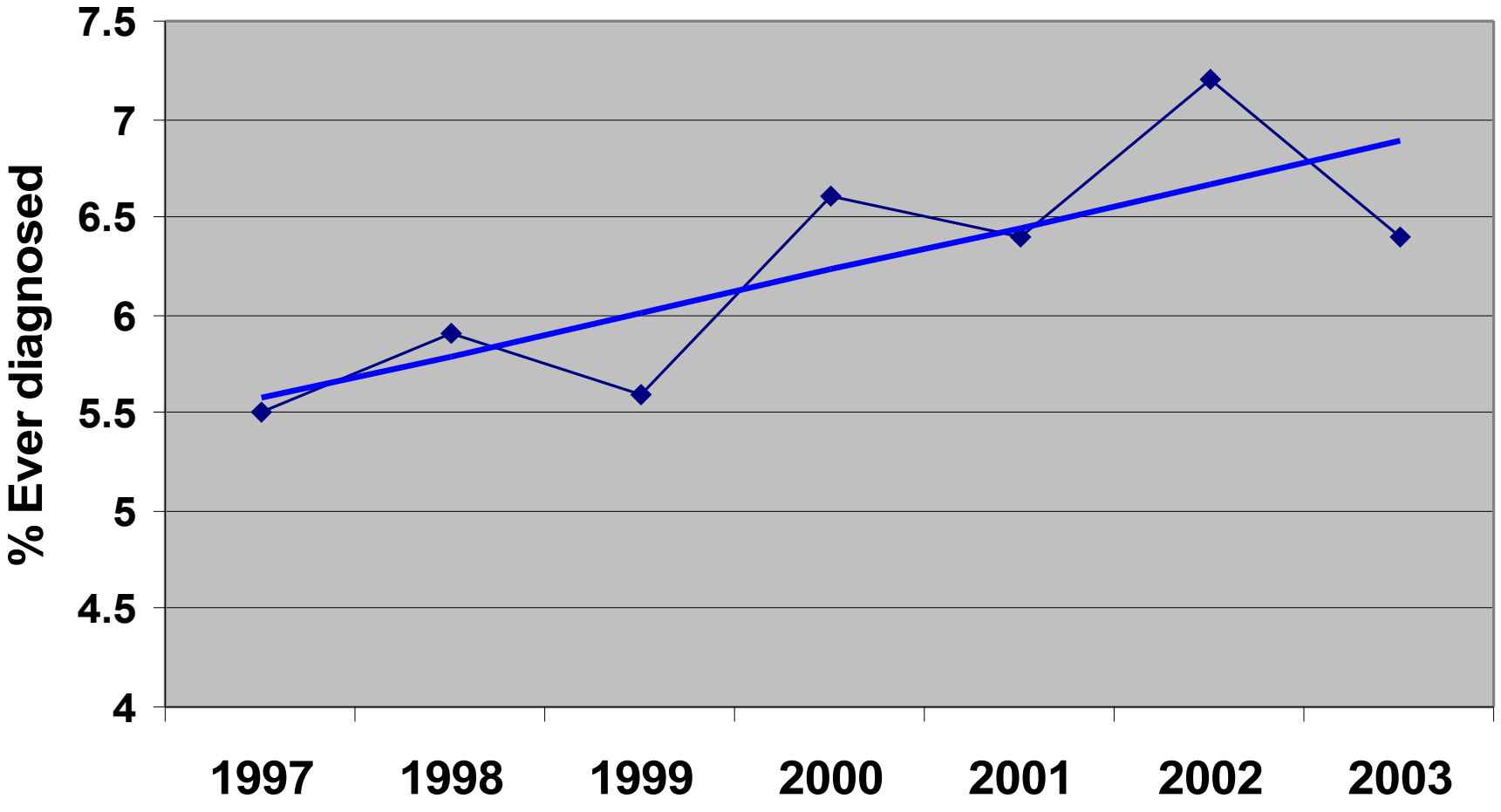


Obesity Trends (%BMI>30 2006)



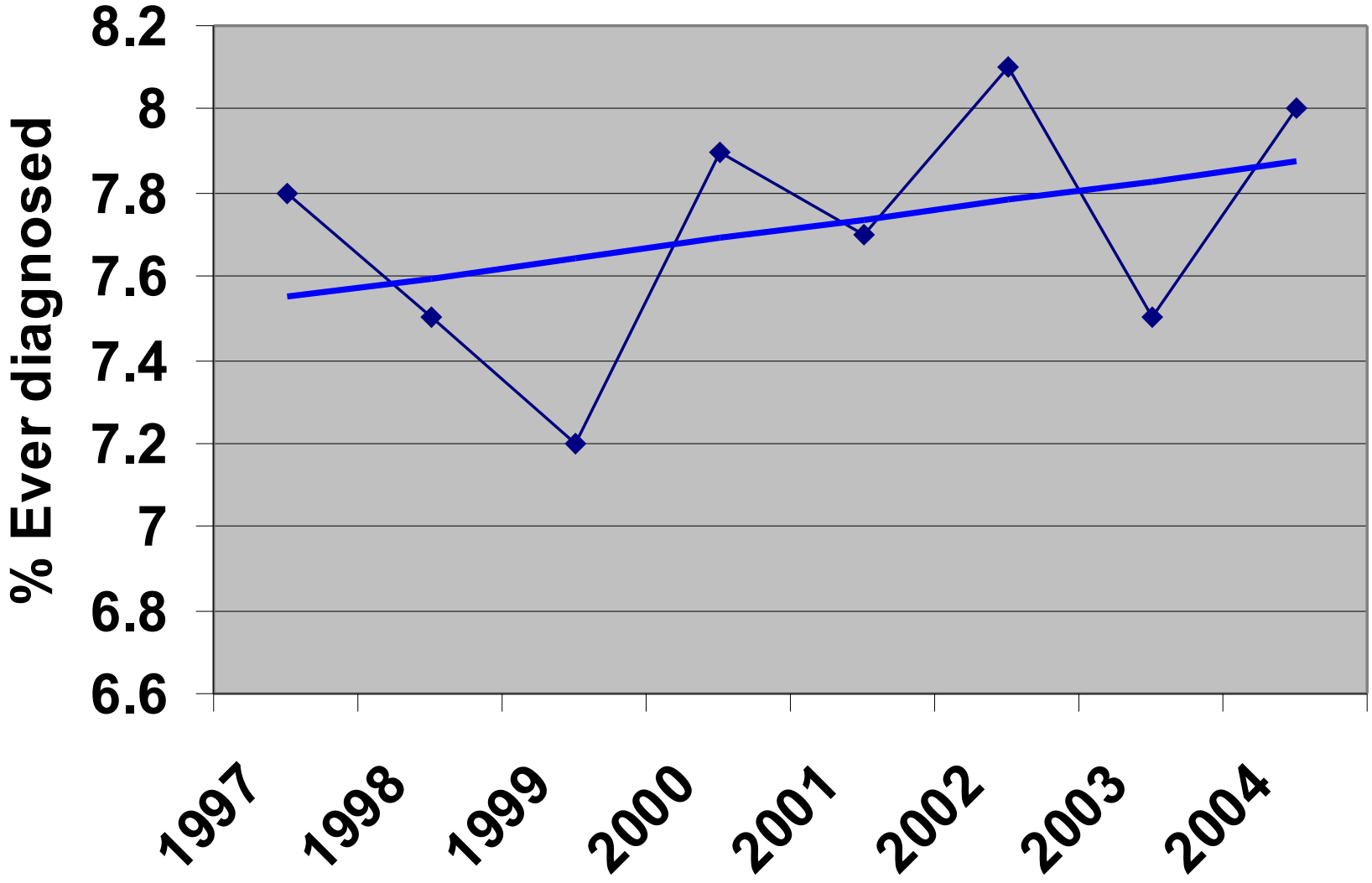

US Elections 2000
WASH 11
OREGON 7
CALIF 54
NEVADA 4
IDAHO 4
MONTANA 3
WYOMING 3
UTAH 5
ARIZONA 8
COLORADO 8
NEW MEXICO 5
N DAK 3
S DAK 3
NEBRASKA 5
KANSAS 6
OKLA 8
TEXAS 32
MINN 10
IOWA 7
MO 11
ARK 6
LA 9
WIS 11
ILL 22
MICH 18
IND 12
OHIO 21
KY 8
TENN 11
MISS 7
ALA 9
GA 13
FLA 25
SC 8
NC 14
VA 13
W VA 5
PA 23
NY 33
VT 3
NH 4
ME 4
MASS 12
RI 4
CONN 8
NJ 15
DEL 3
MD 10
DC 2
HAWAII 4
ALASKA 3
Al Gore
George W. Bush

ADHD ages 3-17 1997-2003 US

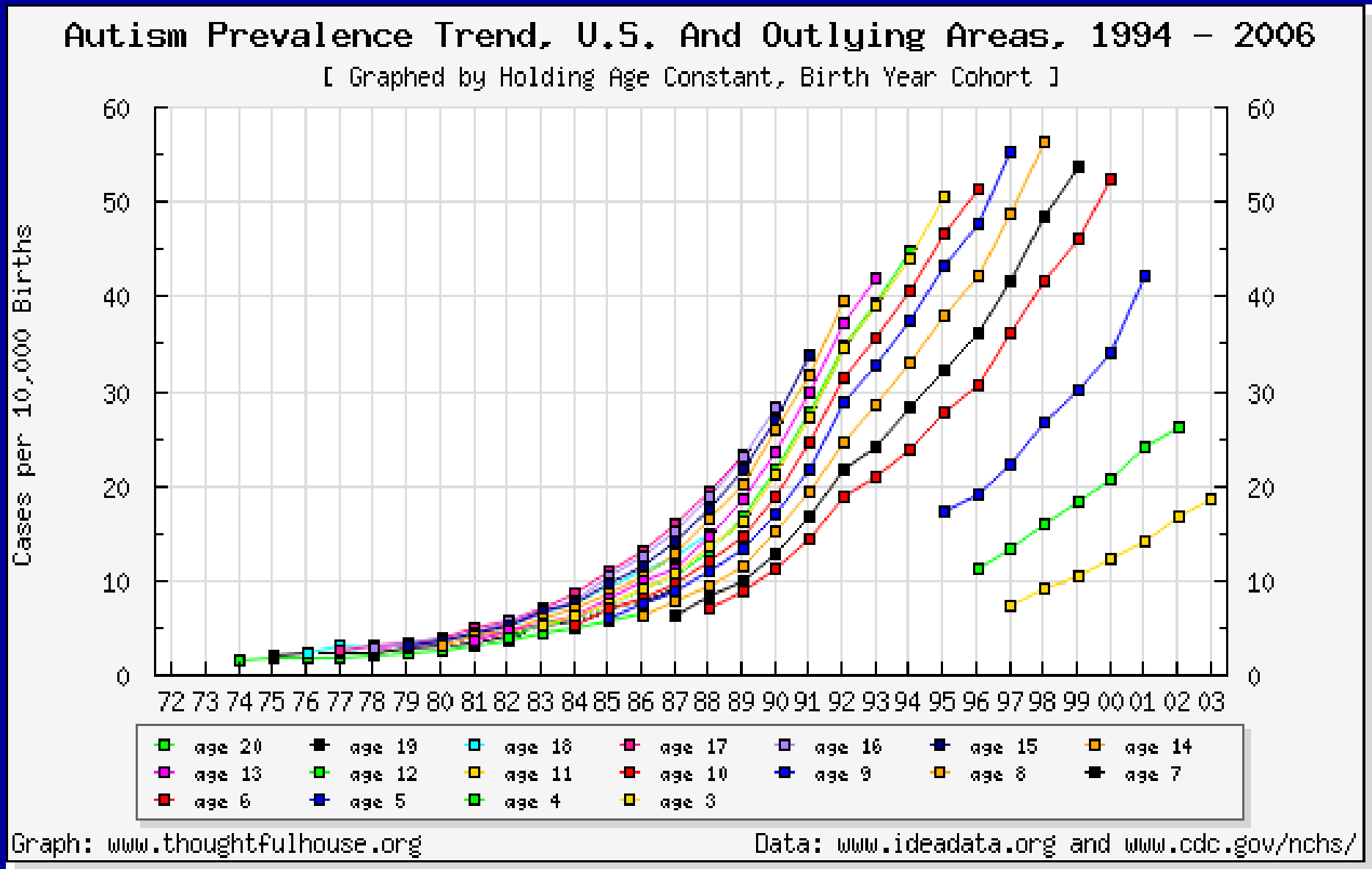


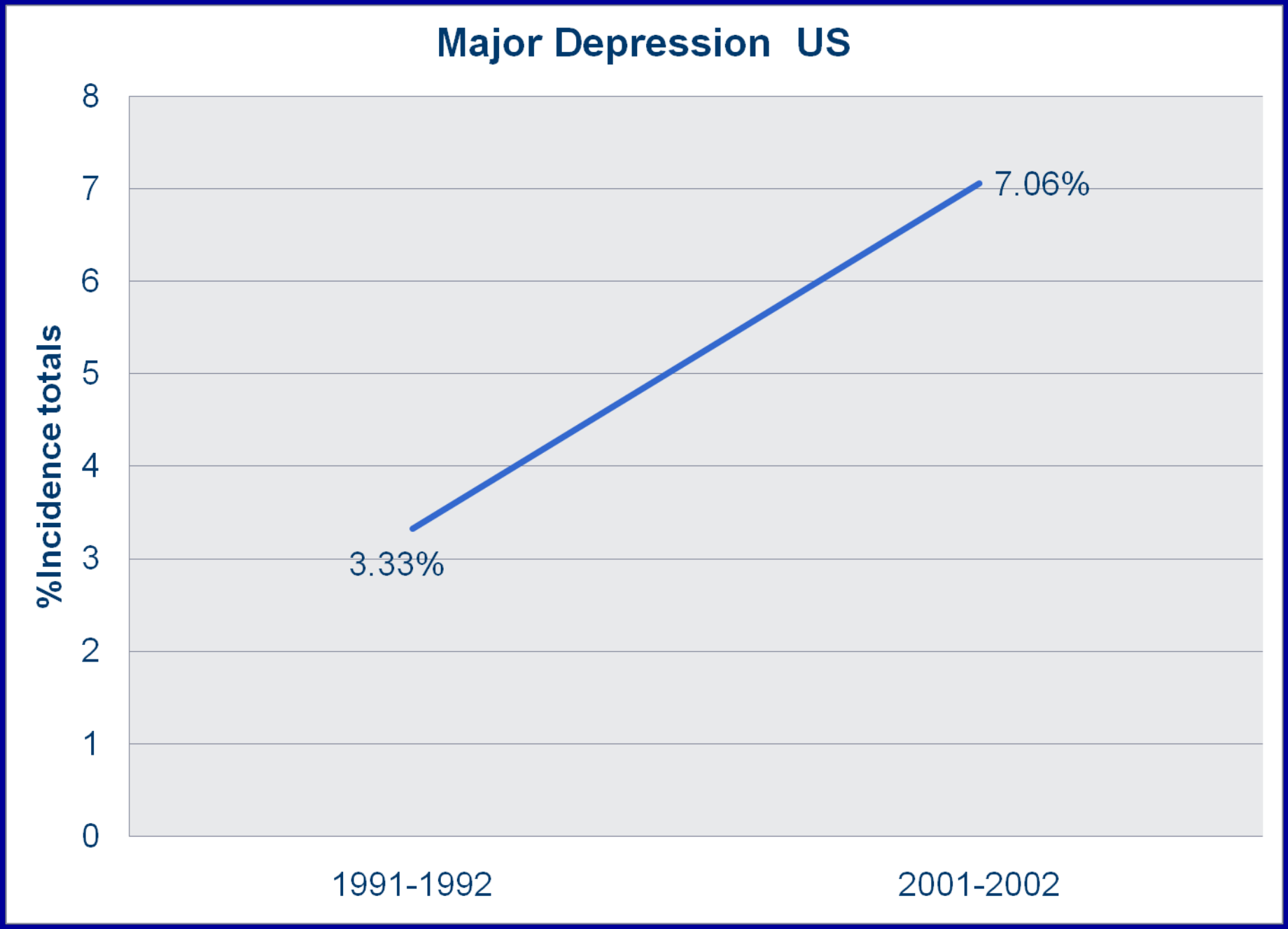
Learning Disabilities ages 3-17

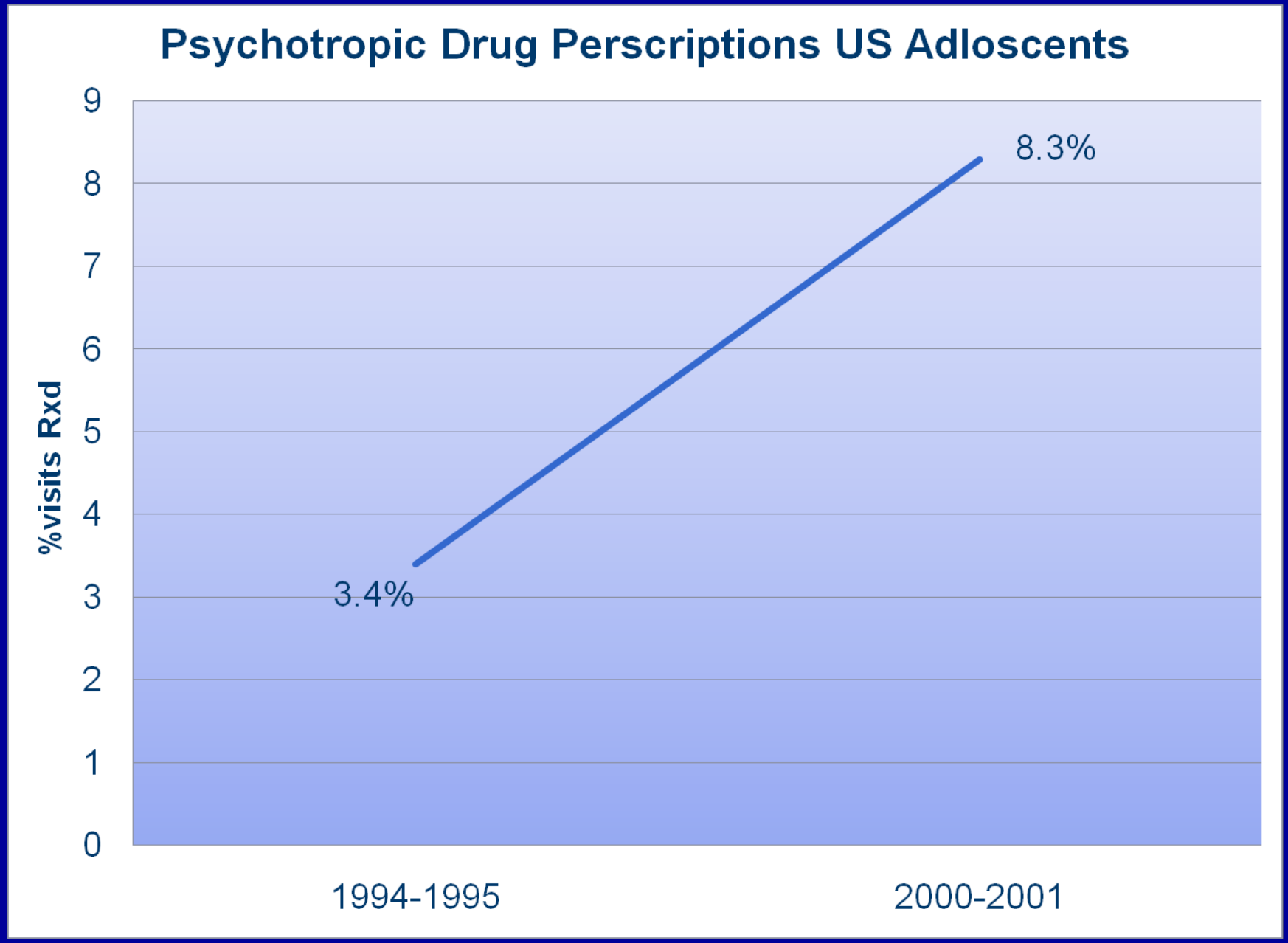
1997-2004 US

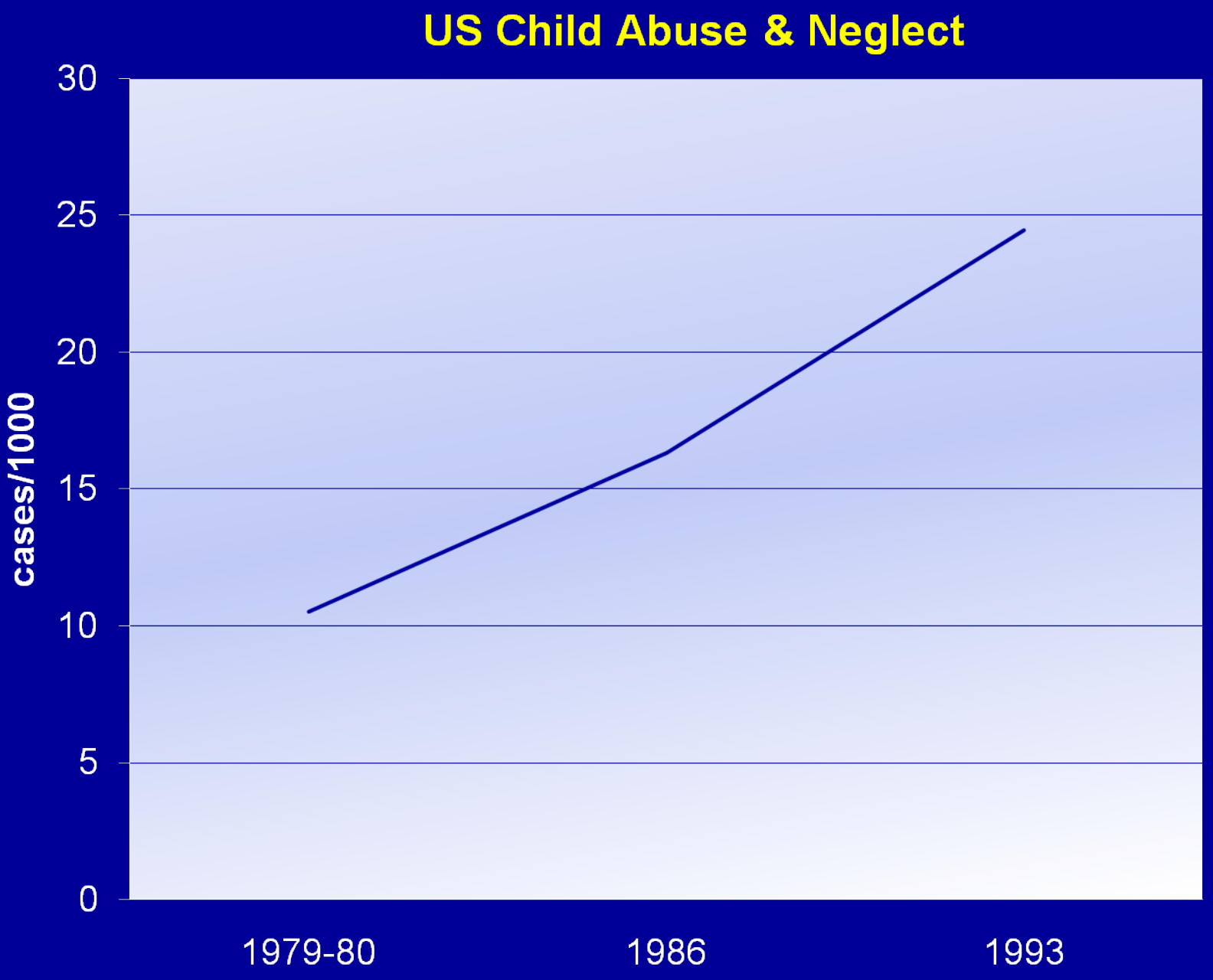


Autism; Fastest Growing Disability

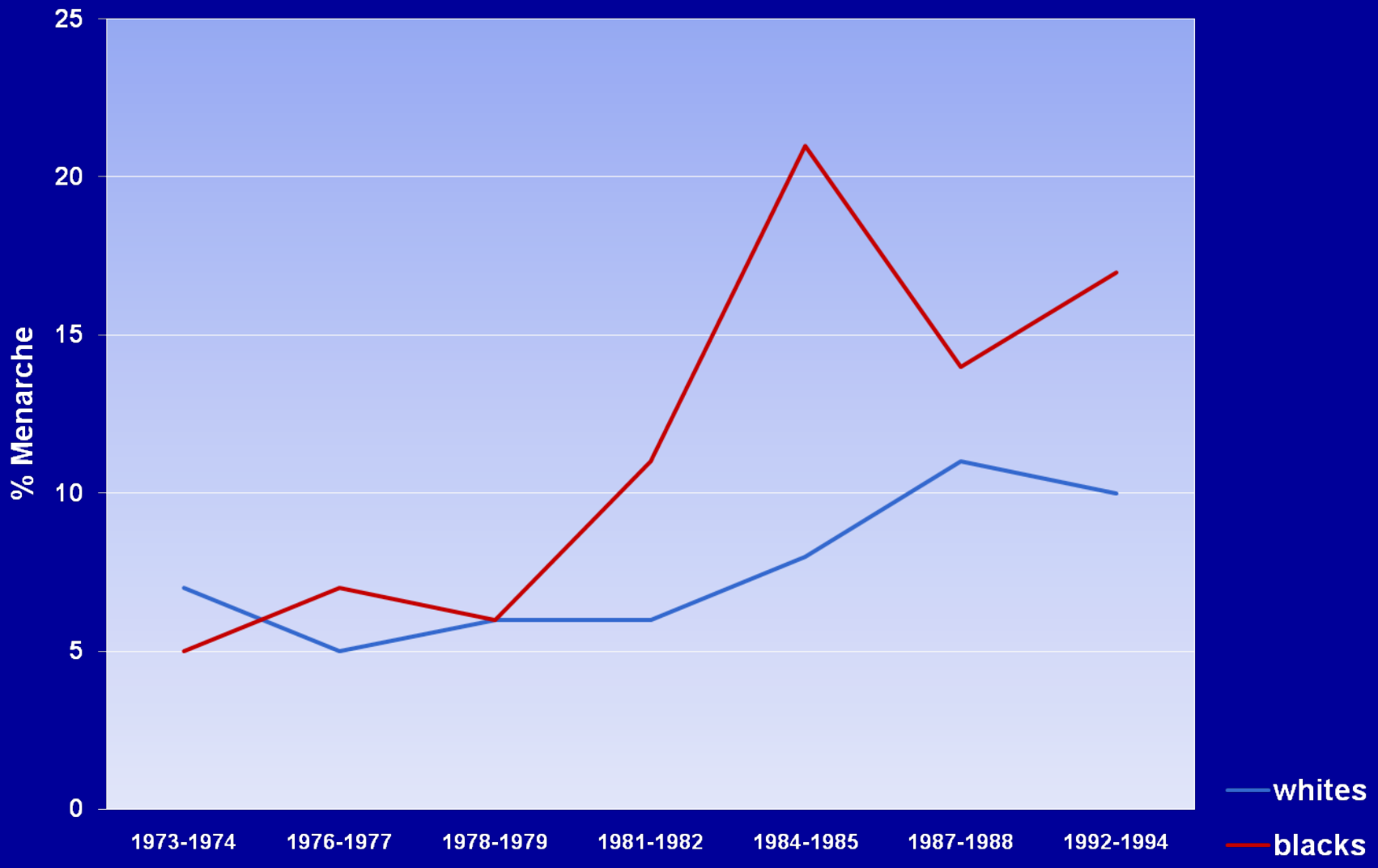



Major Depression US
%Incidence totals
8
7
6
5
4
3
2
1
0
7.06%
3.33%
1991-1992
2001-2002

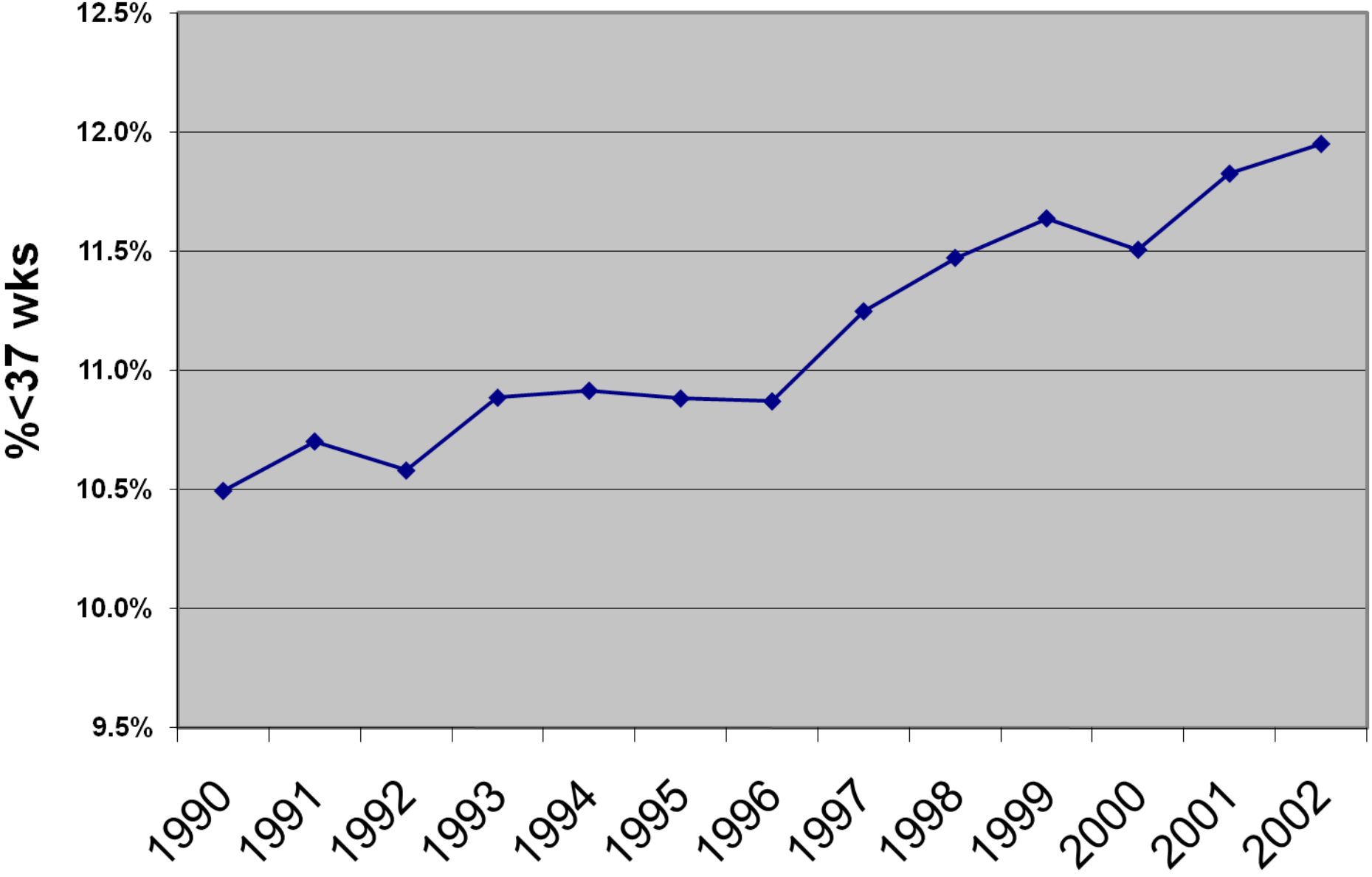

Psychotropic Drug Perscriptions US Adloscents
%visits Rxd
9
8
7
6
5
4
3
2
1
0
8.3%
3.4%
1994-1995
2000-2001


US Child Abuse & Neglect
cases/1000
30
25
20
15
10
5
0
1979-80
1986
1993

Girls with Menarche <11yrs

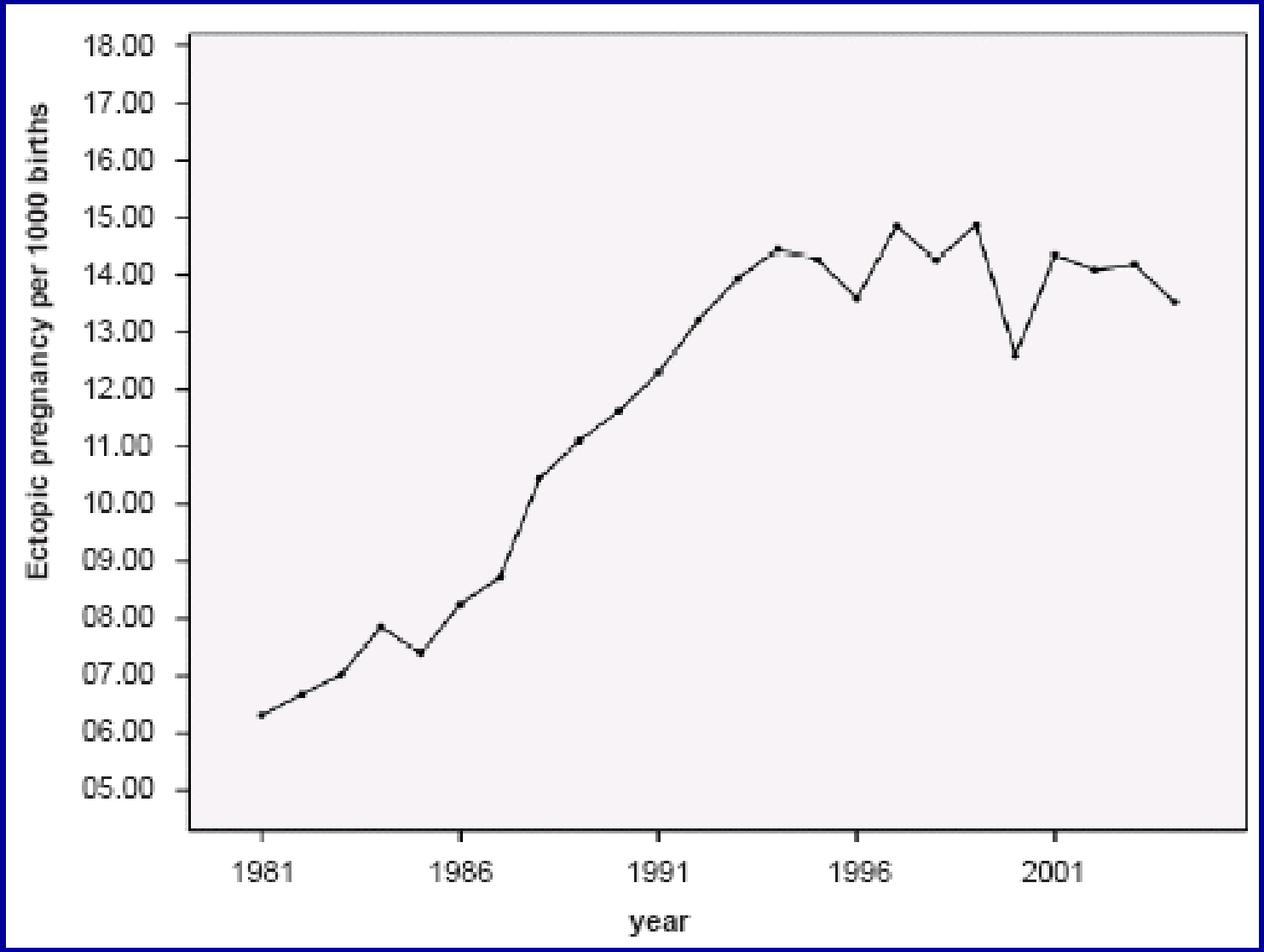


Preterm Birth Rates US 1990-2002



Ectopic Pregnancy Rates

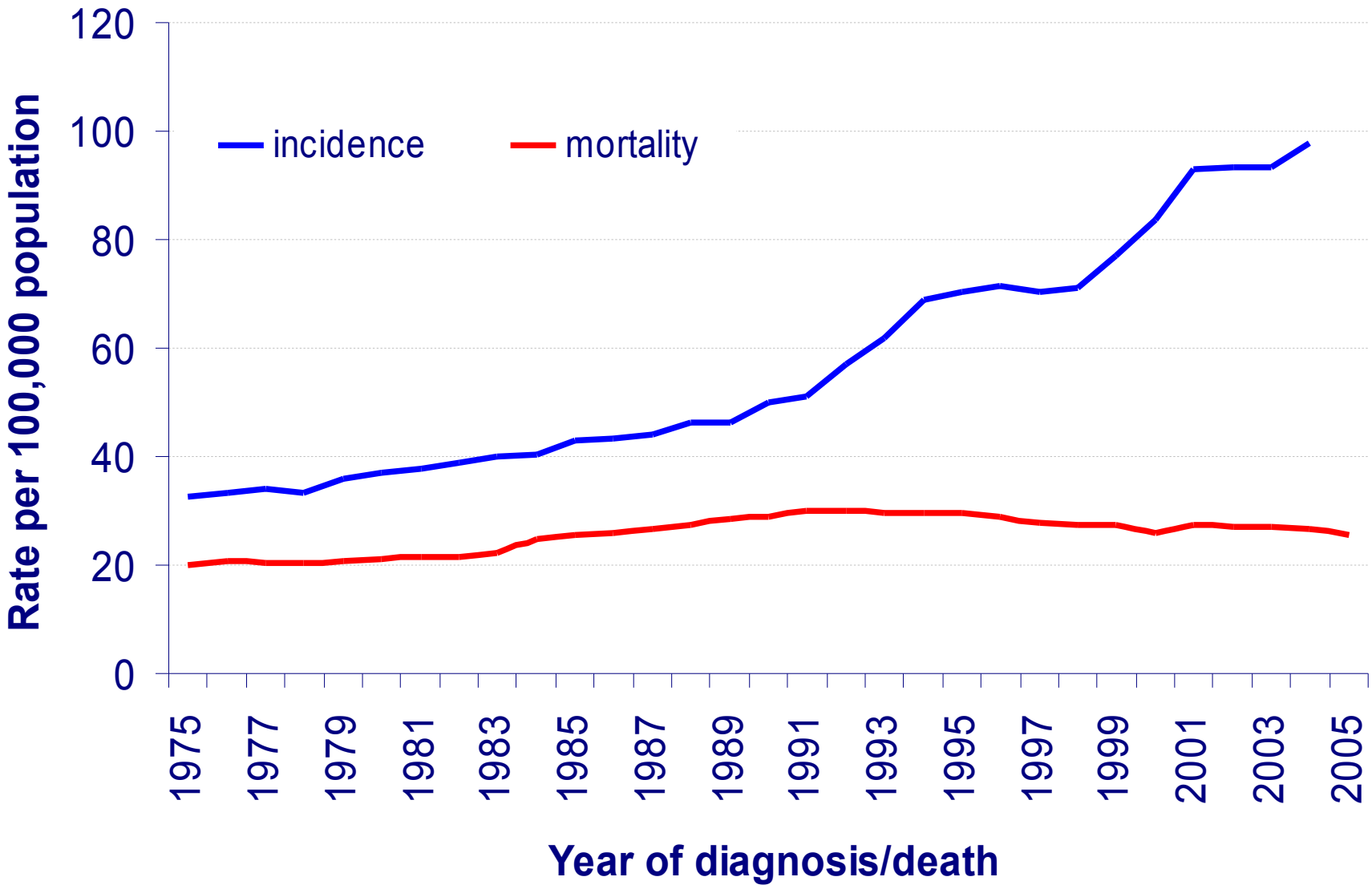
Scottish Perinatal and Infant Mortality and Morbidity Report 2006

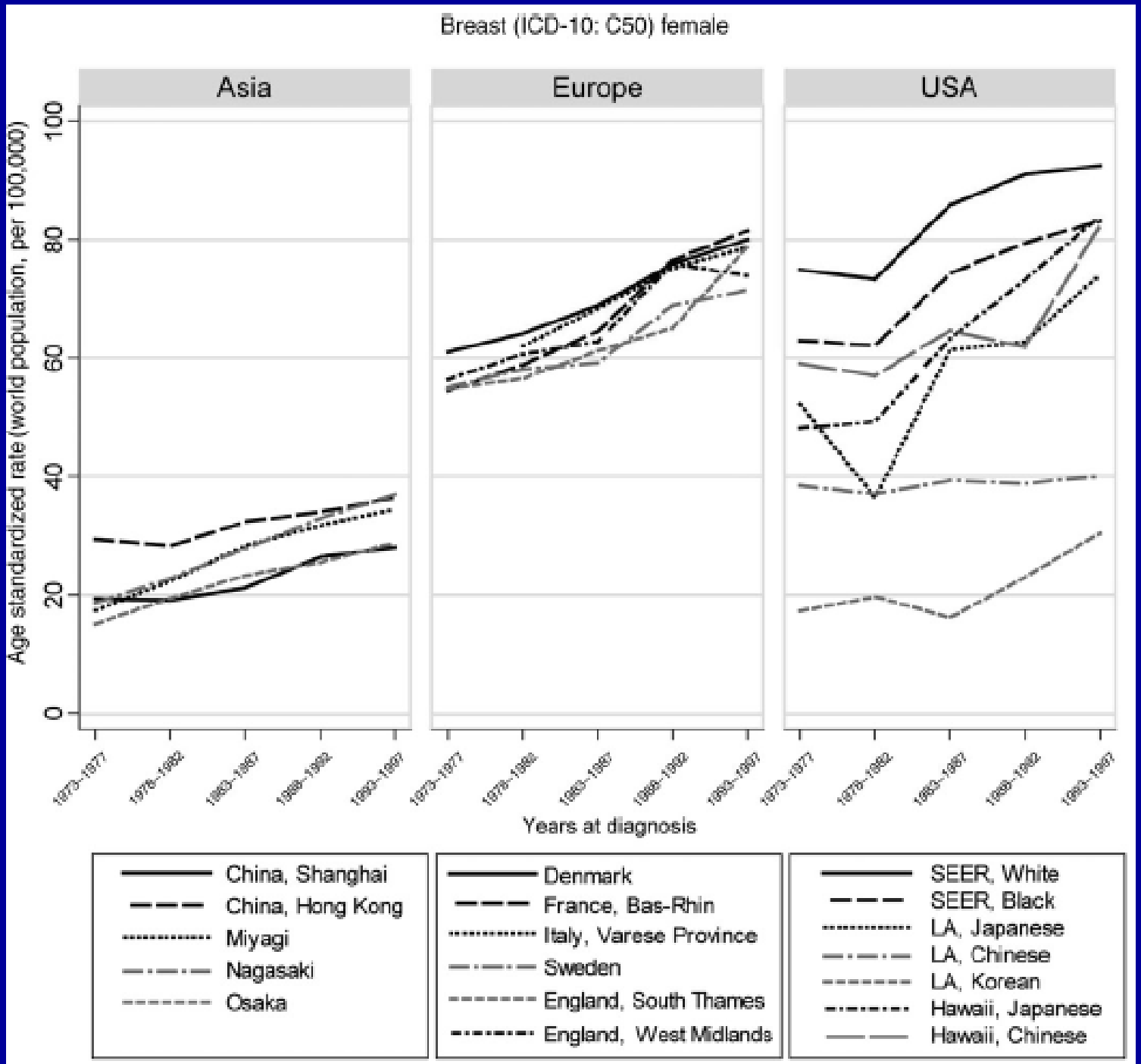


Adult Diseases Also on the Rise

Breast Cancer	**18%**	increase, 1975-2003
Prostate Cancer	**85%**	increase, 1975-2002
Impaired Fertility	**20%**	increase, 1995-2002
Polycystic Ovarian Disease	**5-10%**	of US women of reproductive age
Insulin Resistance	**20%**	of all Americans
Recurrent Miscarriage	**1%**	of all couples trying to conceive

Prostate Cancer European Rates

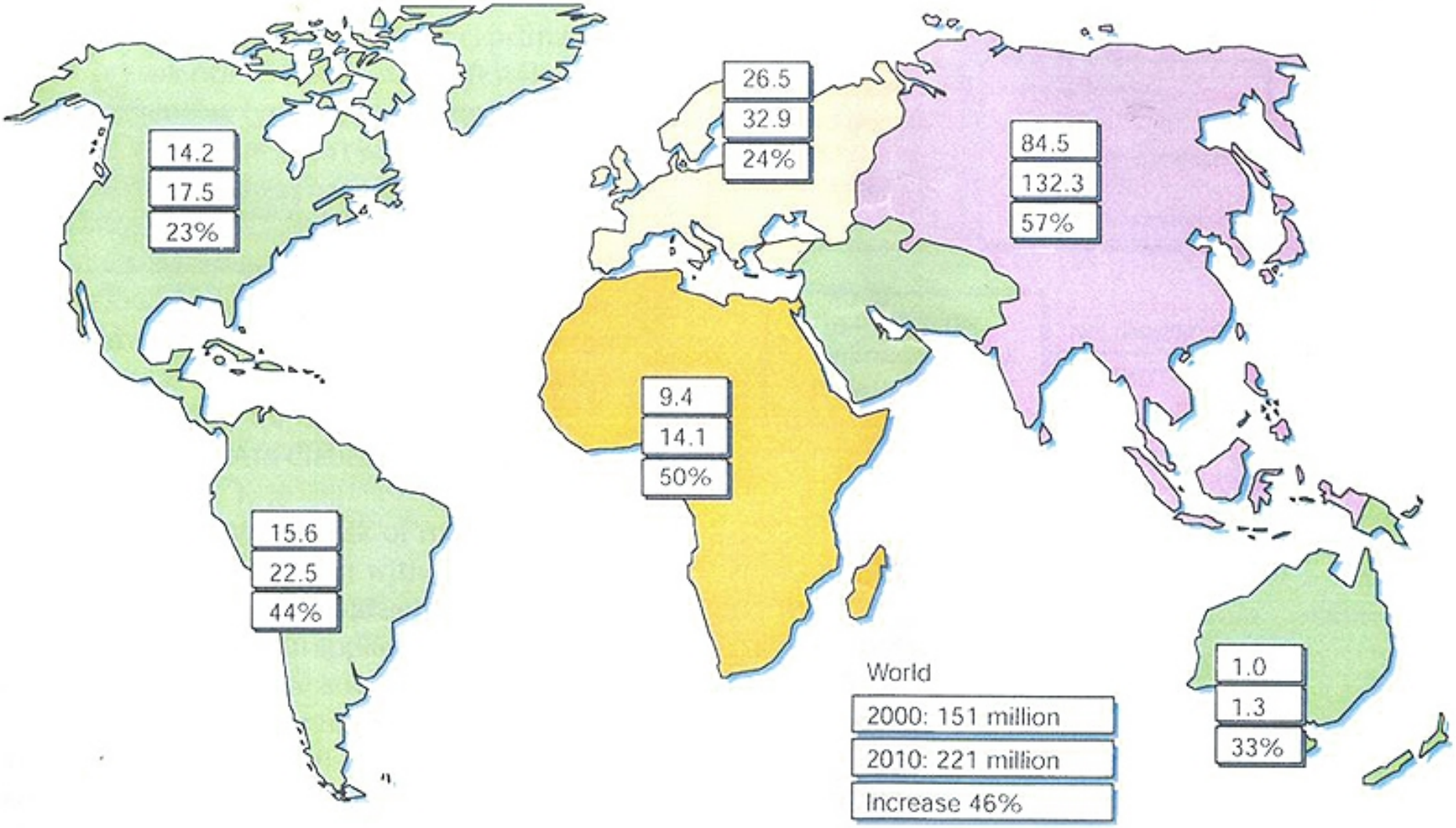




Breast Cancer

Global Increases in Diabetes

Figure 1 Numbers of people with diabetes (in millions) for 2000 and 2010 (top and middle values, respectively), and the percentage increase. Data adapted from ref. 2.



Diabetes type 1; Incidence Increasing

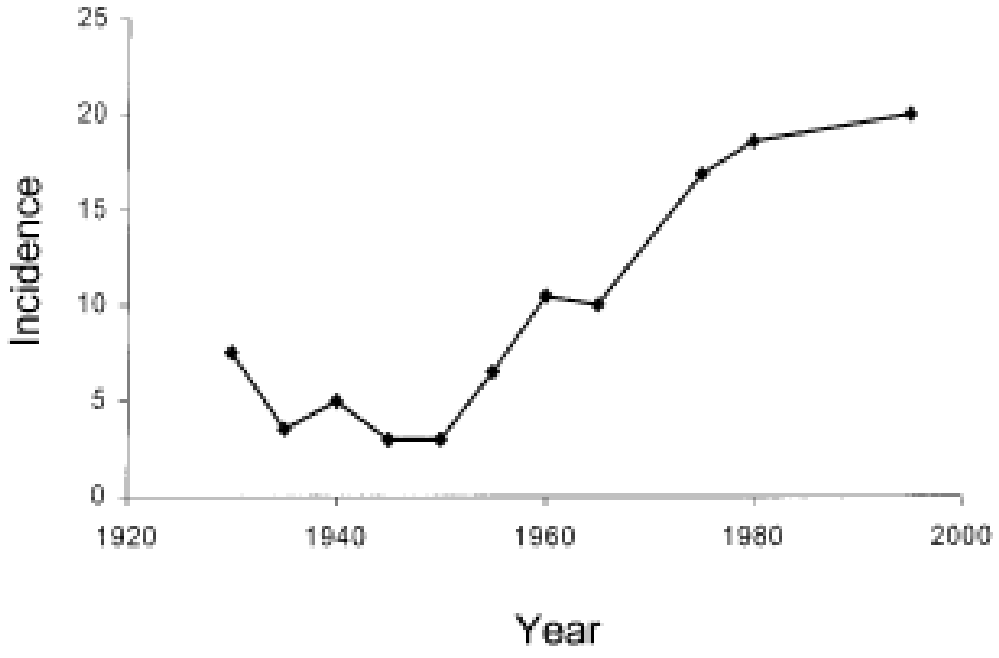


FIG. 2. Incidence of diabetes in children under age 10 years in Norway, 1925–1995. Data from refs. 18,33–36.

Diabetes type 1 ;
Age of Onset Decreasing

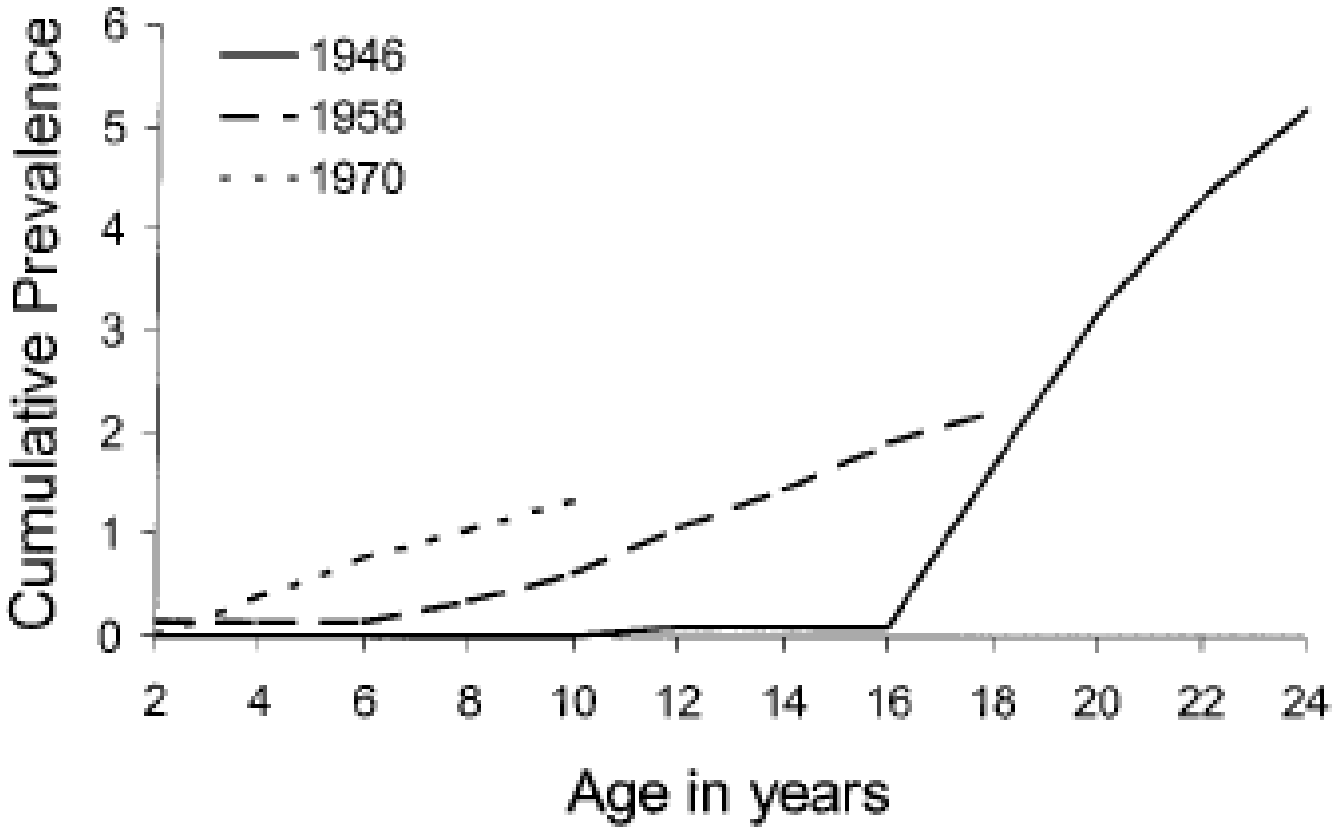


FIG. 3. Cumulative incidence of diabetes from three U.K. birth cohorts. A progressive left shift in age of onset of the disease is shown. Redrawn from data in Kurtz et al. (44).

Increasing Disease Rates

- Improved diagnosis
- Better Reporting
- Environmental Factors

OBGYN Conditions Linked to Environmental Contaminants

Human Reproduction 2006 21(9):2201-2208;

- Bleeding irregularities
- Precocious puberty
- Polycystic Ovary Syndrome (PCOS
- Subfecundity
- Infertility
- Recurrent miscarriage
- Ovarian failure
- Endometriosis
- (Falsetti and Eleftheriou, 1996; Berkson, 2000; Cordain *et al*., 2003; Drbohlav *et al*., 2004; Mlynarcikova *et al*., 2005; Sugiura-Ogasawara *et al*., 2005; Tsutsumi, 2005).) Folia Histochem Cytobiol. 2001;39 Suppl 2:40-3.

A Strong Dose-Response Relation Between Serum Concentrations of Persistent Organic Pollutants and Diabetes

Results from the National Health and Examination Survey 1999–2002

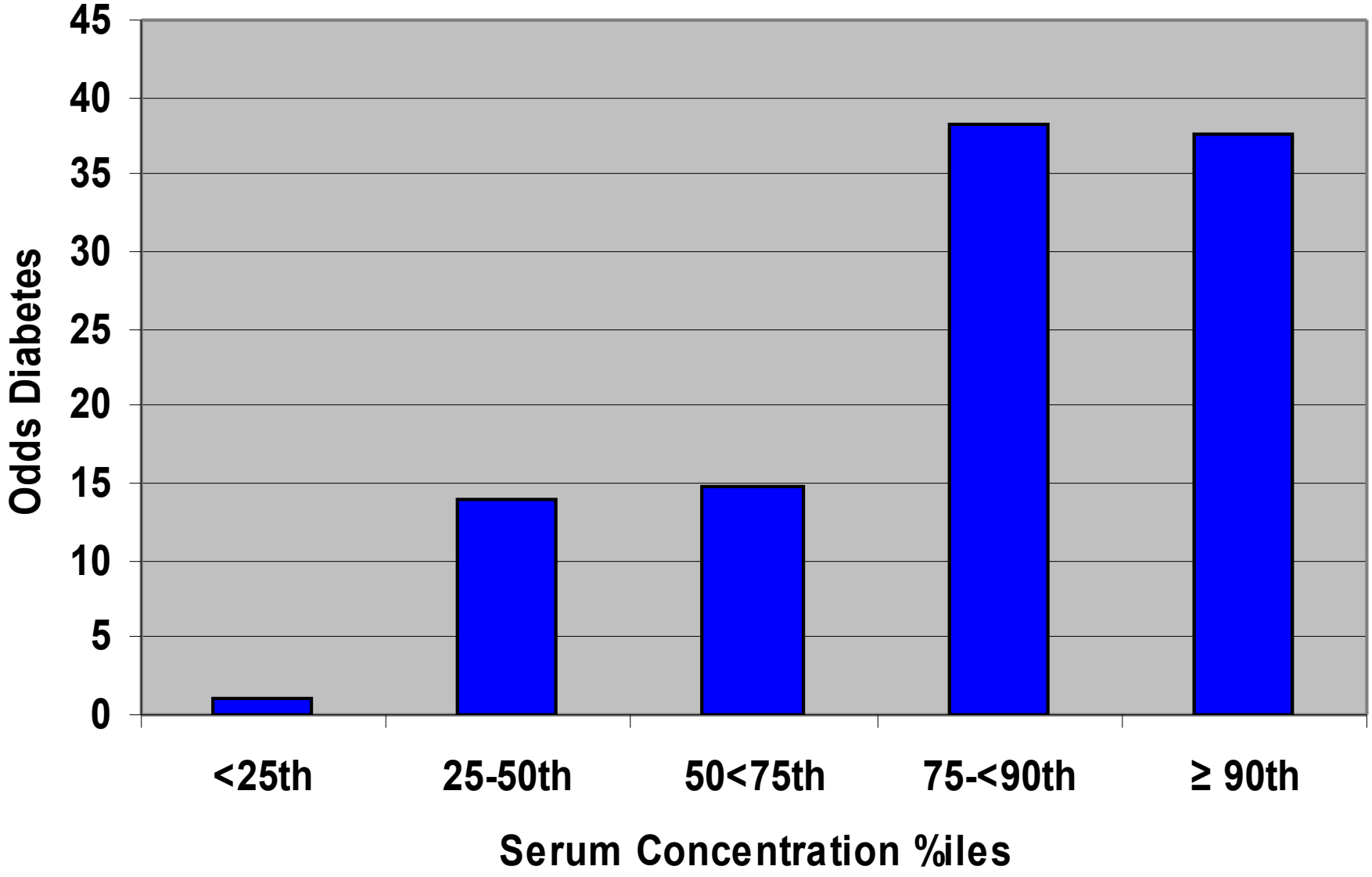
DUK-HEE LEE, MD, PHD1 IN-KYU LEE, MD, PHD 2 KYUNGEUN SONG, MD, PHD 3 MICHAEL STEFFES, MD, PHD 4 WILLIAM TOSCANO, PHD 5 BETH A. BAKER, MD, PHD 5,6 DAVID R. JACOBS, JR., PHD 7,8

Diabetes Care 29:1638–1644, 2006

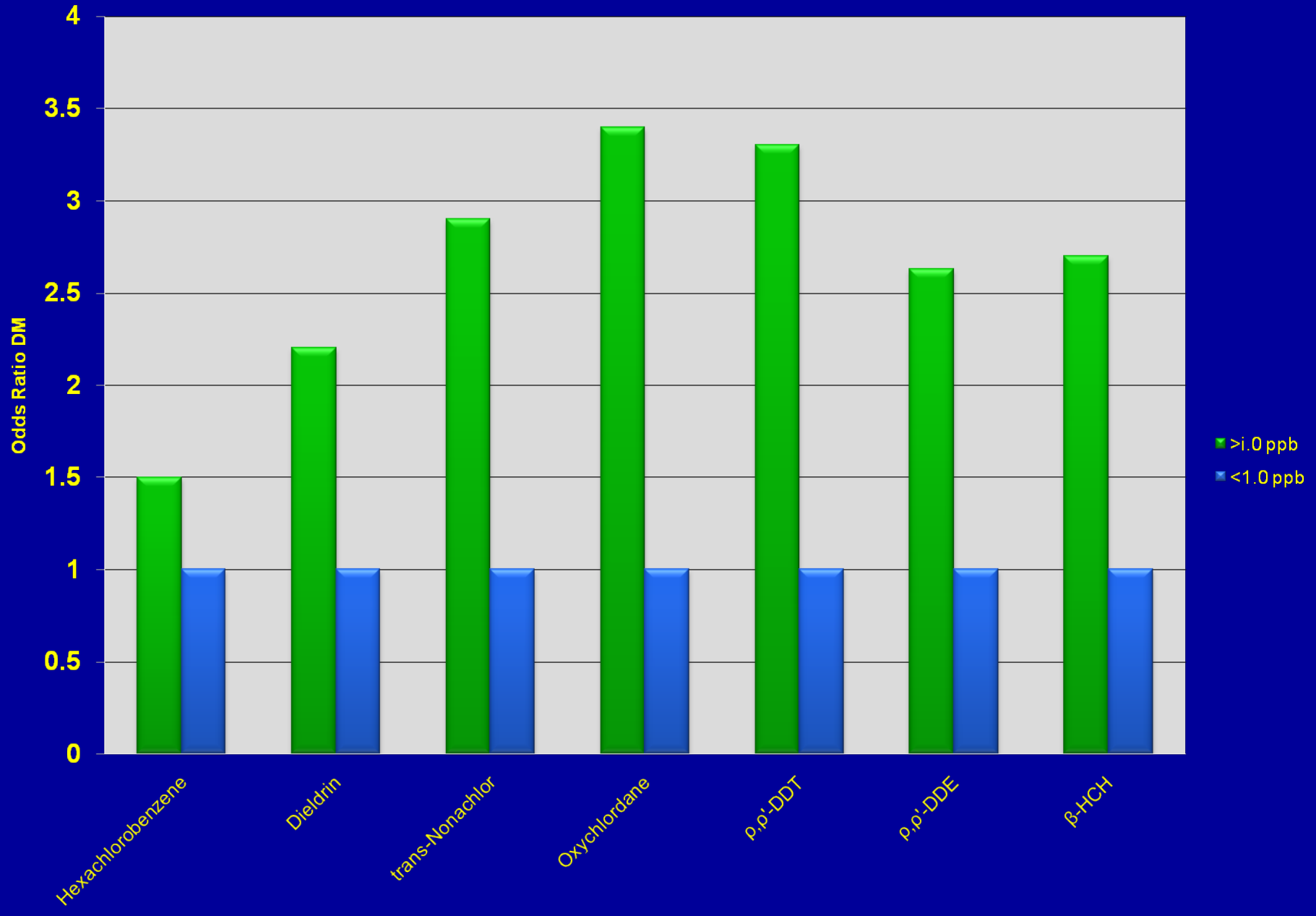
Persistent Organic Pollutants vs Risk of Diabetes

- NHANES 1999-2002
- PCBs, pesticides, dioxins now linked to diabetes
- 100% of US population now has detectable levels

Risk of Diabetes vs Serum Concentration of Organic Pollutants



Diabetes vs Pesticide Levels



Maternal Diabetes

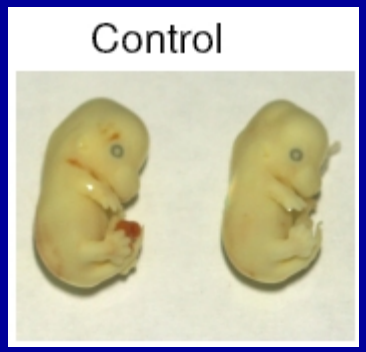
- Increased risk of congenital anomalies
- Increased risk of abnormal fetal growth
- Increased risk of fetal demise
- Greater risk of immature lungs, longer stay in NICU, more likely to have complications of labor and delivery.

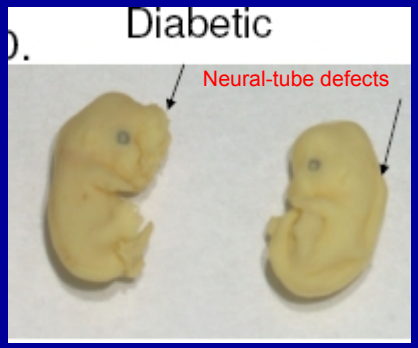
One-cell zygote transfer from diabetic to non-diabetic mouse results in congenital malformations and growth retardation in offspring

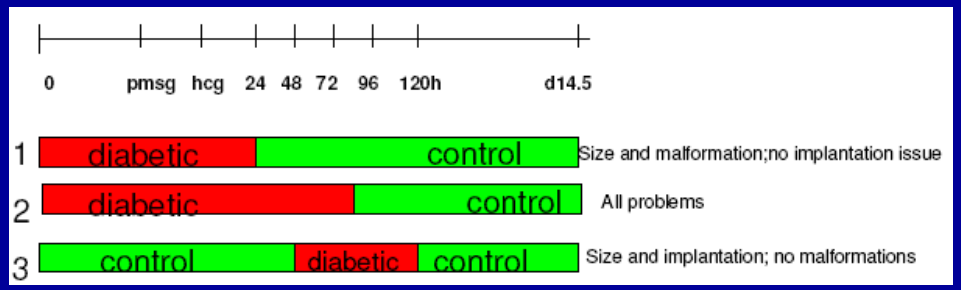
Amanda Wyman, Anil Pinto, Rachael Sheridan and Kelle H. Moley

1Washington University, School of Medicine, Department of Obstetrics and Gynecology, St. Louis, MO; 2Department of Obstetrics and Gynecology. Baylor University Medical Center, Dallas, TX.

Endocrinology. November 26, 2007







Preovulation -24 hour, 1-cell zygote; sufficient exposure to cause malformations even when fetus is removed from diabetic mother's uterus and placed in non DM.

PCBs and Endometriosis

Rier,Turner,Martin,Morris,Lucier,Clark

TOXICOLOGICAL SCIENCES **59, 147–159 (2001)**

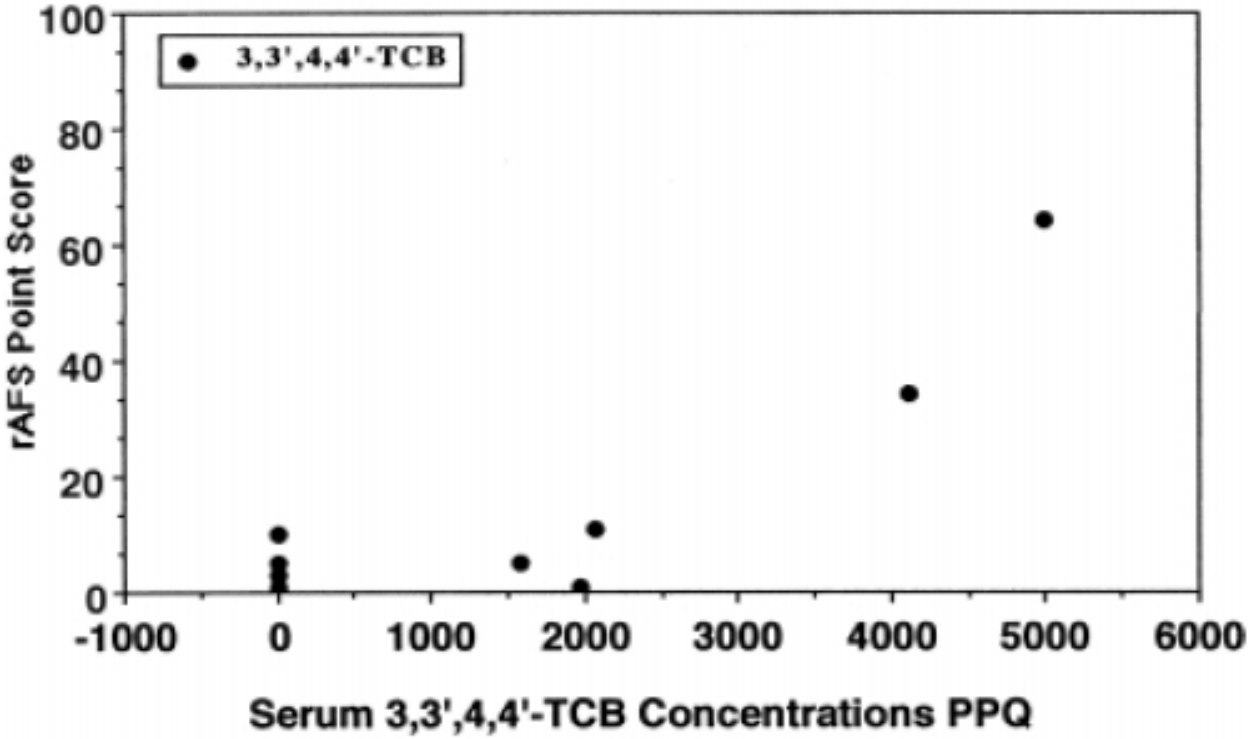
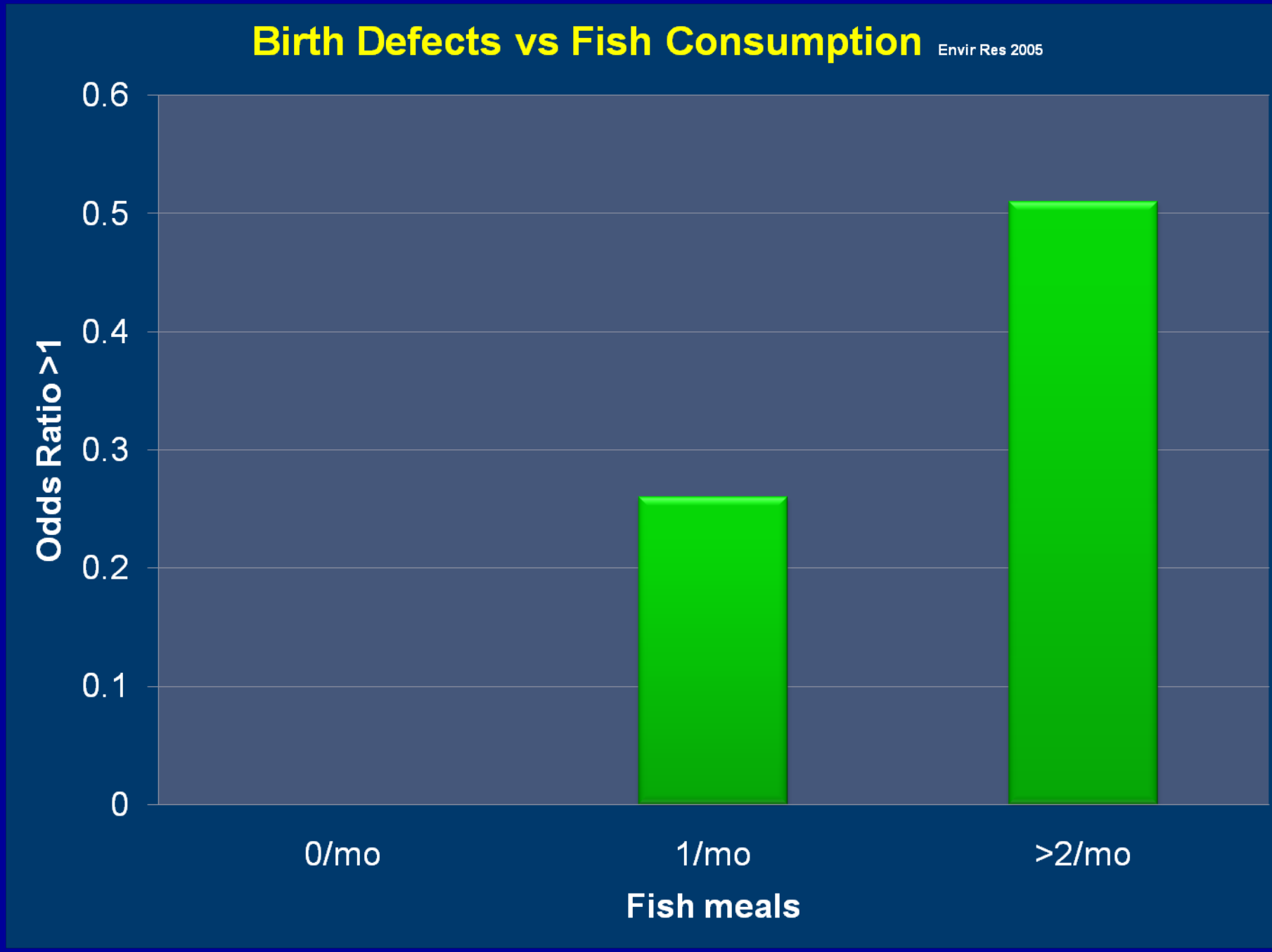
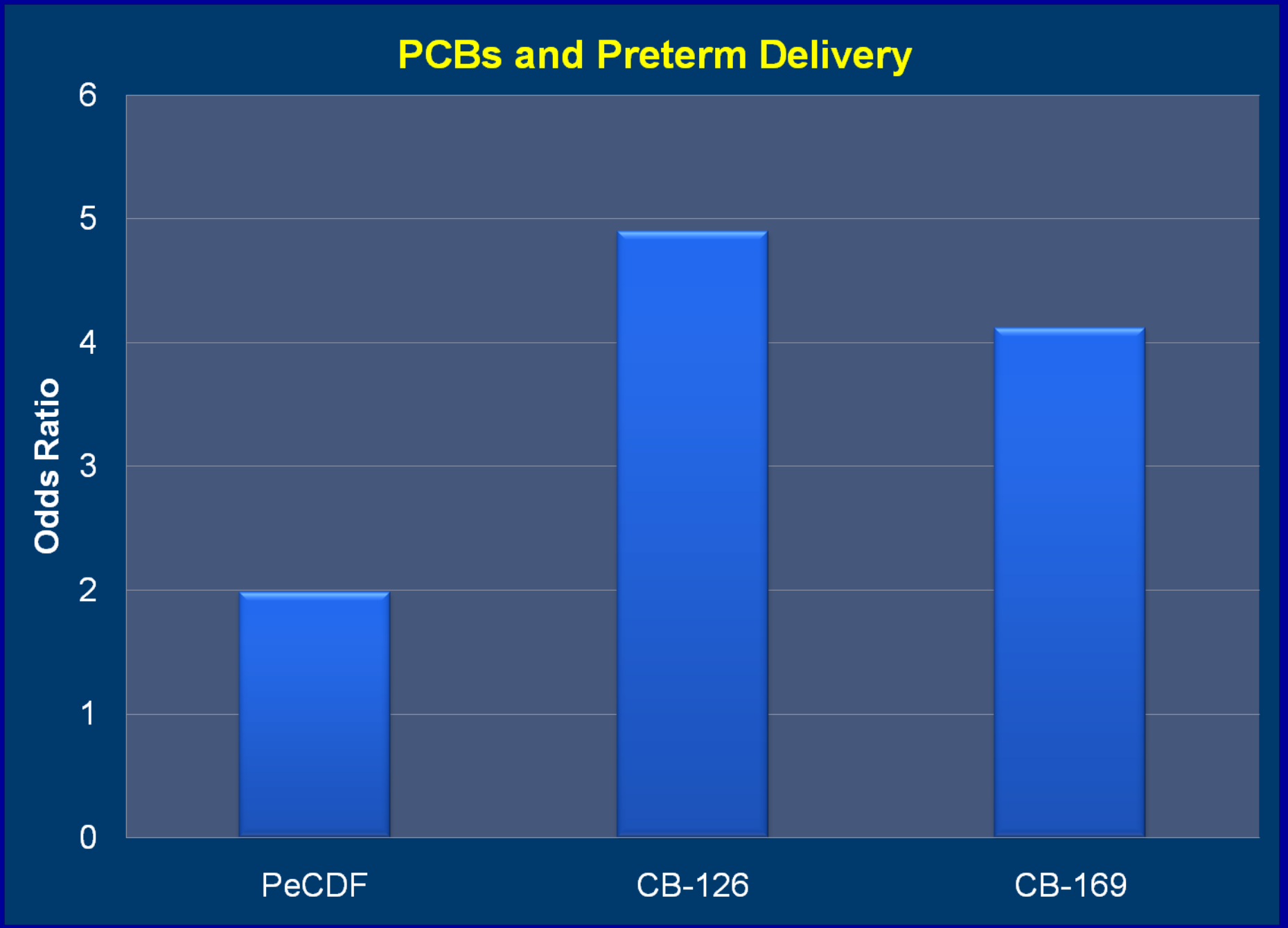


FIG. 2. Serum concentrations of 3,3′,4,4′-TCB versus severity of endometriosis (rAFS point score). The relationship between the degree of endometriosis and serum concentration of 3,3′,4,4′-TCB was evaluated using Spearman's rank correlation coefficient; $n = 15$; $p = 0.02$.


Birth Defects vs Fish Consumption
Envir Res 2005
0.6
0.5
0.4
0.3
0.2
0.1
0
Odds Ratio >1
0/mo
1/mo
>2/mo
Fish meals


PCBs and Preterm Delivery
Odds Ratio
6
5
4
3
2
1
0
PeCDF
CB-126
CB-169

16 Pesticides Cause Cancer

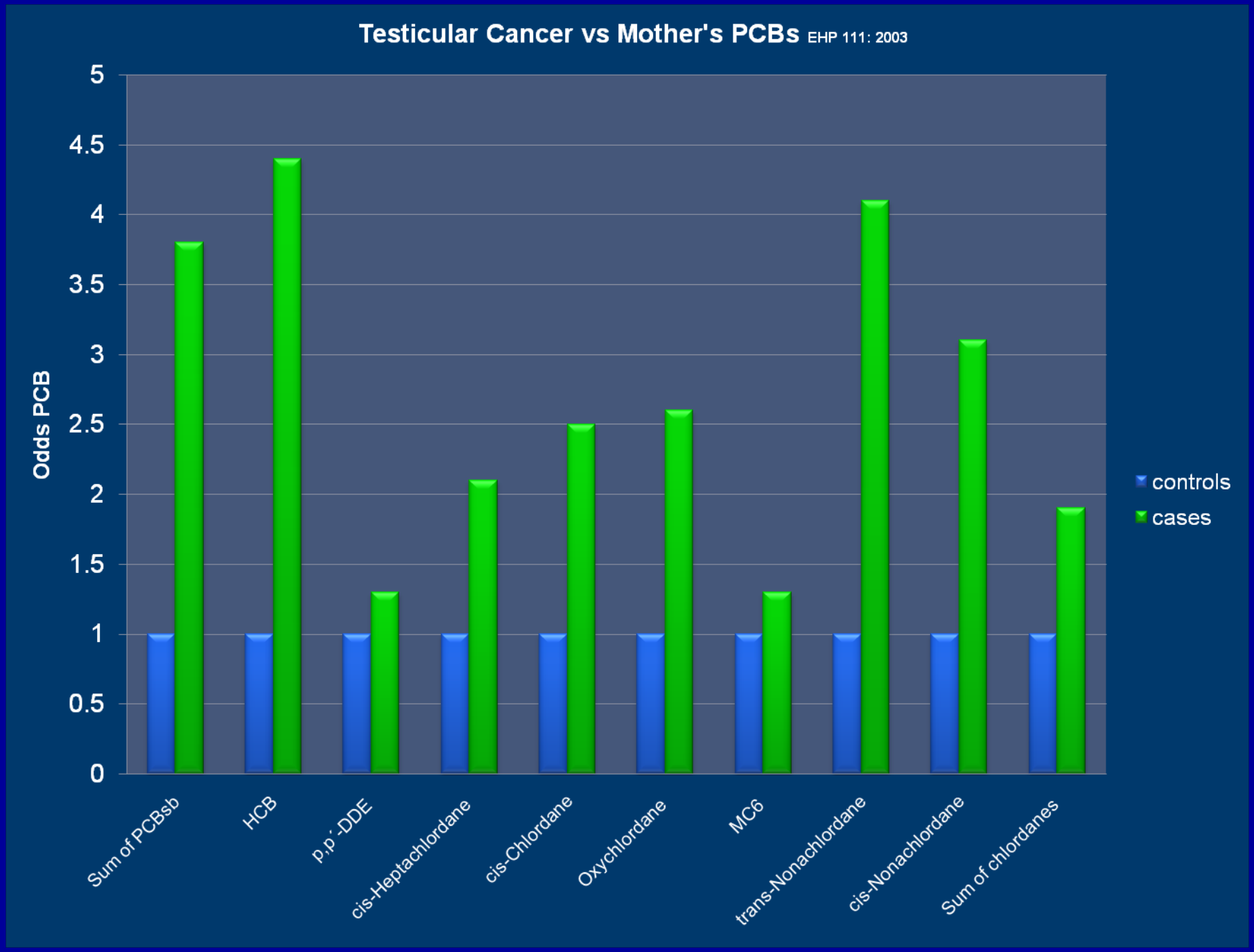
(Agricultural Health Study, National Cancer Institute ,1993-2010)

Dr. Michael Alavanja, captain, NSPHS, Senior Investigator, Division Cancer, Epidemiology,and Genetics,

- Chlorpyrifos
- Coumaphos
- Permethrin
- Diazinon
- Cabofuran
- Pendimethalin
- Alachlor
- Butylate
- Phorate
- Carbaryl
- Paraquat
- Trifluralin
- Lindane
- Metolachlor
- Dicamba
- Fonofos

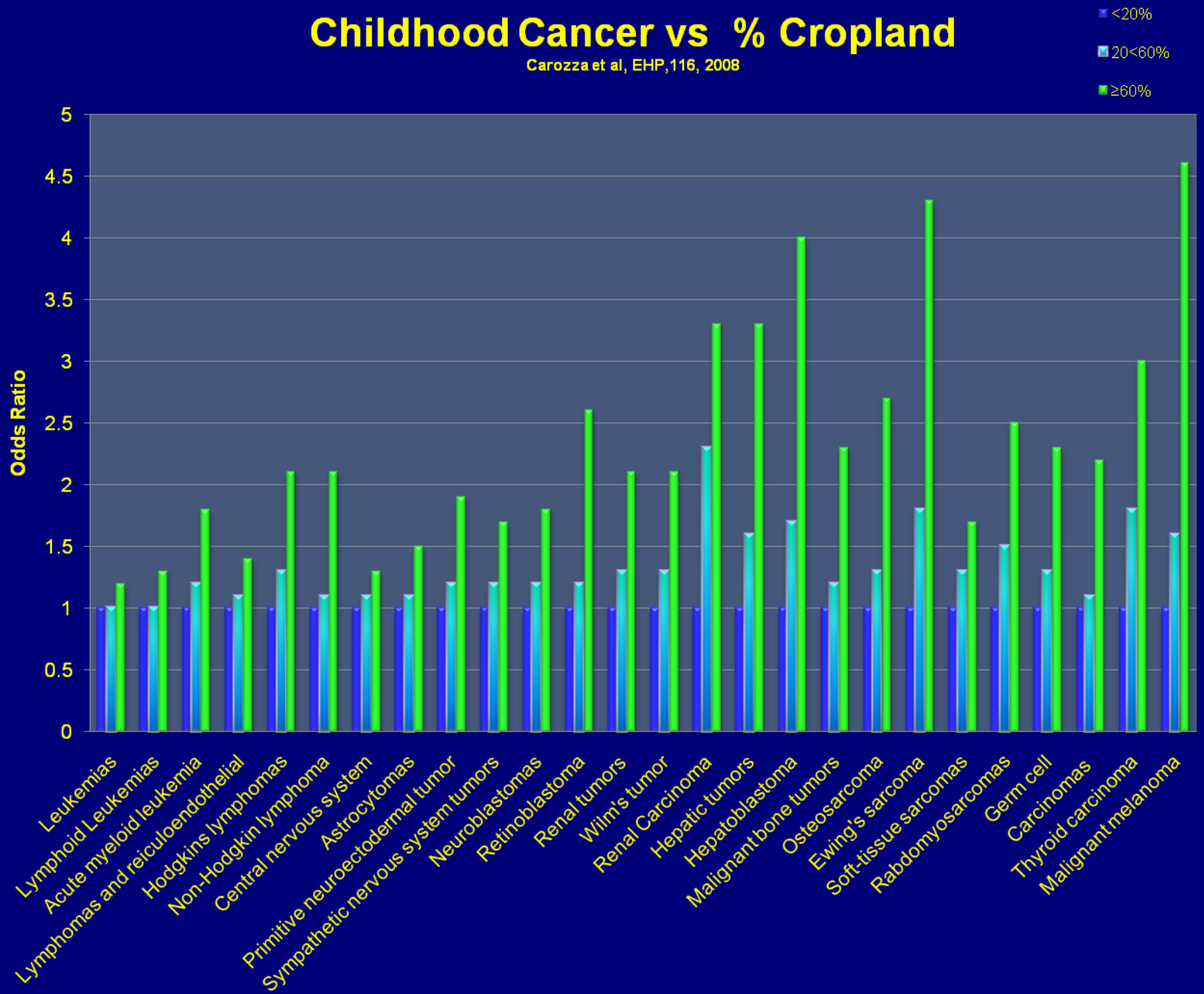
Testicular Cancer
PCBs in the Womb

- **Mothers with higher organochlorine levels are significantly more likely to have given birth to sons who develop testicular cancer**

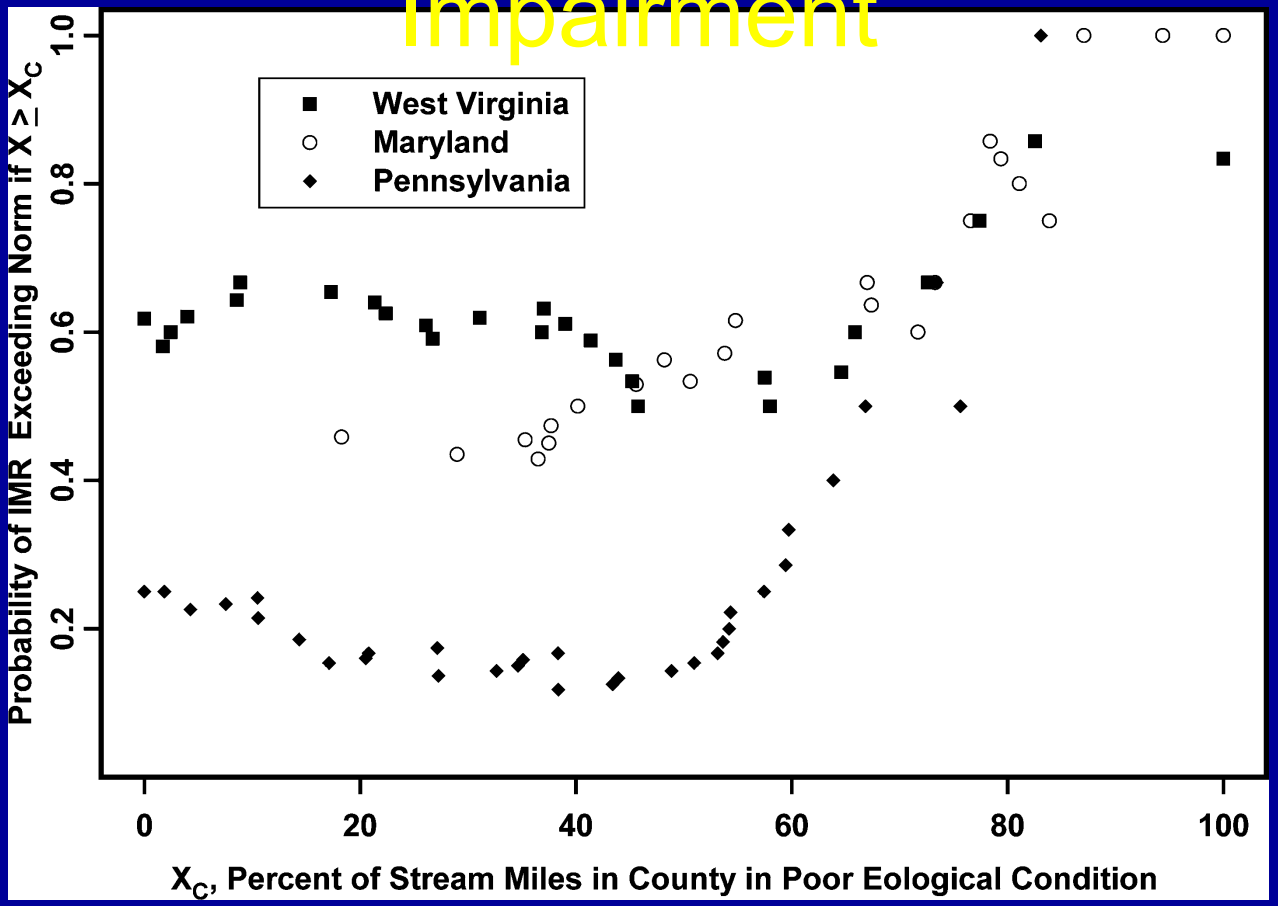

Testicular Cancer vs Mother's PCBs EHP 111: 2003
Odds PCB
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Sum of PCBsb
HCB
p,p´-DDE
cis-Heptachlordane
cis-Chlordane
Oxychlordane
MC6
trans-Nonachlordane
cis-Nonachlordane
Sum of chlordanes
controls
cases

Childhood Cancer vs % Cropland

Carozza et al, EHP,116, 2008



Infant Mortality vs Stream Ecological Impairment

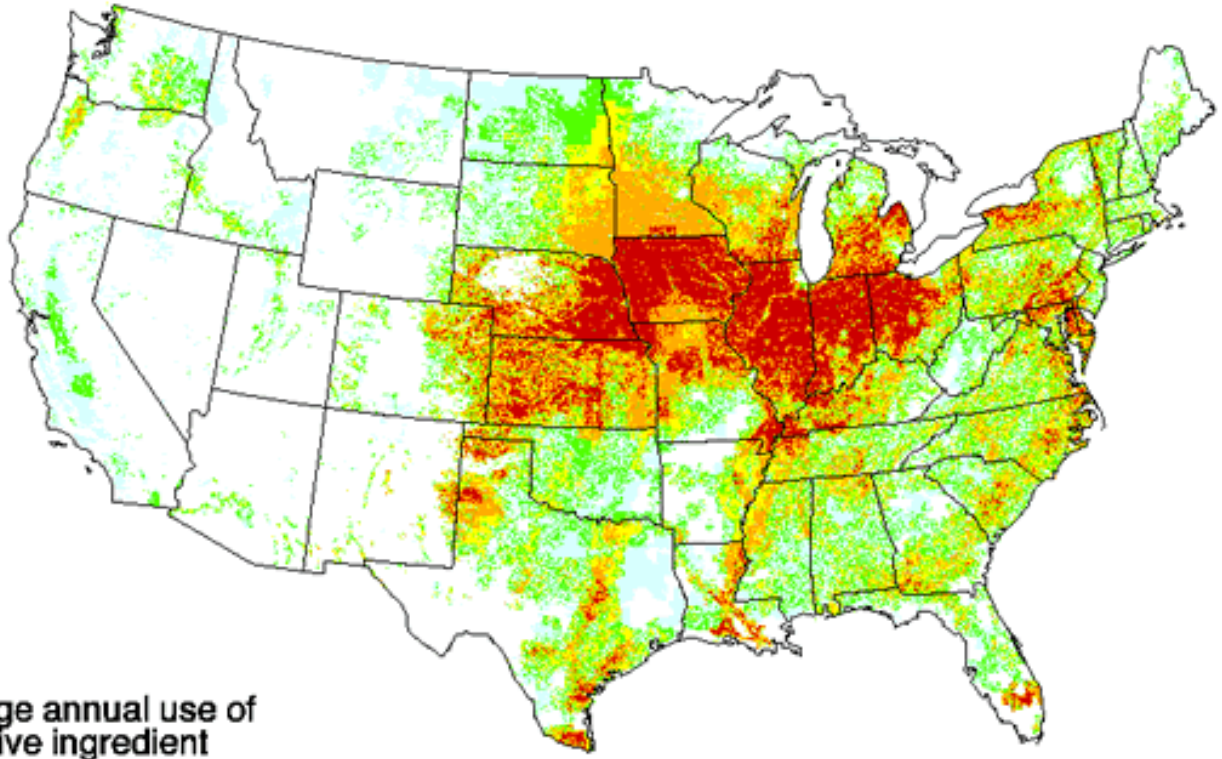


John F. Paul, Michael E. McDonald, and Steven F. Hedtke
National Health and Environmental Effects Research Laboratory,
U.S. Environmental Protection Agency, Research Triangle Park, NC, USA

Human and Ecological Risk Assessment, 14: 728–741, 2008

ATRAZINE - herbicide

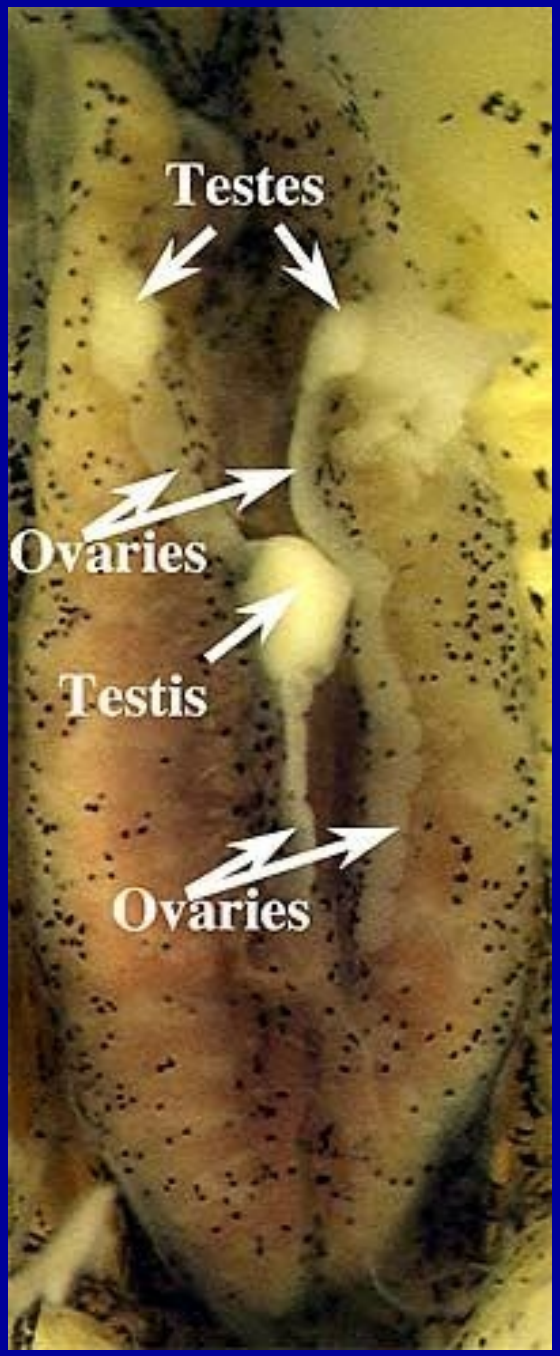
1997 estimated annual agricultural use



Average annual use of active ingredient
(pounds per square mile of agricultural land in county)

- no estimated use
- 0.001 to 0.358
- 0.359 to 2.151
- 2.152 to 9.855
- 9.856 to 32.77
- >= 32.771

Crops	Total pounds applied	Percent national use
corn	62, 381, 038	84. 00
sorghum	6, 750, 038	9. 09
summer fallow	2, 539, 169	3. 42
sugarcane	2, 203, 421	2. 97
sweet corn	340, 452	0. 46
sod harvested	30, 214	0. 04
other hay	13, 224	0. 02
seed crops	5, 833	0. 01



Abnormal gonads in male Xenopus frogs, from exposure to atrazine.

The frog has become a hermaphrodite, with both male (testes) and female (ovaries) sex organs

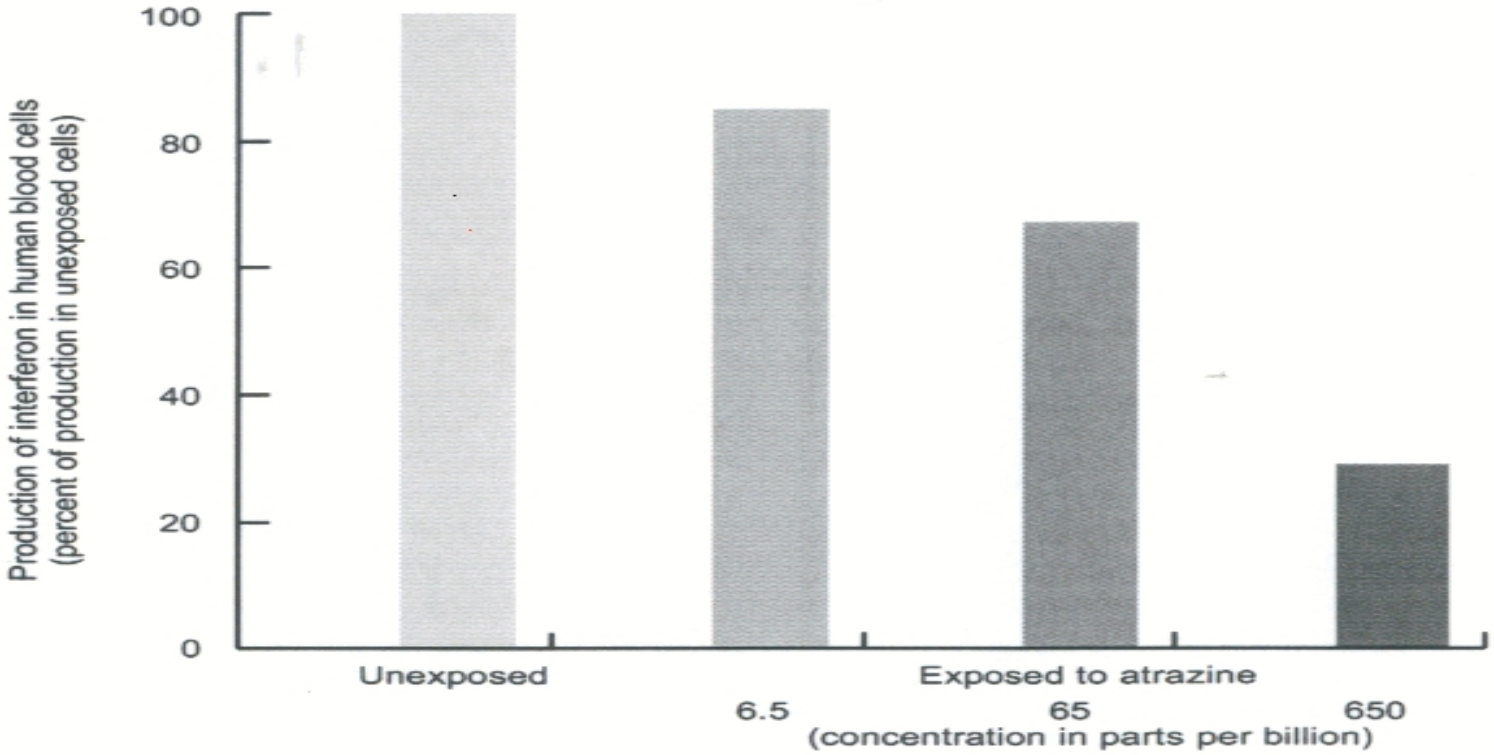
Tyrone Hayes/UC Berkeley, courtesy Proceedings of the National Academy of Sciences

Atrazine Effects

- Hermaphrodite males 0.1ppb
- EPA drinking water safe level is 3ppb
- U shaped curve (greater effects at lower and higher doses, less in middle doses)
- Immune dysfunction
- Aromatase induction (fetal male testosterone converted to estrogen)

Atrazine Toxicity- Immune Function

Figure 2
Atrazine Reduces the Activity of the Immune System



Source: Hooghe, R.J., S. Devos, and E.L. Hooghe-Peters. 2000. Effects of selected herbicides on cytokine production in vitro. *Life Sci.* 66: 2519-2525.

Atrazine reduces the production of interferon by blood cells. Interferon is a protein used by the immune system to fight viral infections.

Flavo-bacterial meningitis prevents this leopard frog from lifting its head. The disease is caused by a normally benign bacteria that takes advantage of the impaired immune systems of pesticide-exposed frogs. (Photos by Tyrone Hayes/UC Berkeley)

Atrazine-Mixtures and Metabolites

- N-nitroso atrazine no EPA guidelines potent mitogen
- Most contaminated streams and reservoirs contain mixtures of atrazine and other pesticides
- No EPA guidelines for mixtures

Pesticide Mixtures, Endocrine Disruption, and Amphibian Declines: Are We Underestimating the Impact?

Tyrone B. Hayes, Paola Case, Sarah Chui, Duc Chung, Cathryn Haeffele, Kelly Haston, Melissa Lee, Vien Phoung Mai, Youssra Marjuoa, John Parker, and Mable Tsui

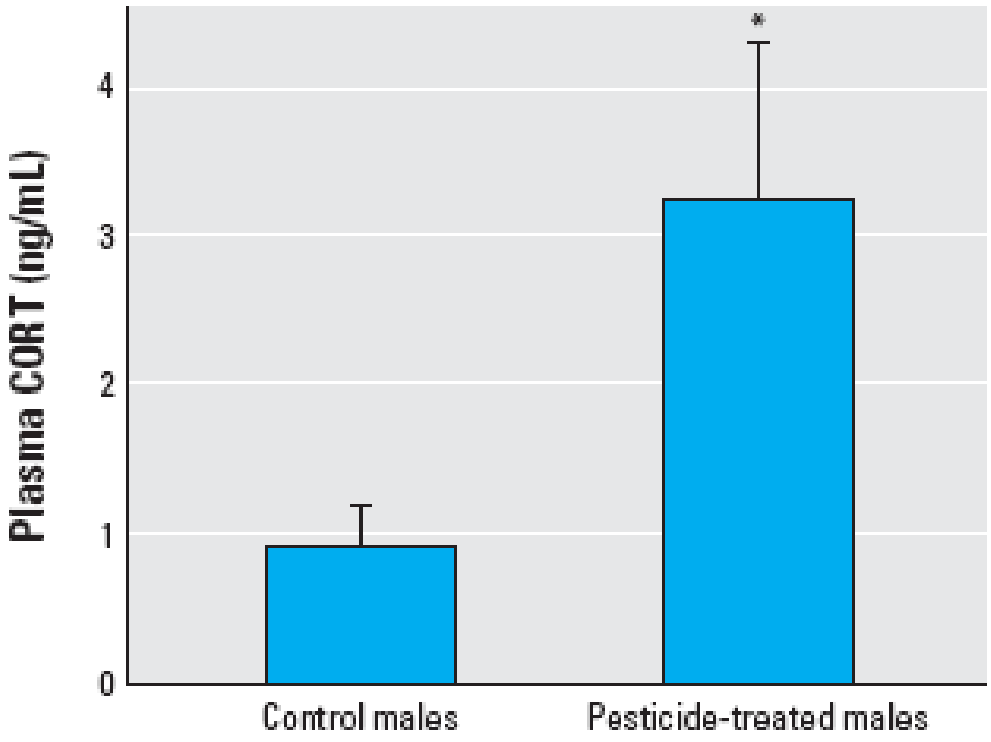
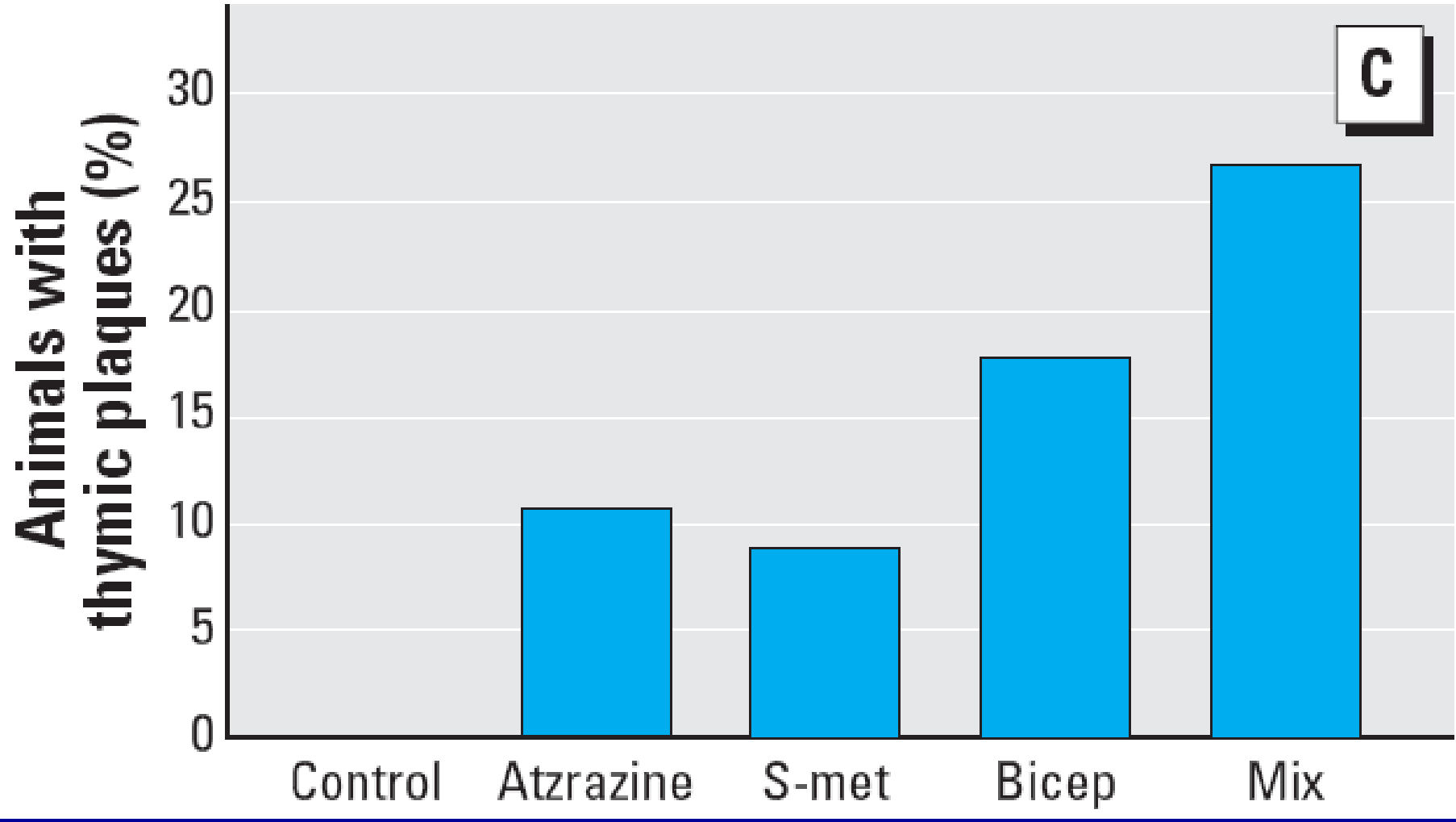


Figure 10. Effect of the pesticide mixture on plasma corticosterone levels in adult male African clawed frogs (*X. laevis*). Error bars show SEM.
*Statistical significance ($p < 0.05$).

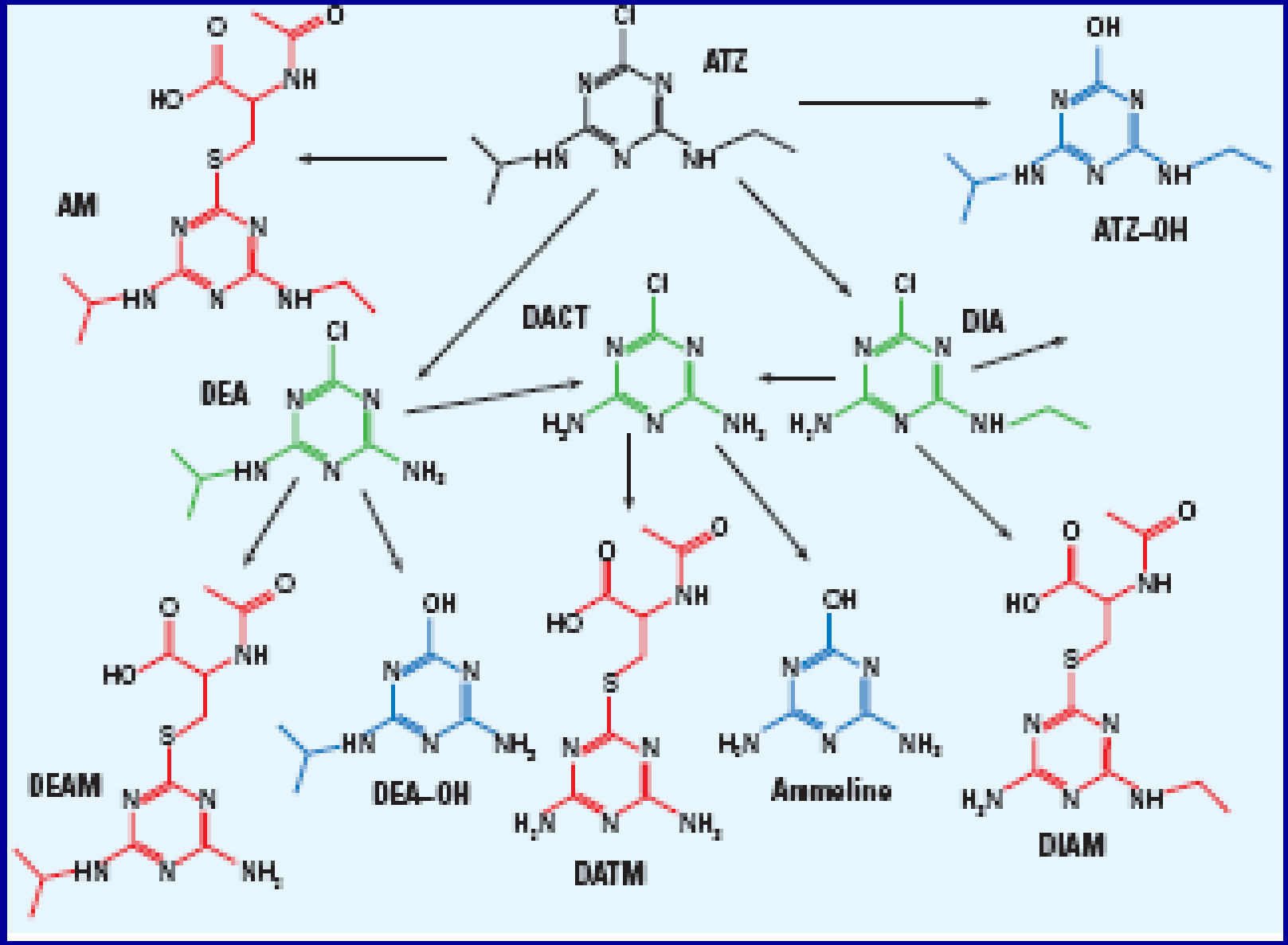
The frequency of animals with detectable damage to the thymus.



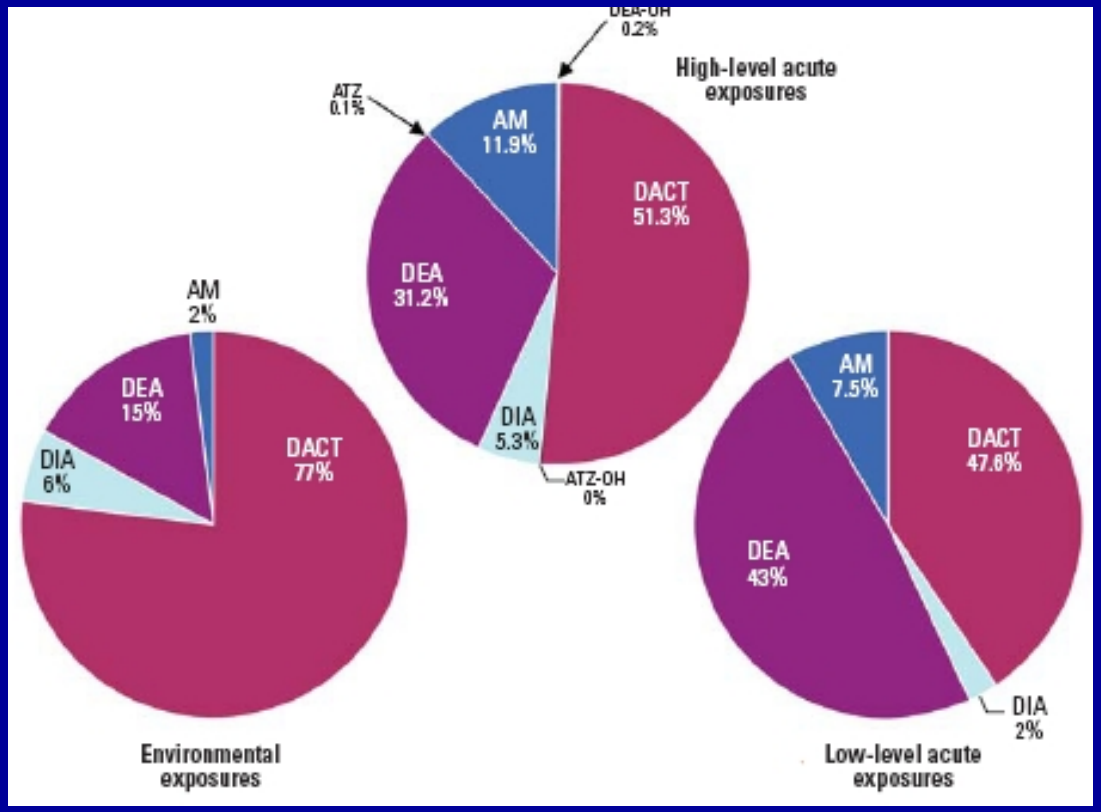
OOPS! CDC Can't Find Atrazine in US population

- Atrazine is most applied pesticide in US
- In the Centers for Disease Control and Prevention (CDC) *National Report on Human Exposure to Environmental Chemicals* (CDC 2001, 2003, 2005), AM, the only ATZ metabolite measured, was typically detected in < 5% of participants
- Multiple metabolites must be measured to accurately assess exposure to ATZ.

Atrazine : At least one metabolite in All of Us



EHP Oct. 2007. "**We have likely been underestimating population-based exposures by measuring only one urinary ATZ metabolite "**

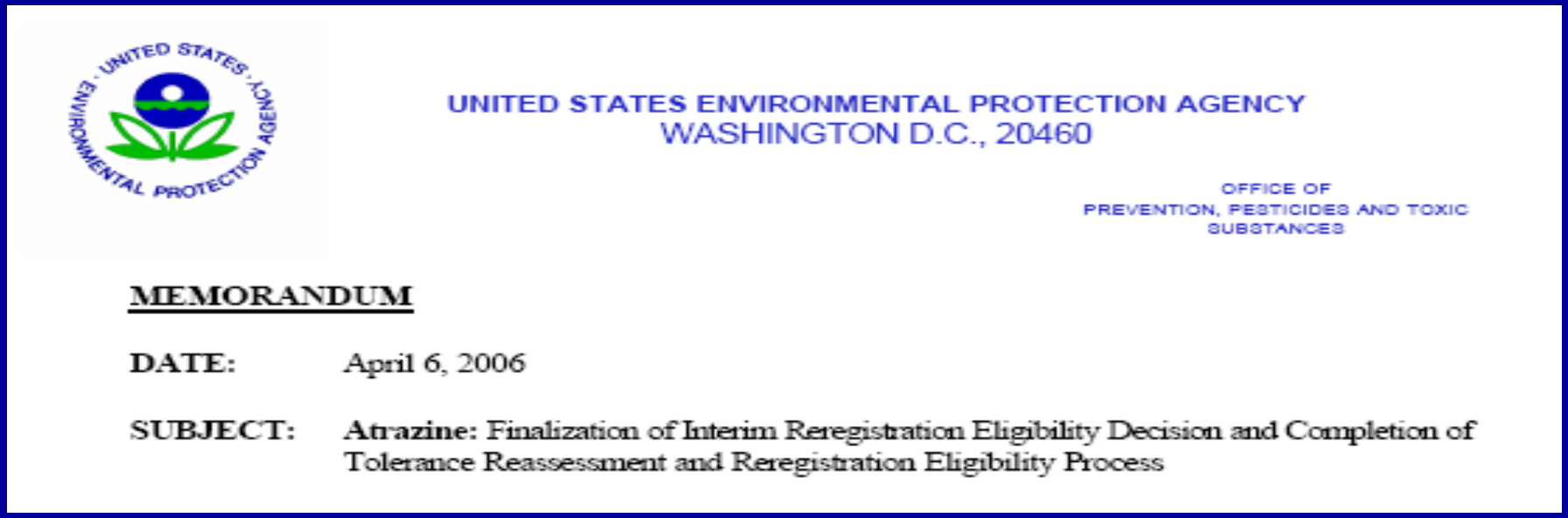


Assessing Exposure to Atrazine and Its Metabolites Using Biomonitoring

Dana B. Barr, Parinya Panuwet, Johnny V. Nguyen, Simeon Udunka, and Larry L. Needham

Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

Environ Health Perspect. 2007 October;
115(10): 1474–1478.



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C., 20460

OFFICE OF
PREVENTION, PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

DATE: April 6, 2006

SUBJECT: **Atrazine:** Finalization of Interim Reregistration Eligibility Decision and Completion of Tolerance Reassessment and Reregistration Eligibility Process

"the Agency has found that there is a reasonable certainty that no harm will result to the general U.S. population, infants, children, or other major identifiable subgroups of consumers from aggregate exposure (from food, drinking water, and non-occupational sources) to cumulative residues of atrazine and the other chlorinated triazine pesticides "

Greenwood HS Research Laboratory: Atrazine & Frogs 2008

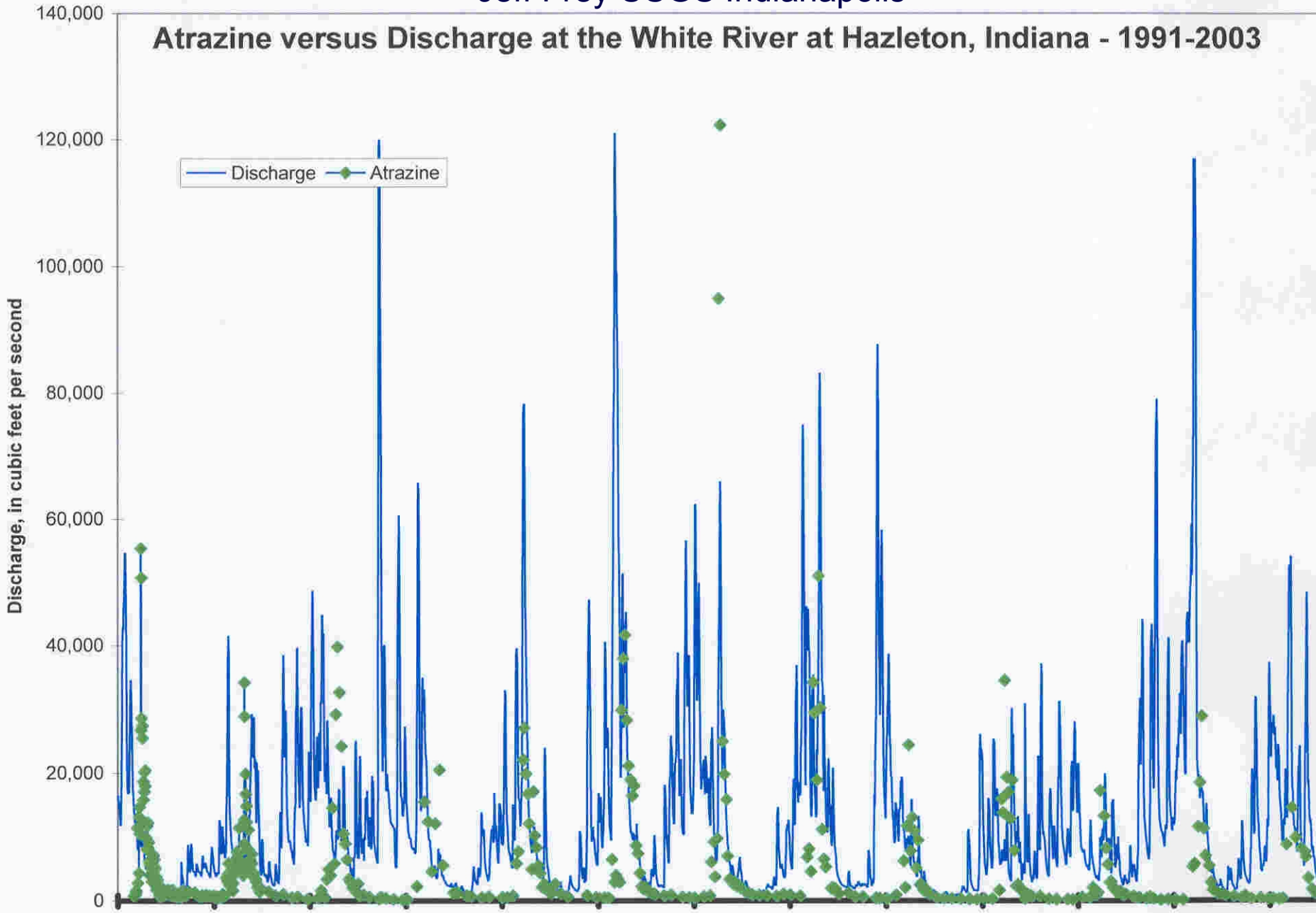
Eric Smith
Honor's Biology

Control

0.1ppb atrazine

25ppb atrazine

Jeff Frey USGS Indianapolis



Atrazine in Indiana Surface Water 1991-2001

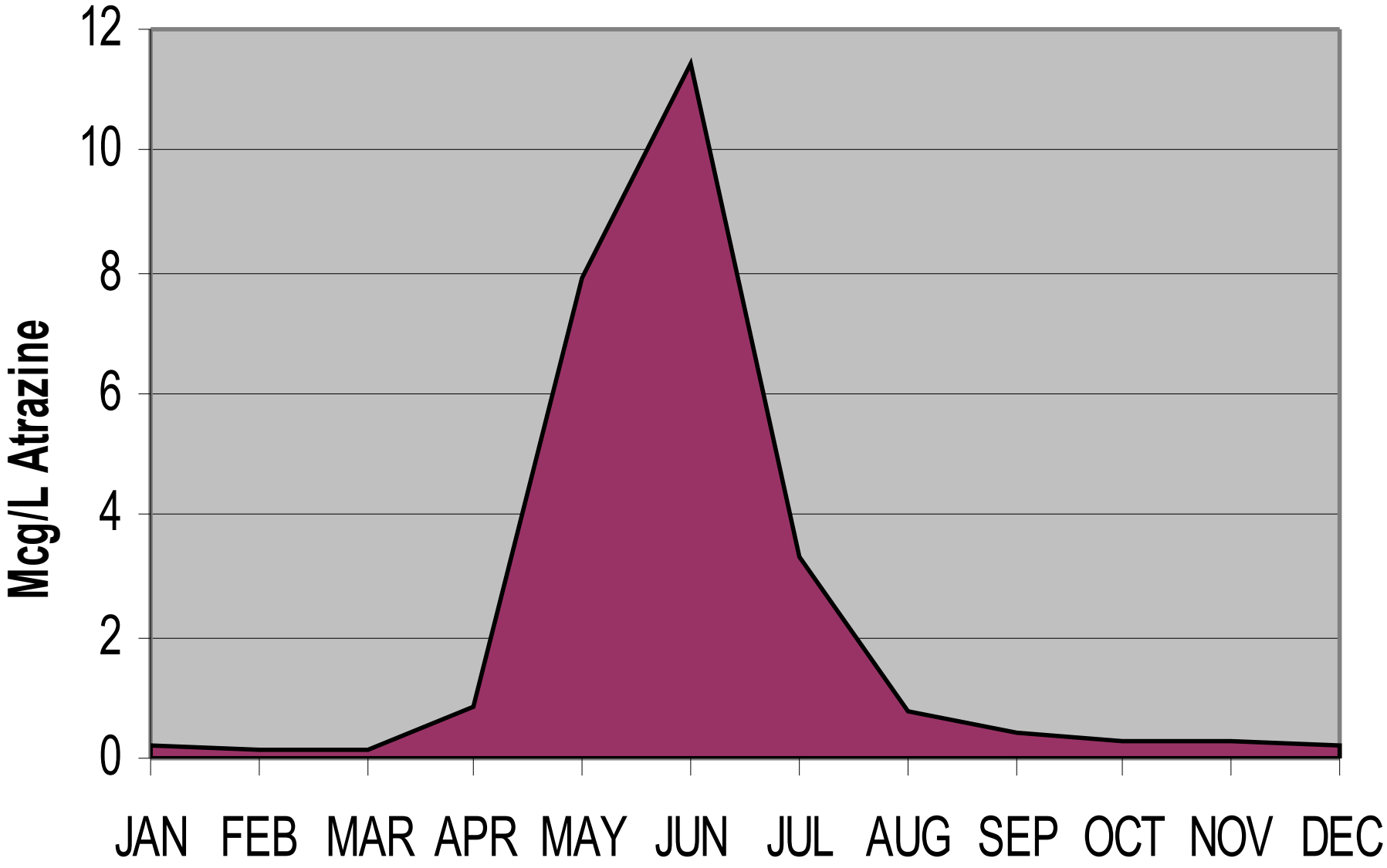


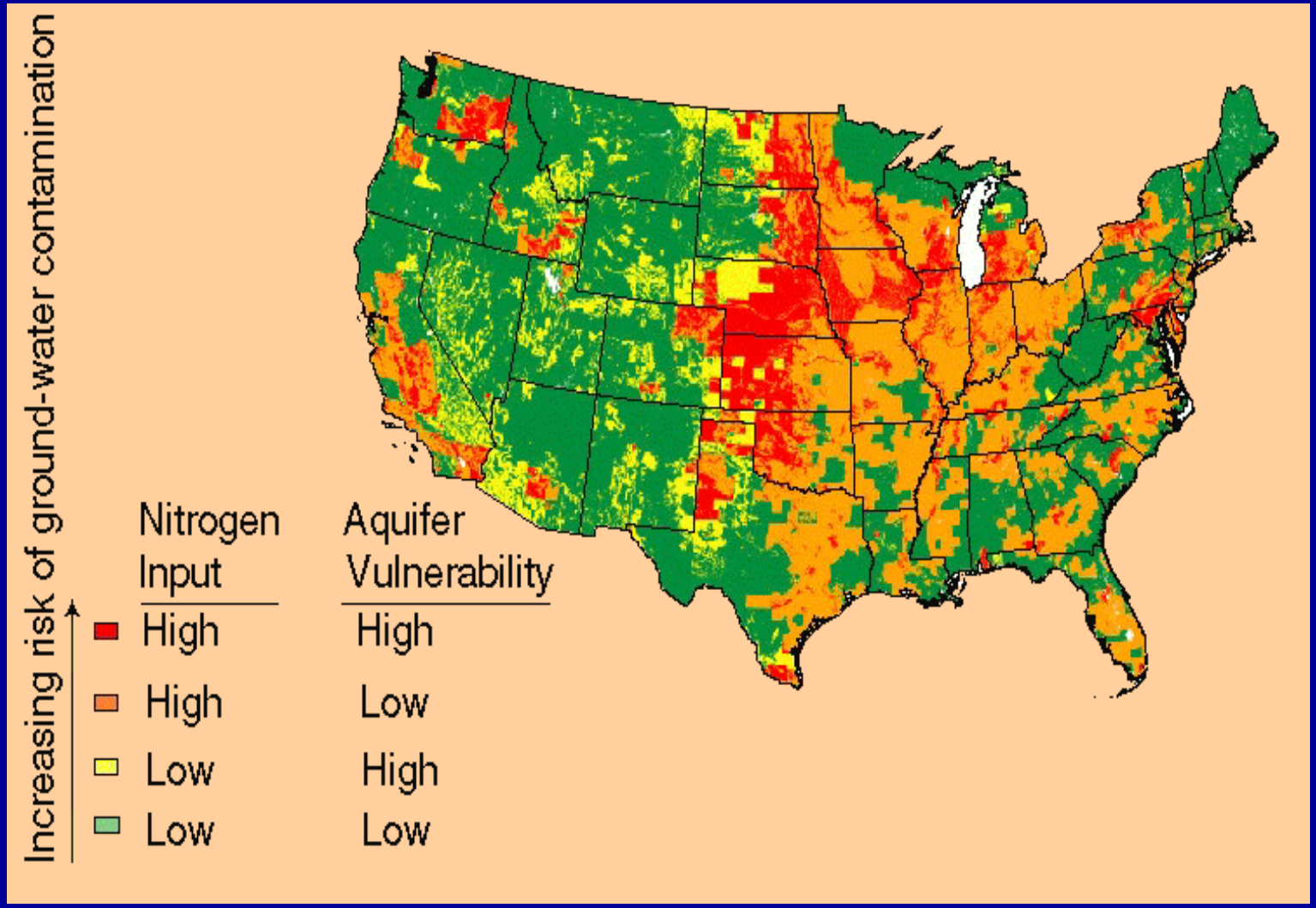
Table 1. Community Water Systems in Atrazine Monitoring Programs

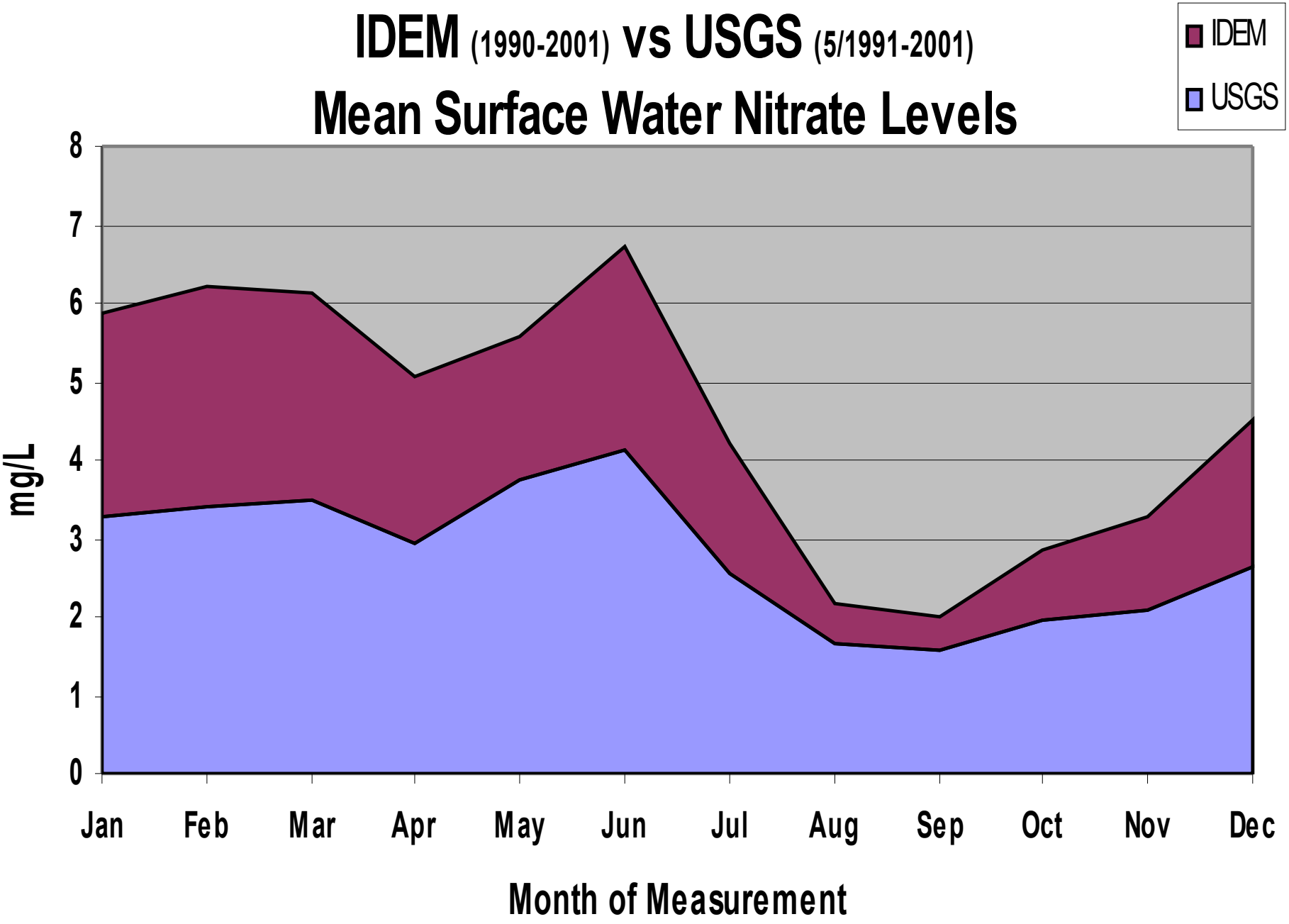
Community	Watershed Area (square miles)	Percent Land in Agricultural Use	Population Served
Batesville	5	86	4,140
Bedford	5,033	79	14,390
Fort Wayne	1,089	90	173,072
Indianapolis (Eagle Creek)	163	89	678,000
Jasper	277	39	11,340
Logansport	805	93	12,261
Santee Utiliites	279	92	678,000
Stucker Fork	355	57	*
Versailles	107	0	1,550
Westport	98	84	1,440
Winslow	603	53	1,242

*Current data on the population served by the Stucker Fork community water system was not available at the time of printing.

Nitrate Contamination Risk

Nolan, Bernard T. et. al, National Water Quality Assessment Program, USGS,2001




IDEM (1990-2001) vs USGS (5/1991-2001)
Mean Surface Water Nitrate Levels
IDEM
USGS
mg/L
0
1
2
3
4
5
6
7
8
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month of Measurement

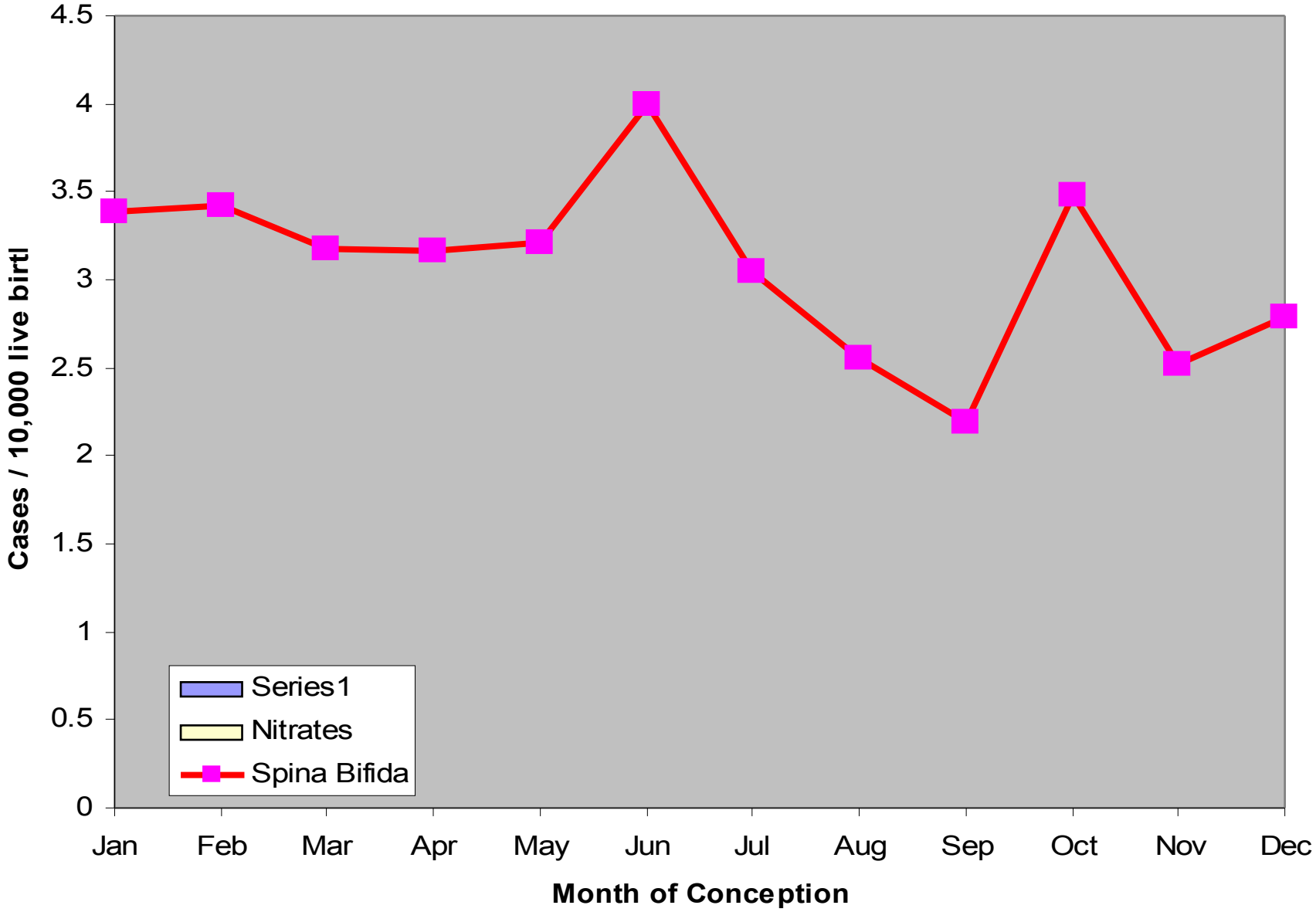
What We Did in Indiana

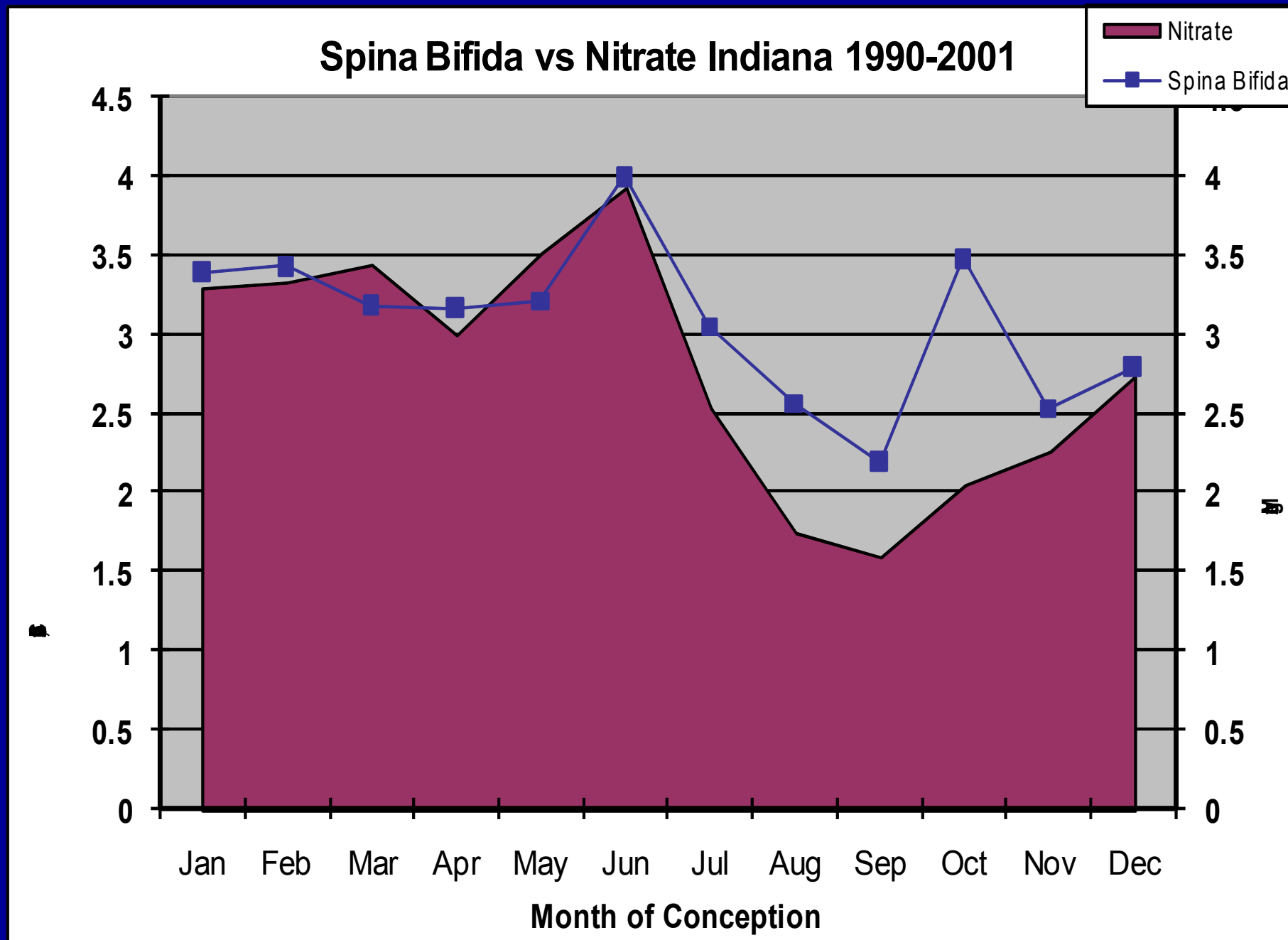
- Are Birth Defects more likely in certain months? Does Indiana have more birth defects?
- Calculated birth defect risk by month of conception 1990-2001(ISHD)
- Compared birth defects with mean concentrations of atrazine and nitrates (USGS, IDEM)

Spina Bifida
(Meningomyelocele)

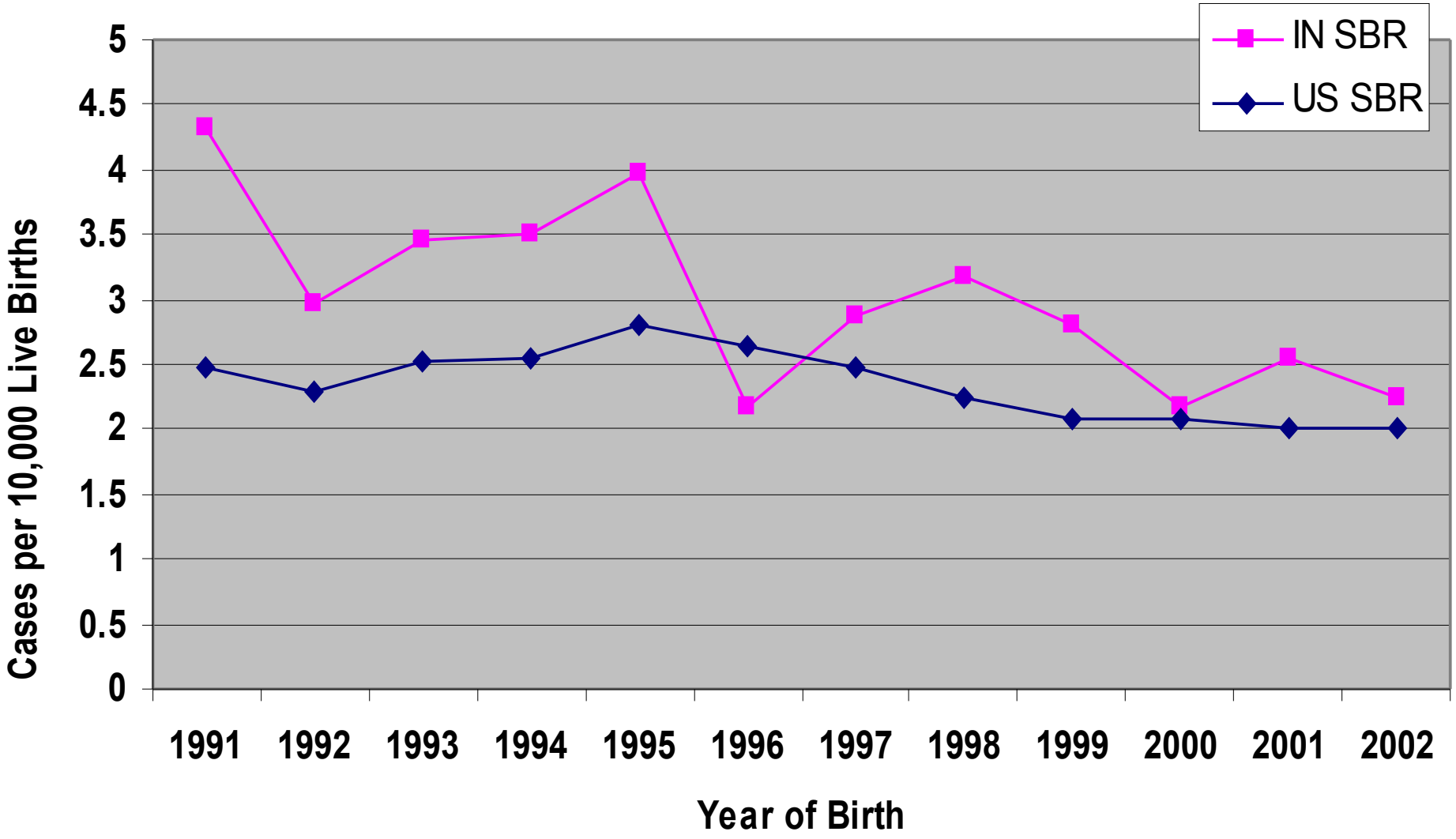
Photos contributed by Joel Boaz, M.D.,
Department of Neurosurgery,
Riley Hospital for Children

Spina Bifida vs Mean Nitrate Rates In Indiana 1990-2001

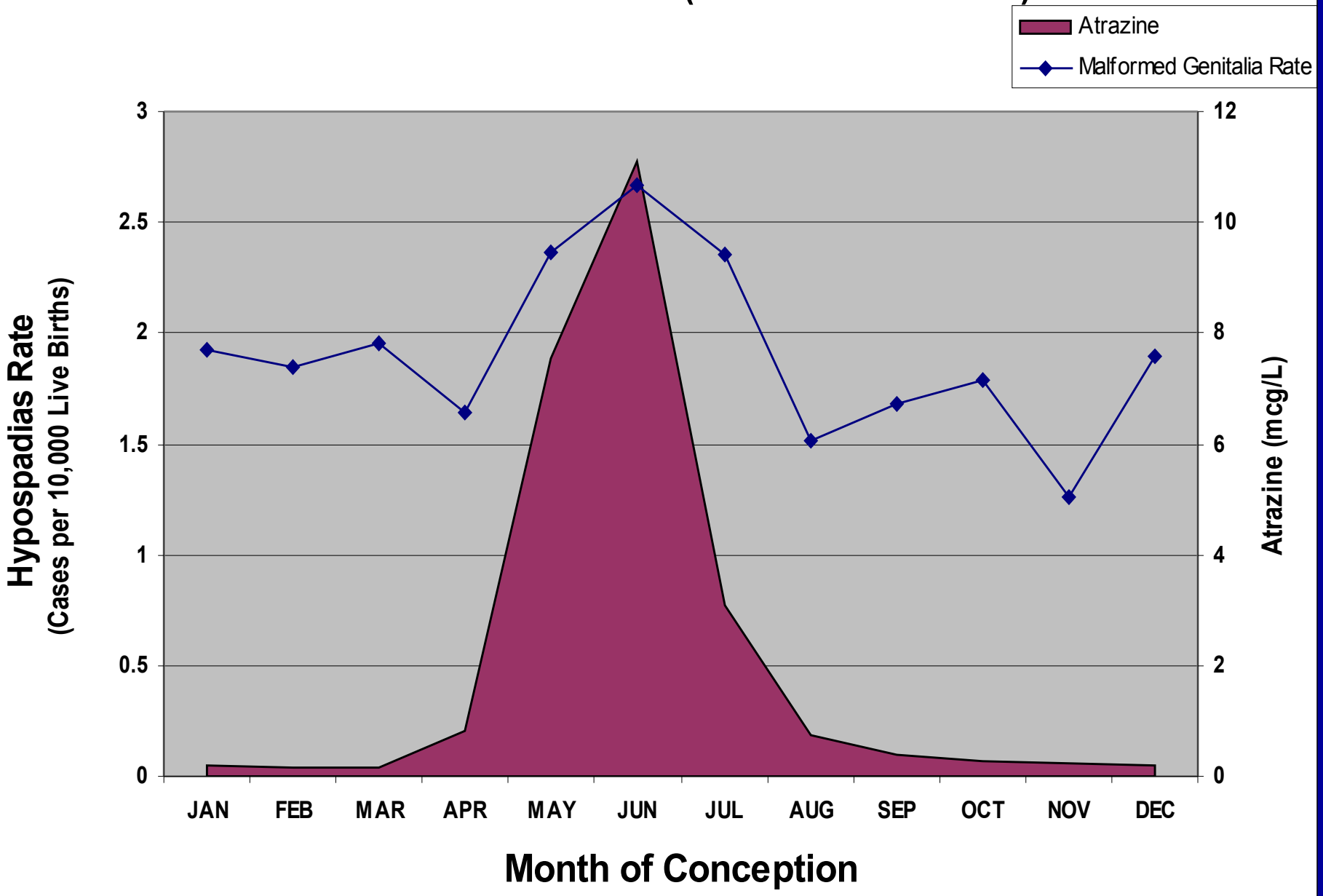



Spina Bifida vs Nitrate Indiana 1990-2001
Nitrate
Spina Bifida
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month of Conception

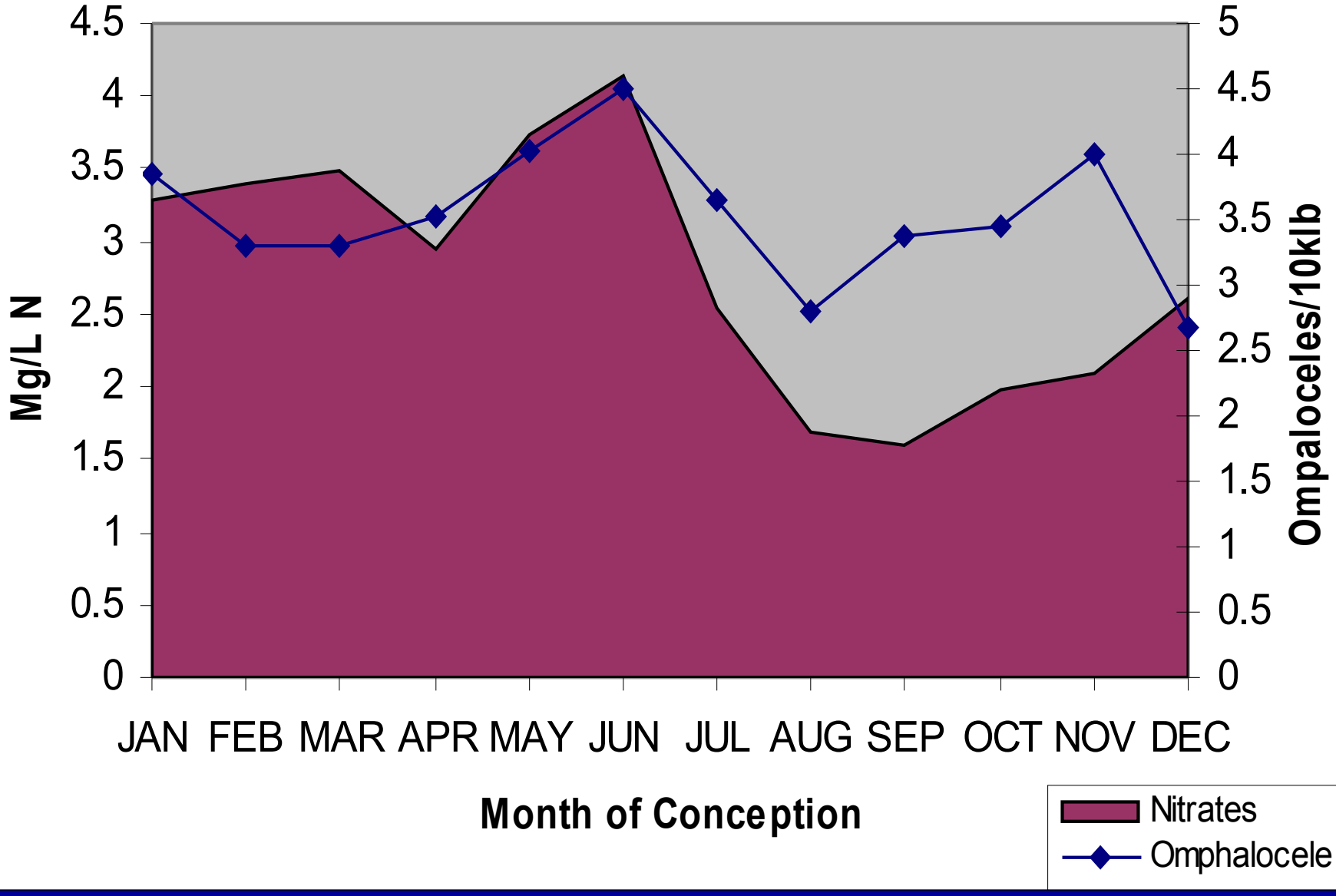
Indiana vs USA Spina Bifida Rate (SBR)
1991-2002



Malformed Genitalia Rates per Month of Conception vs. Atrazine in White River (Indiana 1990-2001)



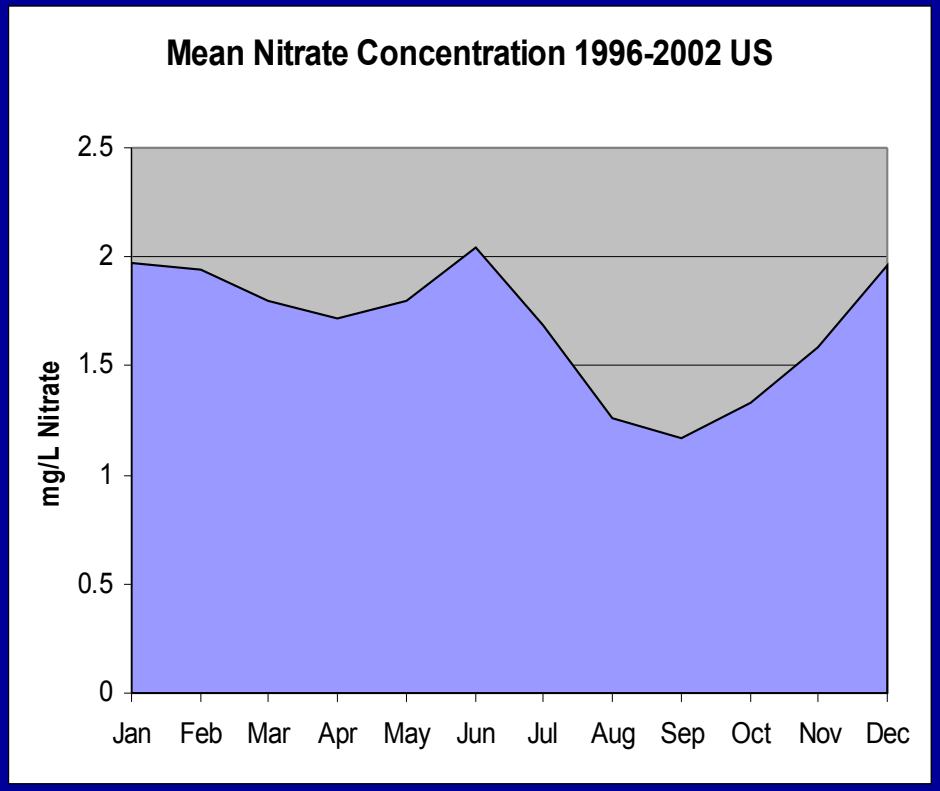
Omphalocele vs Nitrates Indiana 1990-2002

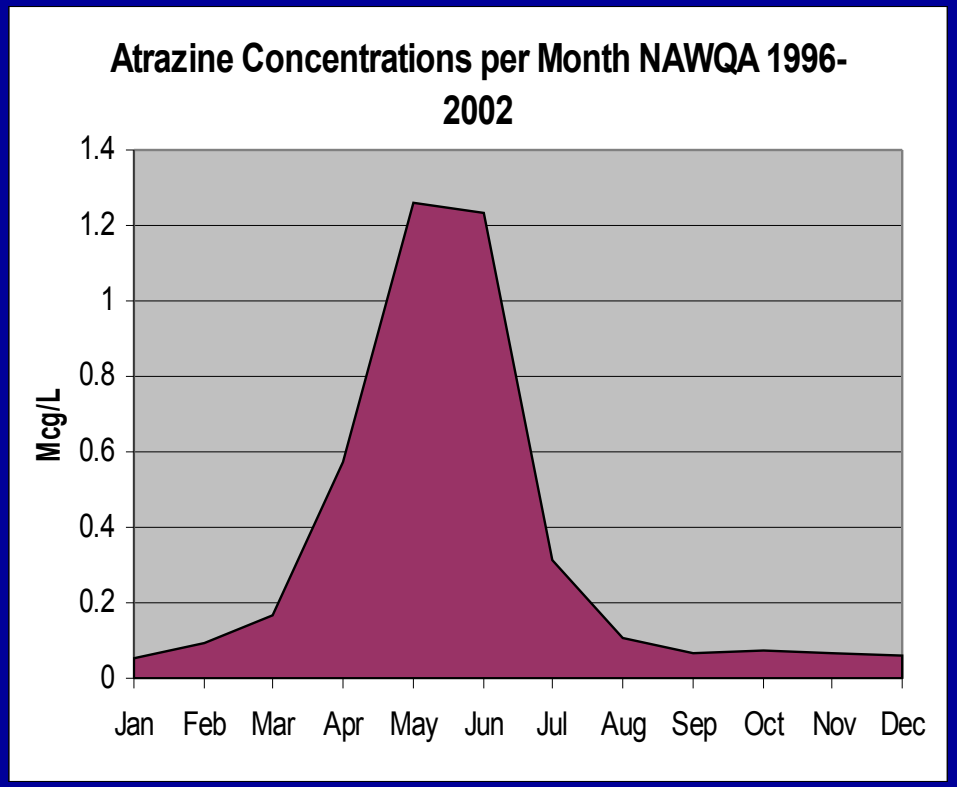


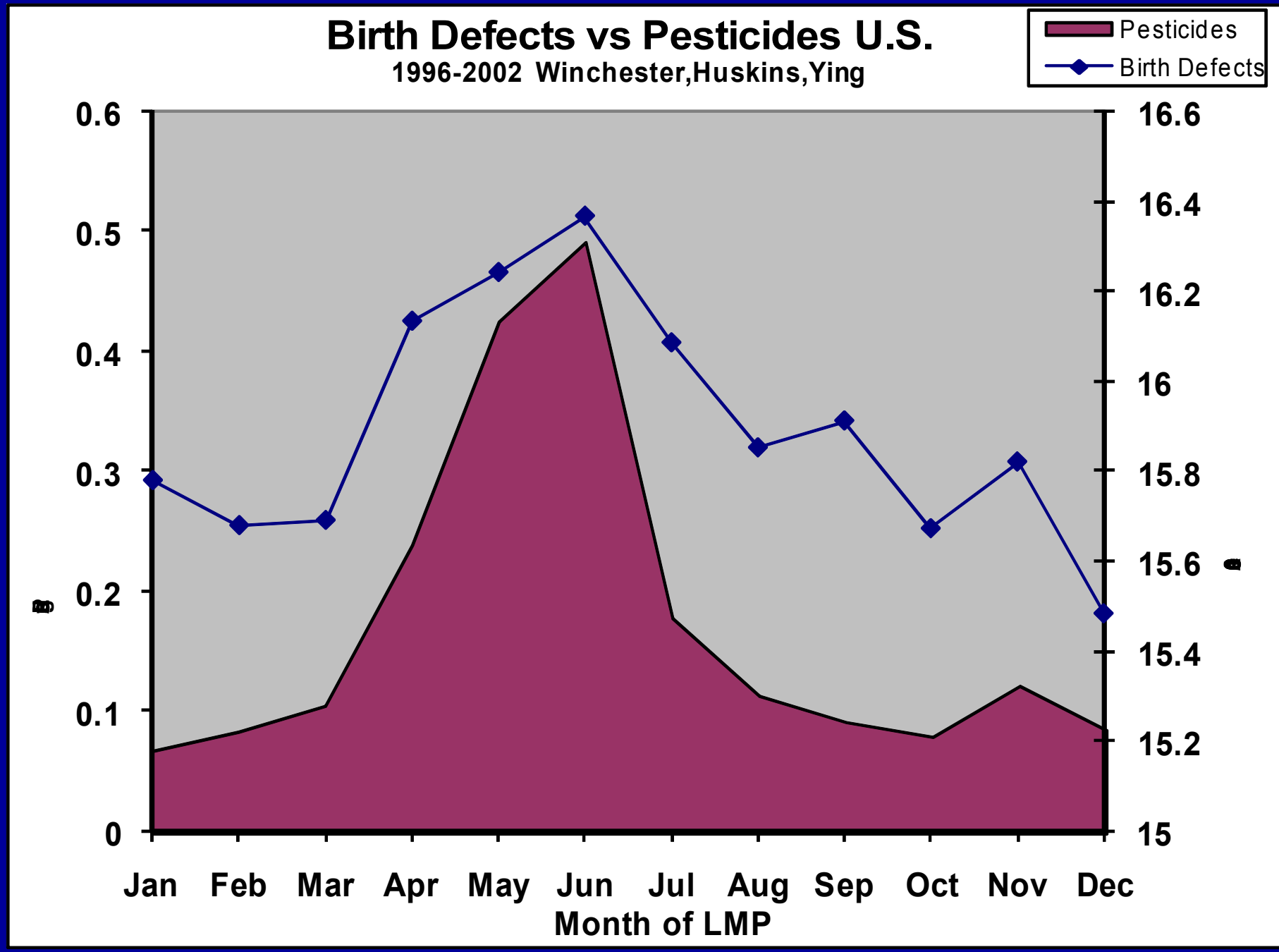
National Study

- We collected the CDC natality Data for the entire US
- Calculated the Birth Defect Rate by Month of conception
- Collected the NAWQA water data for the entire US for 1990-2002
- Calculated the mean nitrate and pesticide concentrations per month

Nitrates and Pesticides Peaked in June USGS NAWQA Study






Birth Defects vs Pesticides U.S.
1996-2002 Winchester,Huskins,Ying
Pesticides
Birth Defects
0.6
0.5
0.4
0.3
0.2
0.1
0
16.6
16.4
16.2
16
15.8
15.6
15.4
15.2
15
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month of LMP

Illinois Adverse Pregnancy Outcomes Project

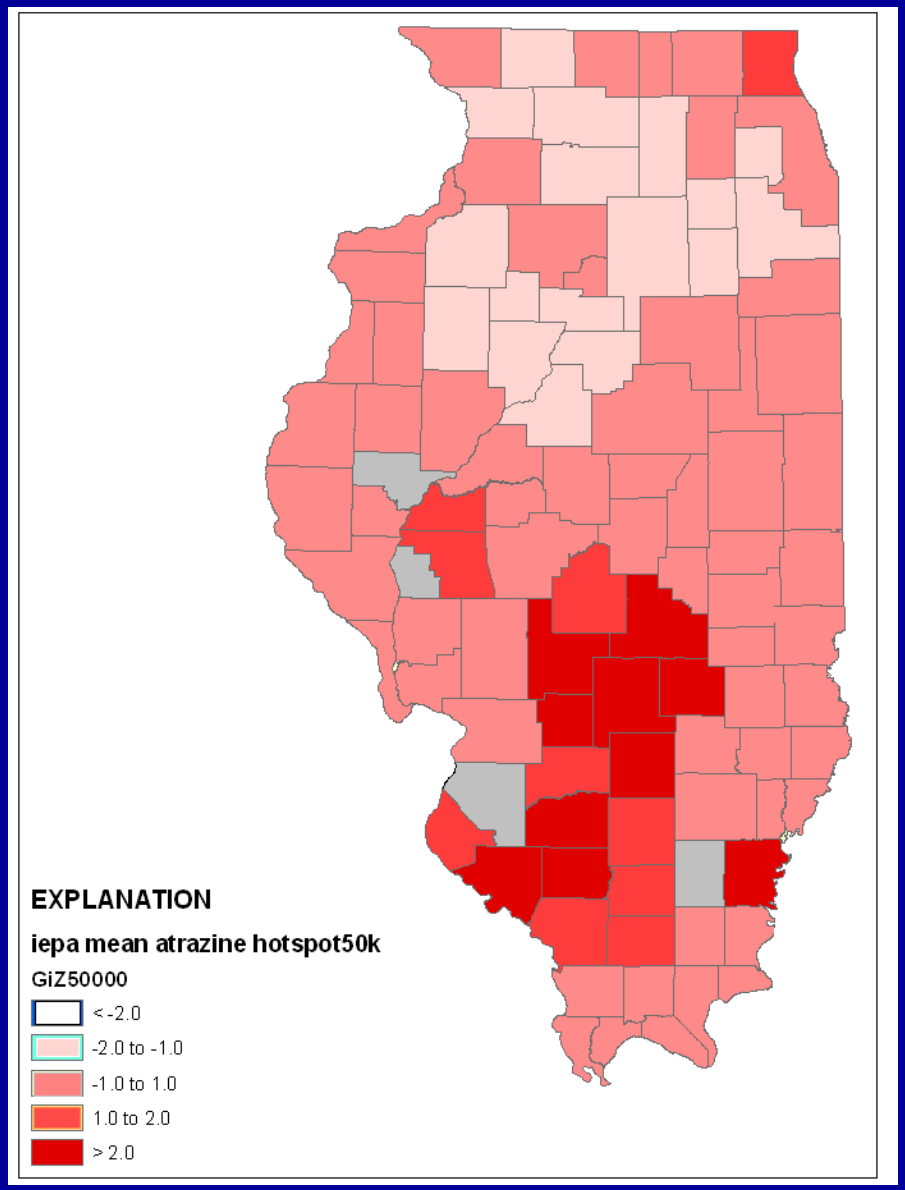
Mohanty,MK, Shang,B, Dupre,D, Arnold,TL, 2007

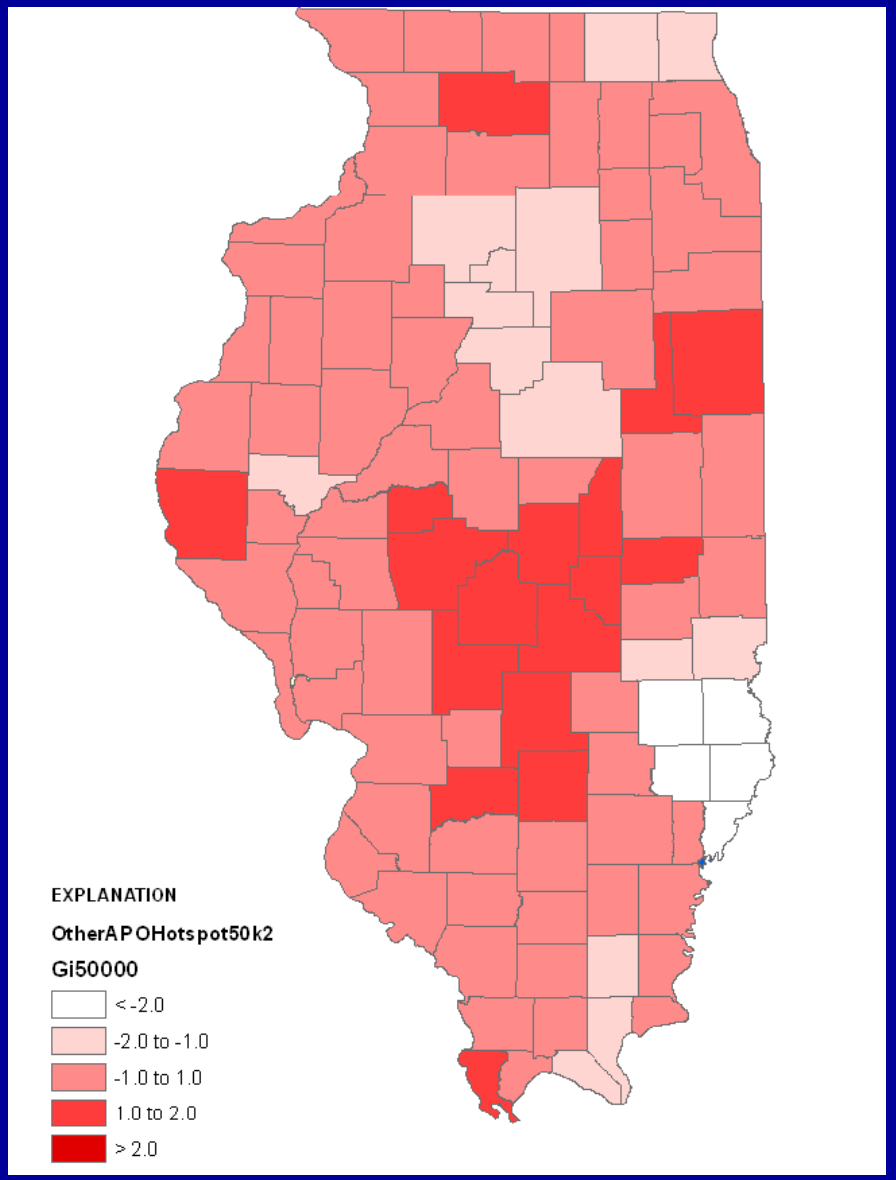
- Birth Defects and Adverse Pregnancy Outcomes 1998-2002 Illinois calculated for each county.
- Public Water Contaminants; Nitrate,Nitrite,Atrazine,TTHM,HAA5 for each county.
- Mulitple regression Models Correlating Untoward Outcomes with contaminants.

Model Predicted Birth Defects and Adverse Pregnancy Outcomes

- Atrazine best single predictor of birth defects and adverse pregnancy outcomes
- Atrazine :$R_{2=}$ -37.5604 , SE=10.6847 , t = -3.5154, p= 0.0025

Atrazine vs Adverse Outcomes

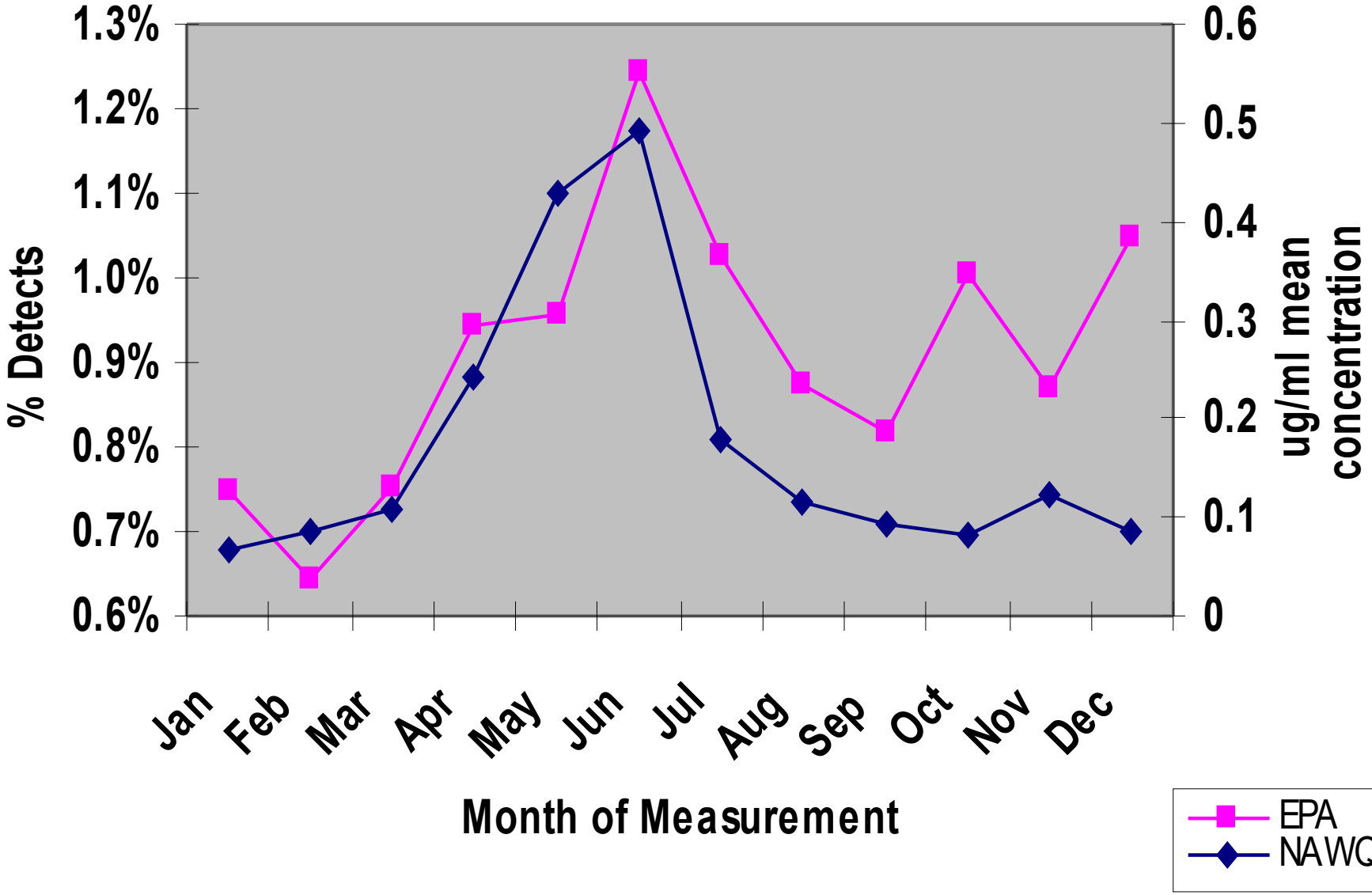


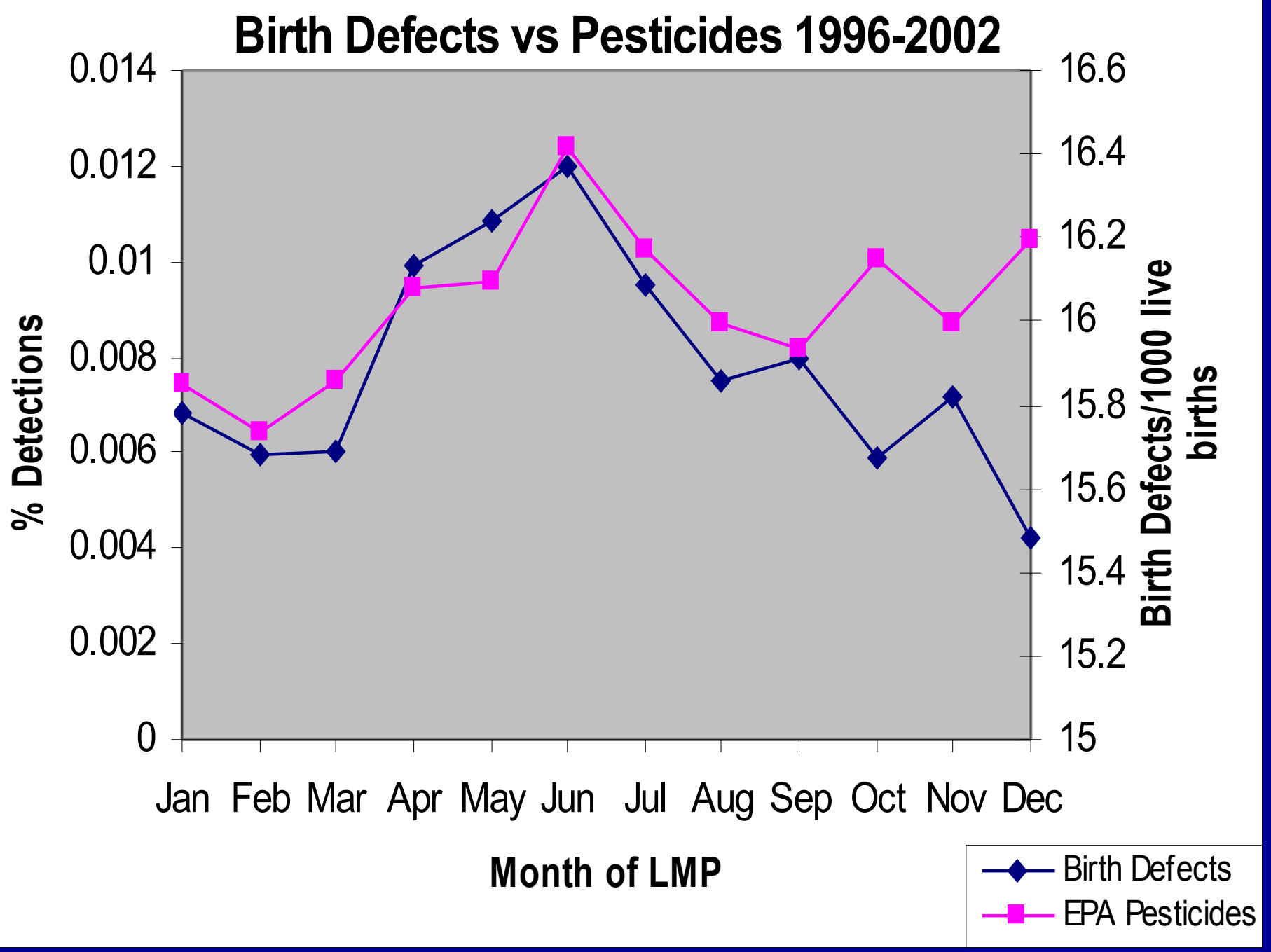


Summary “June Effect”

- Women with LMP in April-July are more likely to have a child with a birth defect
- Mean concentrations of nitrates, atrazine and other pesticides are highest in April –July.
- There is a significant correlation between birth defect rates and concentrations of pesticides and nitrates at the time of conception
- **Munger, R et al. 1992.Birth defects and pesticide-contaminated water supplies in Iowa. Amer J. Epidemiol.136:959.)**

Pesticides in Stream and Ground Water vs NAWQA & Drinking Water Pesticides in U.S.




Birth Defects vs Pesticides 1996-2002
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
% Detections
16.6
16.4
16.2
16
15.8
15.6
15.4
15.2
15
Birth Defects/1000 live births
Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec
Month of LMP
Birth Defects
EPA Pesticides

County-Specific Birth Defect Rates and Pesticide Applications in the US

Paul D Winchester, Jun Ying, Sandy Williamson, Cathy Proctor and Ed Liechty

Indiana University School of Medicine, University of Cincinnati Medical Center, US Geological Survey, St Francis Hospital Indianapolis

Objective

- This project was designed to compare **birth defect risk** with **pesticide application** rates at the county-level across the US.
- The hypothesis tested is whether birth defect risk increases with increasing pesticide usage across US counties?

Design/Methods

- Birth defect data was collected from the CDC natality data sets from 1996-2002. (courtesy of T.J.Mathews), for 45 US states.
- Pesticide applications (total lbs/acre) were calculated from USGS data sets for the same 45 states. Application data from 1997, and 2002 were used to represent pesticide usage for each county in the study time period. (Sandy Williams USGS)

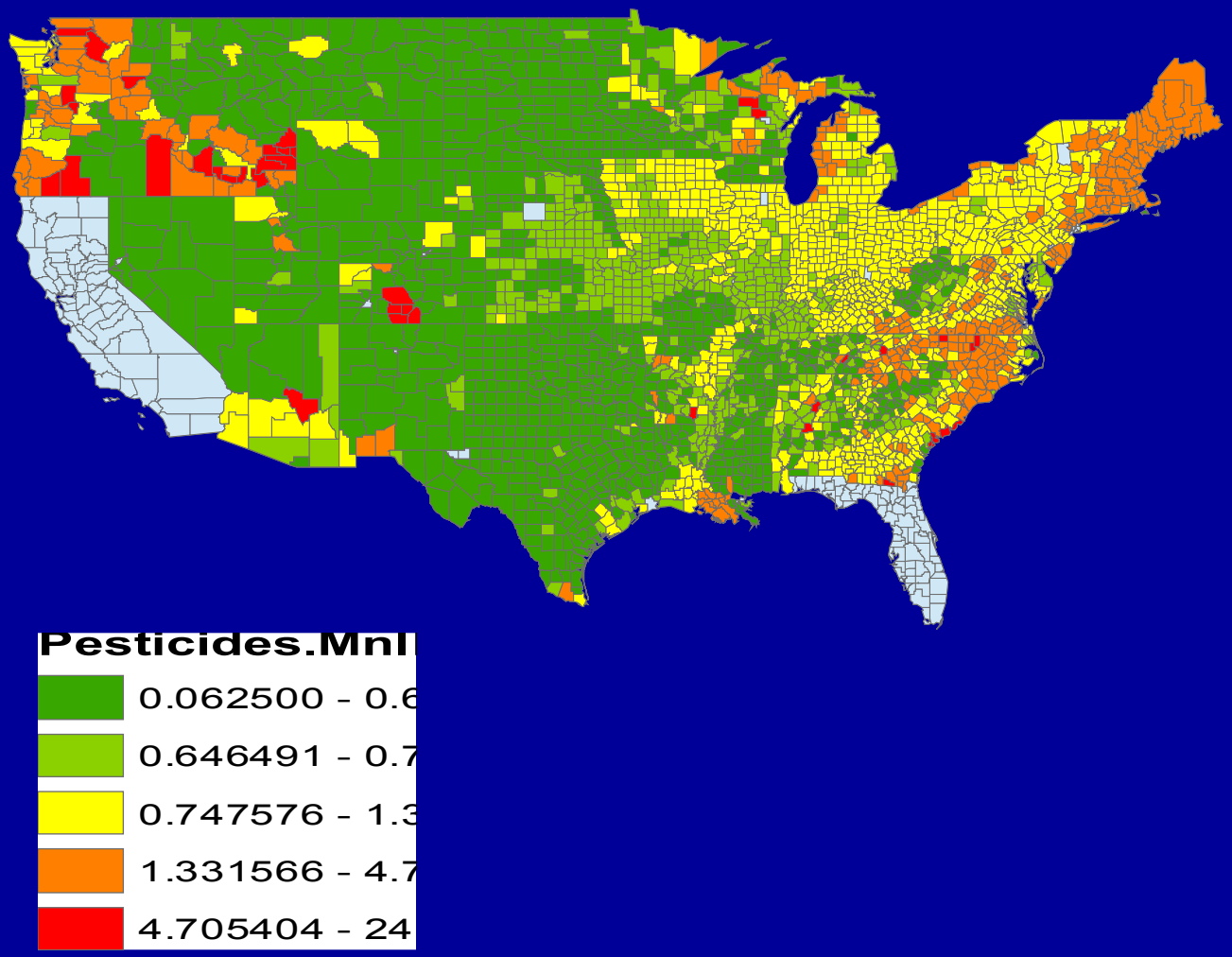
Statistical Methods

- The association between birth defects and pesticide usage was tested using logistical regression models. The GEE method was used to account for within-state correlations.

Results

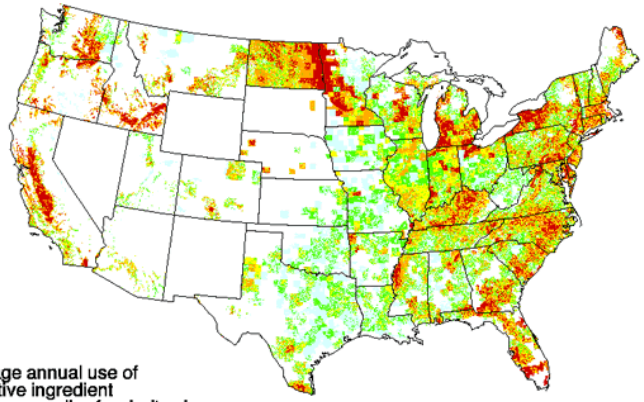
- 447 counties (excluded Ala, Ha, Ca, Fl)
- 220 chemicals ranked by lbs/acre
- Mean birth defect rate was 1.69% (1.41-2.02)
- Birth defect rates in low exposure counties were 61% lower than in high exposure counties.

Pesticide Usage US Map



MANCOZEB - fungicide

1997 estimated annual agricultural use



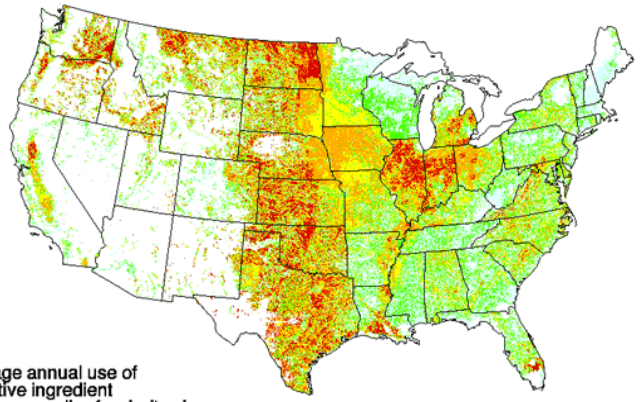
Average annual use of active ingredient (pounds per square mile of agricultural land in county)

- no estimated use
- 0.001 to 0.019
- 0.02 to 0.095
- 0.096 to 0.421
- 0.422 to 2.004
- >= 2.005

Crops	Total pounds applied	Percent national use
potatoes	3,219,885	36.25
apples	1,323,779	14.90
tomatoes	935,930	10.54
sugarbeets	802,128	9.03
grapes	431,347	4.86
tobacco	355,719	4.00
dry onions	295,082	3.32
watermelons	282,252	3.18
wheat	271,315	3.05
sweet corn	265,843	2.99

2,4-D - herbicide

1997 estimated annual agricultural use



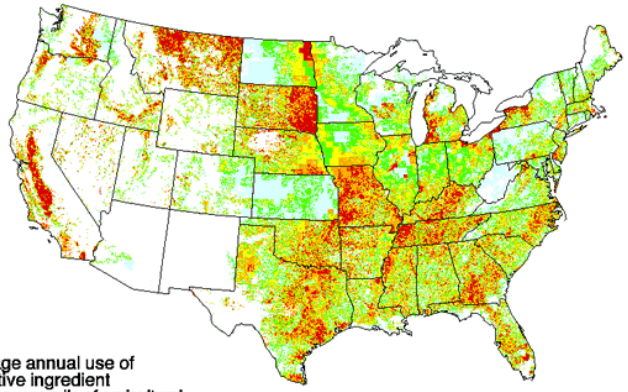
Average annual use of active ingredient (pounds per square mile of agricultural land in county)

- no estimated use
- 0.001 to 0.857
- 0.858 to 3.302
- 3.303 to 7.584
- 7.585 to 13.806
- >= 13.807

Crops	Total pounds applied	Percent national use
pasture	16,938,583	42.33
wheat	8,270,062	20.67
corn	3,876,945	9.69
soybeans	3,236,869	8.09
summer fallow	2,334,330	5.83
other hay	1,391,518	3.48
sugarcane	1,315,471	3.29
barley	762,806	1.91
sorghum	555,275	1.39
rice	491,916	1.23

CARBARYL - insecticide

1997 estimated annual agricultural use



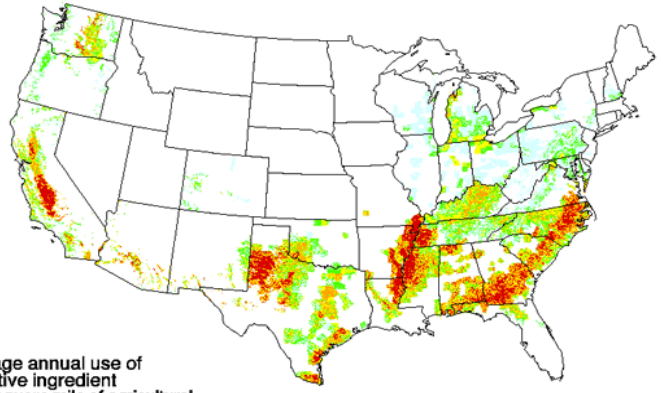
Average annual use of active ingredient (pounds per square mile of agricultural land in county)

- no estimated use
- 0.001 to 0.05
- 0.051 to 0.177
- 0.178 to 0.483
- 0.484 to 1.378
- >= 1.379

Crops	Total pounds applied	Percent national use
wheat	1,092,135	23.13
other hay	983,699	20.83
pecans	389,337	8.24
apples	291,740	6.18
alfalfa hay	240,737	5.10
citrus	234,686	4.97
soybeans	151,088	3.20
corn	133,032	2.82
grapes	131,106	2.78
potatoes	86,448	1.83

ETHEPHON - other pesticides

1997 estimated annual agricultural use



Average annual use of active ingredient (pounds per square mile of agricultural land in county)

- no estimated use
- 0.001 to 0.009
- 0.01 to 0.094
- 0.095 to 0.565
- 0.566 to 3.867
- >= 3.868

Crops	Total pounds applied	Percent national use
cotton	5,174,767	96.28
tobacco	101,569	1.89
apples	42,199	0.79
tomatoes	19,535	0.36
walnuts english	12,438	0.23
grapes	10,136	0.19
cherries	8,681	0.16
chile peppers	2,703	0.05
barley	1,053	0.02
bell peppers	691	0.01

Pesticide Usage vs Birth Defects

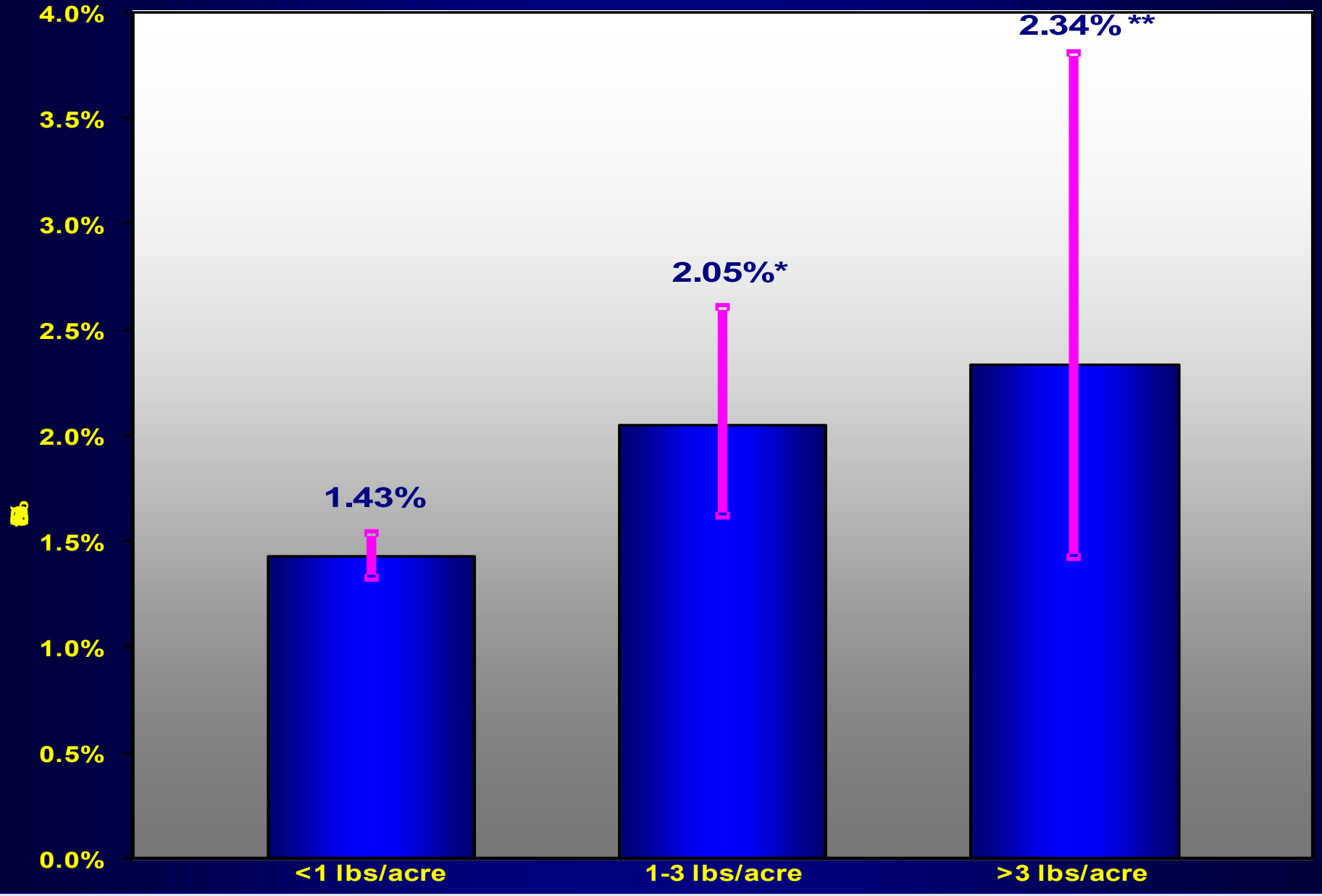
Pesticide Usage	Birth Defect Rate	95%	Confidence
<1lb/acre	1.43 %	1.33%	1.54%
1-3lb/acre	2.05 % *	1.62%	2.61%
>3lb/acre	2.34 %**	1.42%	3.81%

* p<.01

**p=.05

Birth Defects vs Pesticide Usage

*p<.01
**P=.05

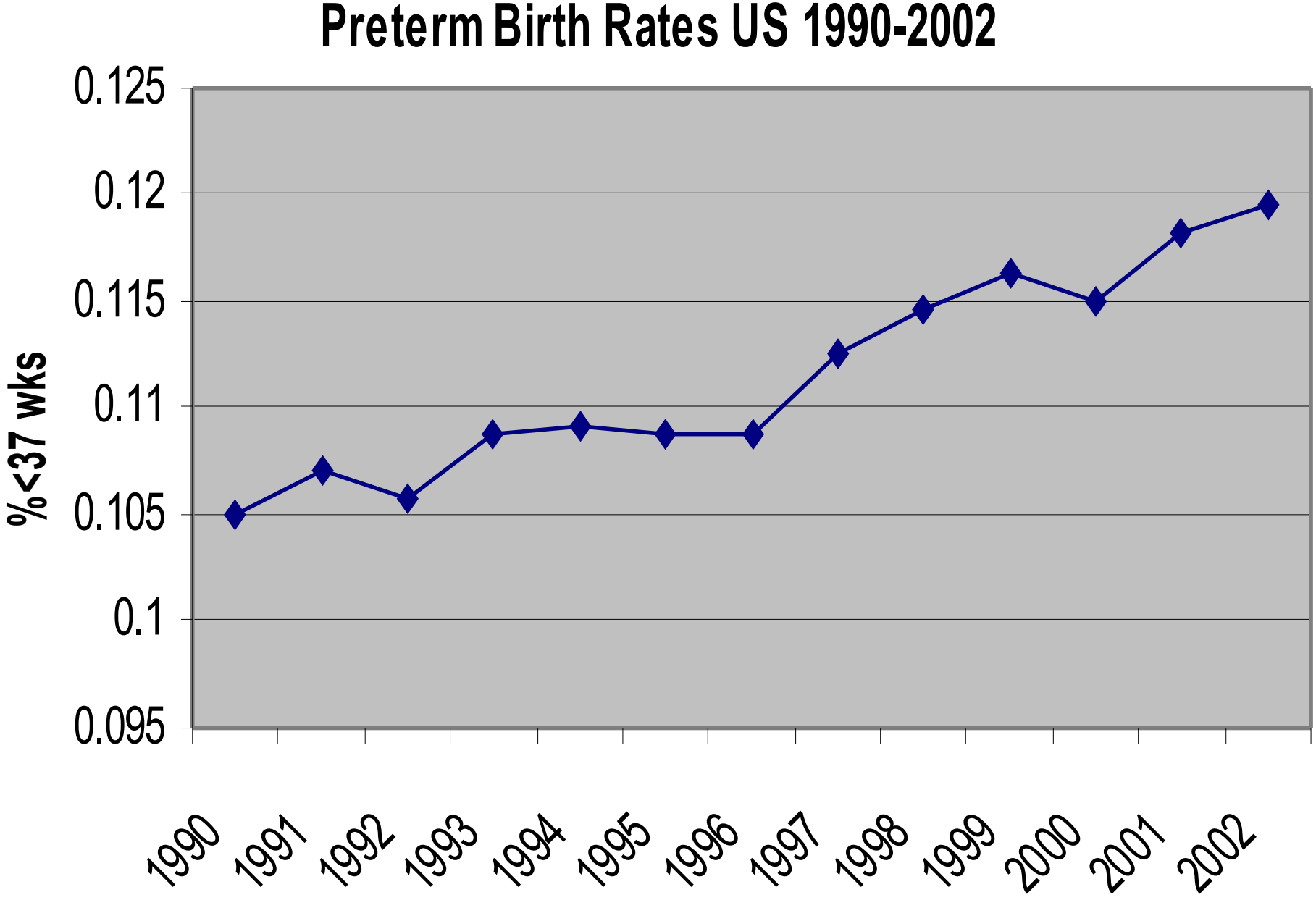


Conclusions

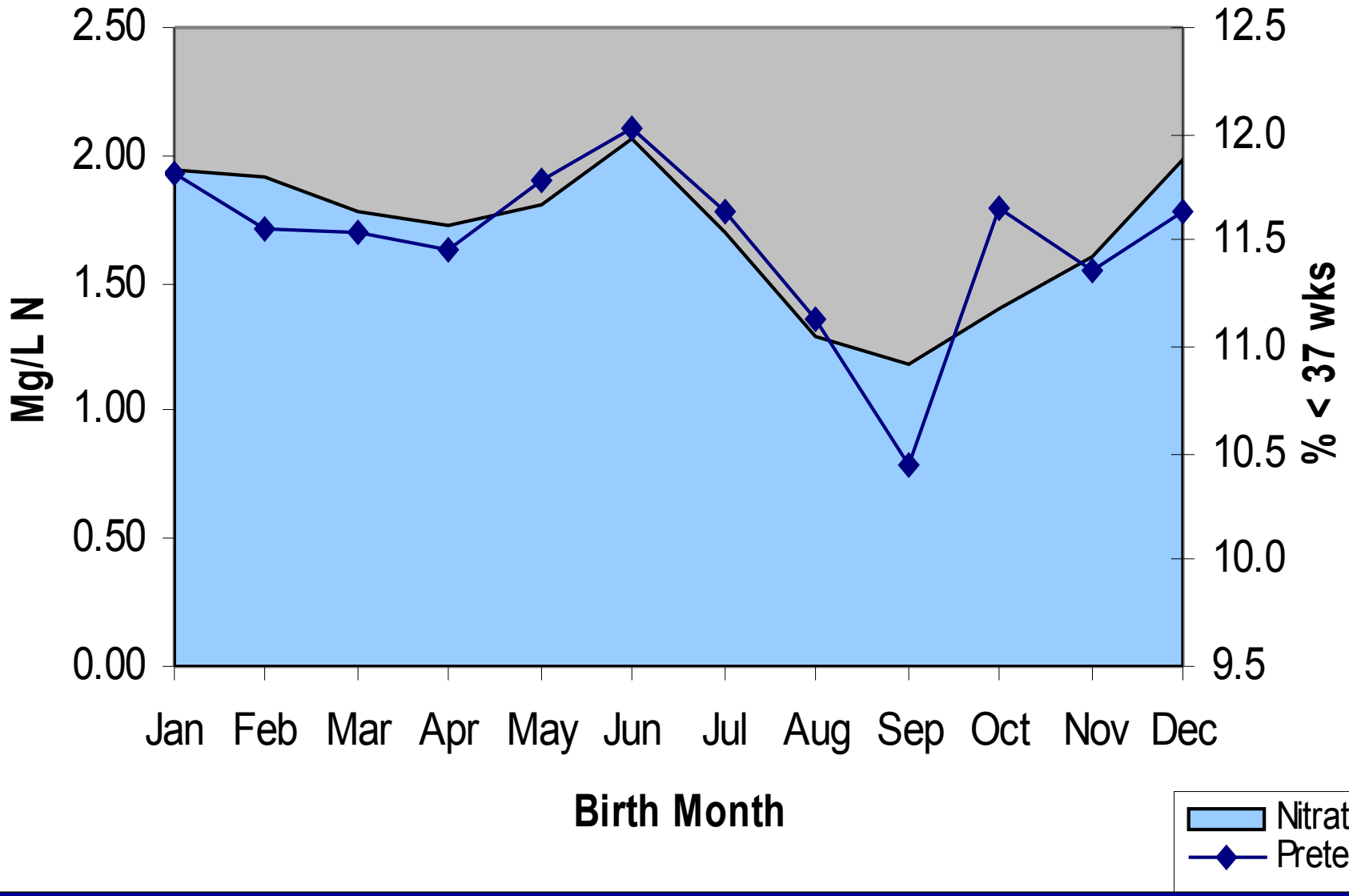
- County-level birth defect rates are significantly associated with pesticide usage in US.
- A dose-response relationship between pesticide usage and birth defect risk suggests a potential causal link.
- The ecological nature of this study precludes definite conclusions.

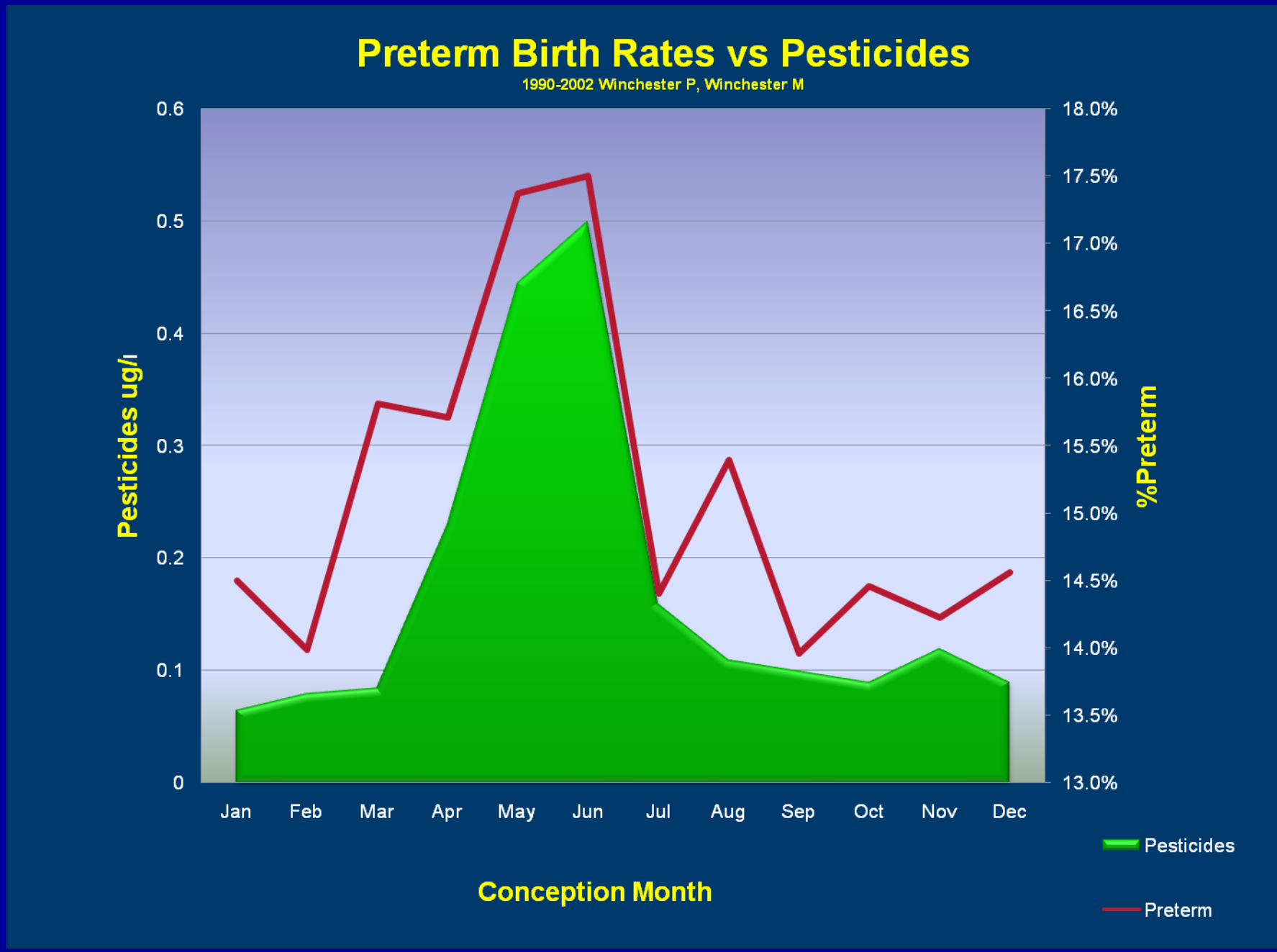
What Else Have We Found?

- Preterm birth
- Birth Weight
- SIDS
- Scholastic Achievement


Preterm Birth Rates US 1990-2002
%<37 wks
0.125
0.12
0.115
0.11
0.105
0.1
0.095
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002

Preterm Birth vs. Nitrates 1996-2002 US



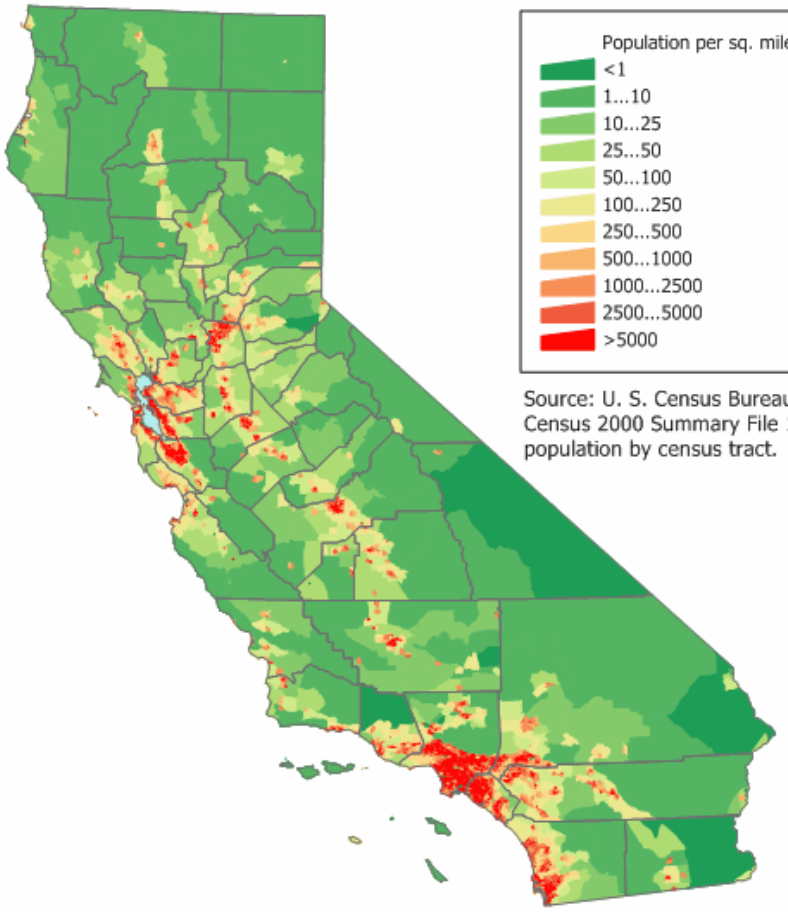

Preterm Birth Rates vs Pesticides
1990-2002 Winchester P, Winchester M
Pesticides ug/l
%Preterm
0.6
0.5
0.4
0.3
0.2
0.1
0
18.0%
17.5%
17.0%
16.5%
16.0%
15.5%
15.0%
14.5%
14.0%
13.5%
13.0%
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Conception Month
Pesticides
Preterm

Reported Pesticide Use in California, 1999

Total Pounds of Active Ingredient Applied Per Square Mile

Pesticide Use
lbs / square mile

- 1 - 5,000
- 5,001 - 15,000
- 15,001 - 35,000
- 35,001 - 60,000
- 60,001 - 180,000
- > 200,000
- Water
- County boundaries



Population per sq. mile
- <1
- 1...10
- 10...25
- 25...50
- 50...100
- 100...250
- 250...500
- 500...1000
- 1000...2500
- 2500...5000
- >5000

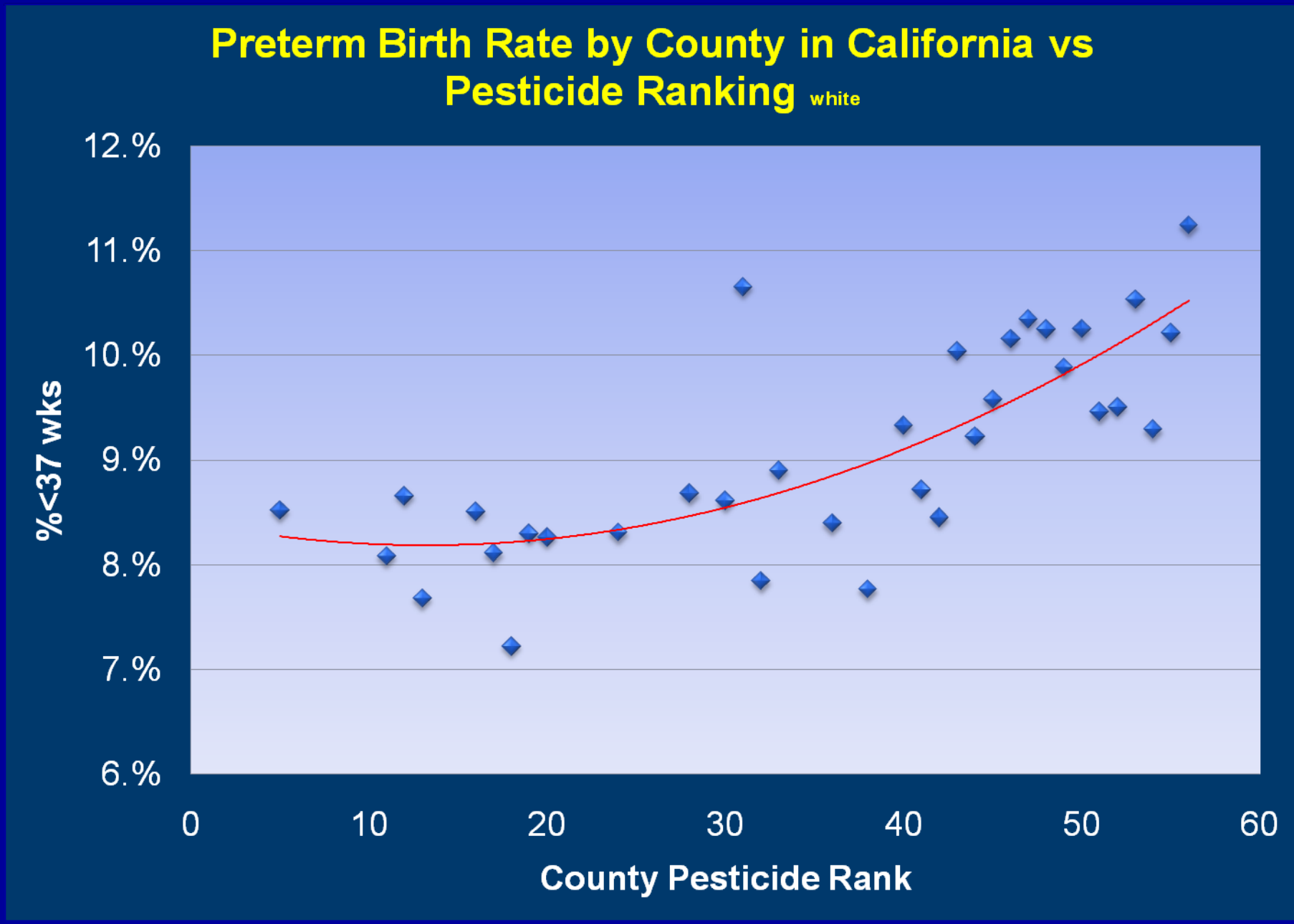
Source: U. S. Census Bureau
Census 2000 Summary File 1
population by census tract.

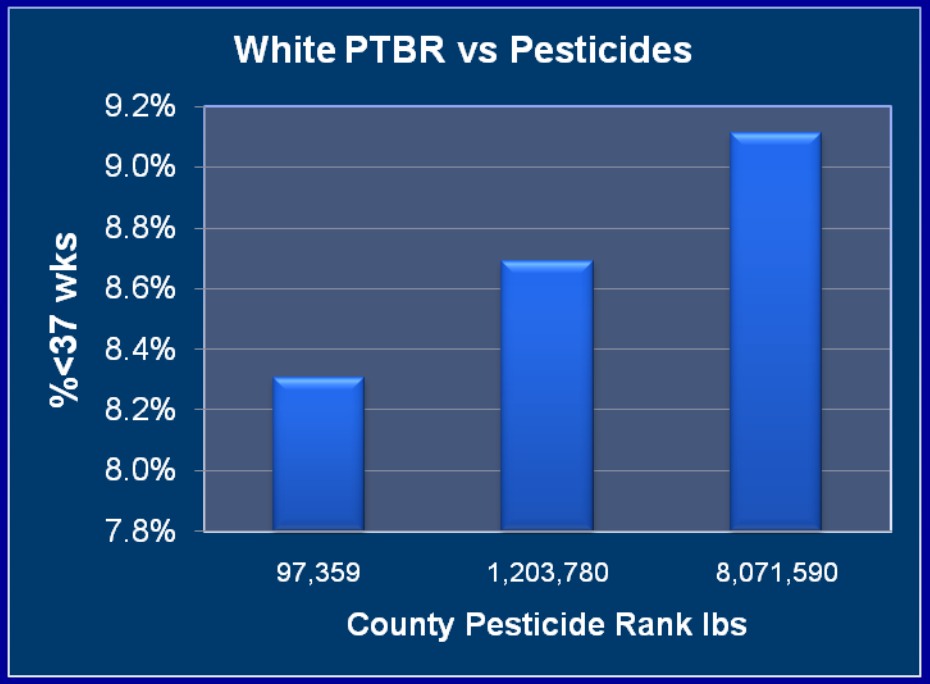
Pesticide Action Network

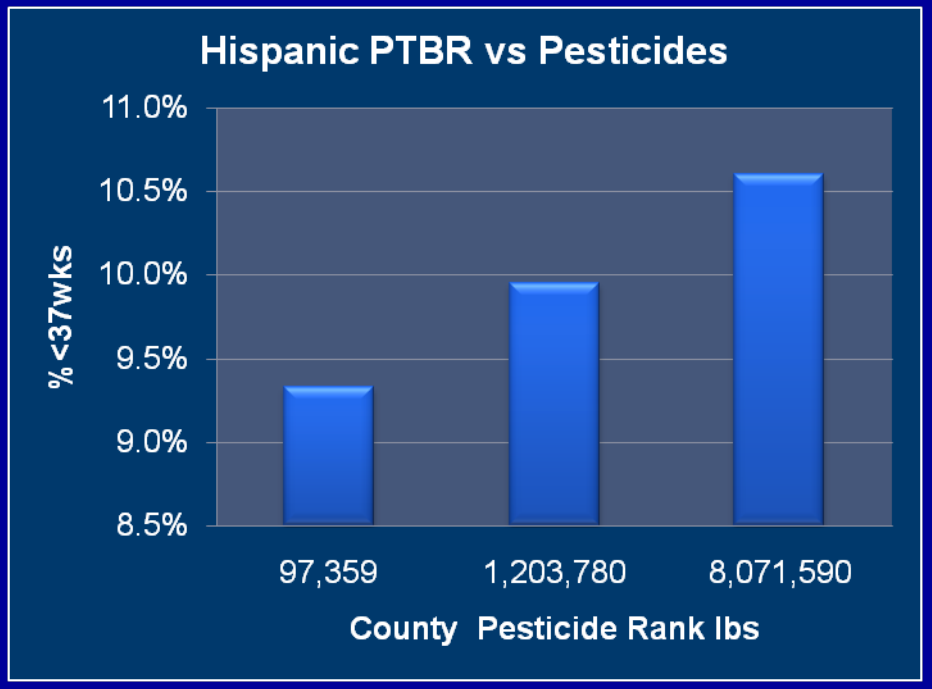
Association of *in Utero* Organophosphate Pesticide Exposure and Fetal Growth and Length of Gestation in an Agricultural Population

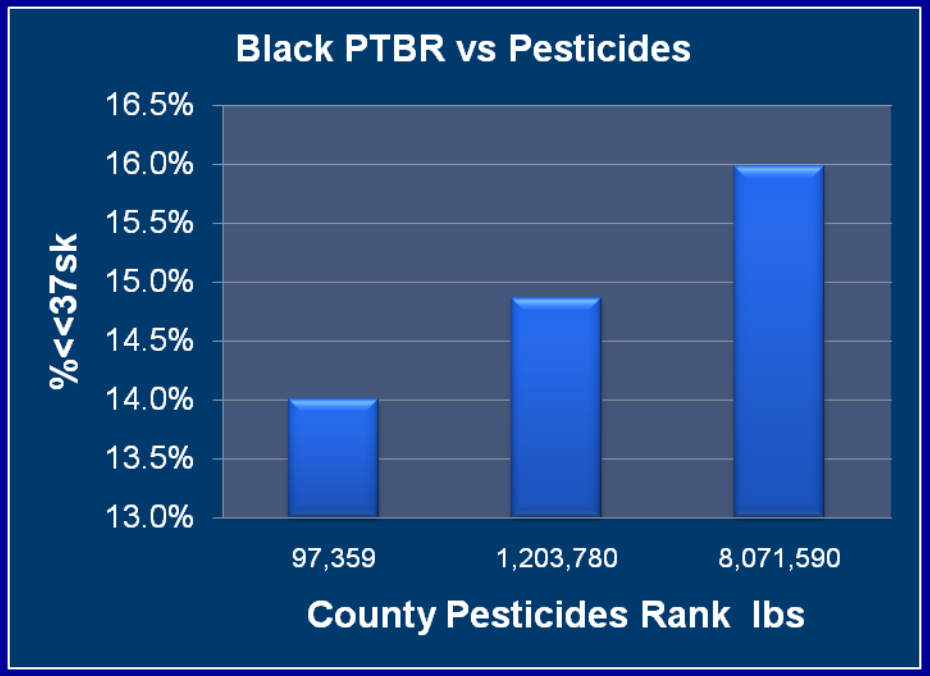
Brenda Eskenazi,1 Kim Harley,1 Asa Bradman,1 Erin Weltzien,1 Nicholas P. Jewell,1 Dana B. Barr,2 Clement E. Furlong,3 and Nina T. Holland1
EnvironHealth Perspect112:1116–1124 (2004

Exposure to dimethyl organophosphate compounds such as malathion were associated with shortened gestation in California


Preterm Birth Rate by County in California vs Pesticide Ranking white
12.%
11.%
10.%
9.%
8.%
7.%
6.%
%<37 wks
0
10
20
30
40
50
60
County Pesticide Rank



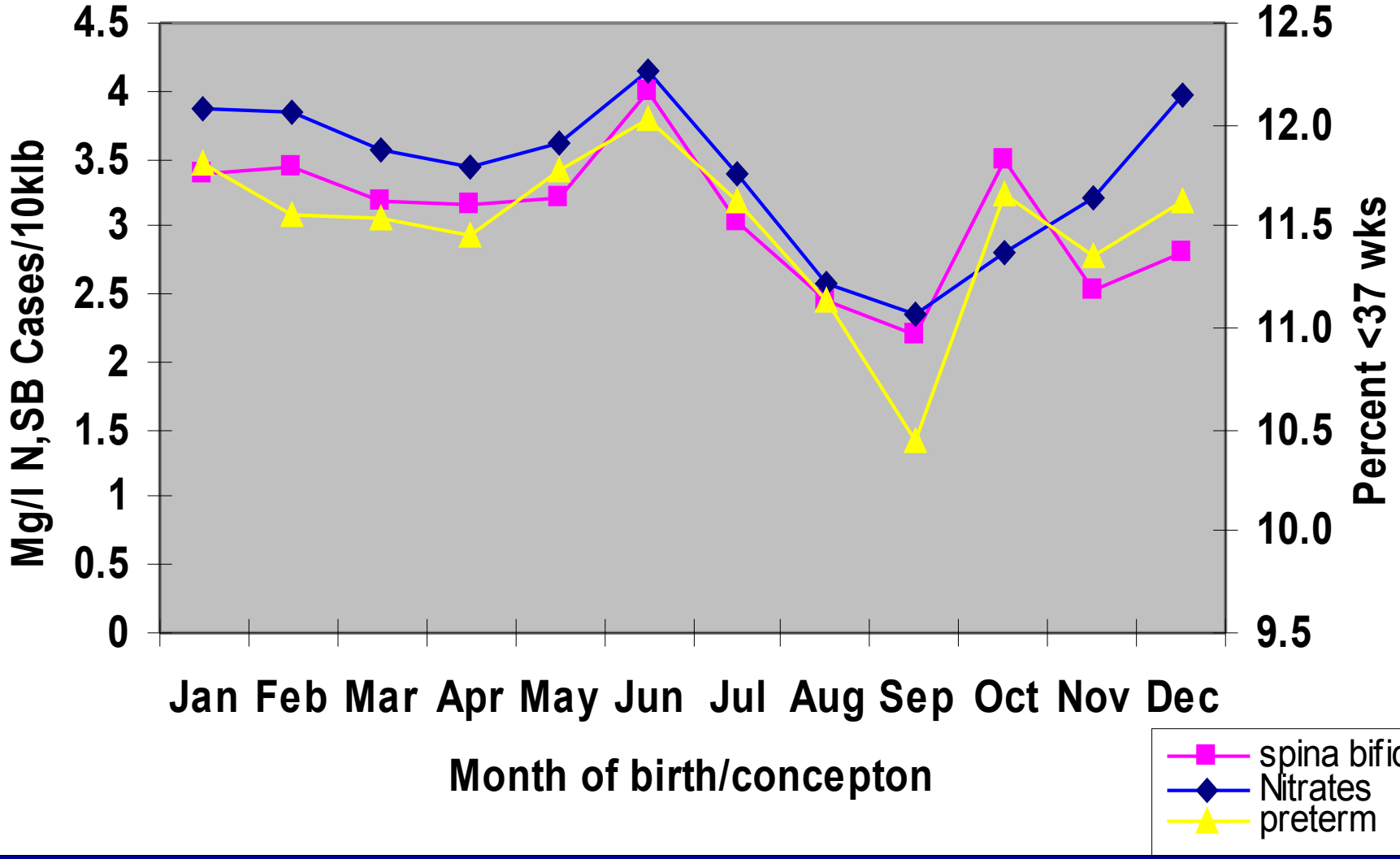




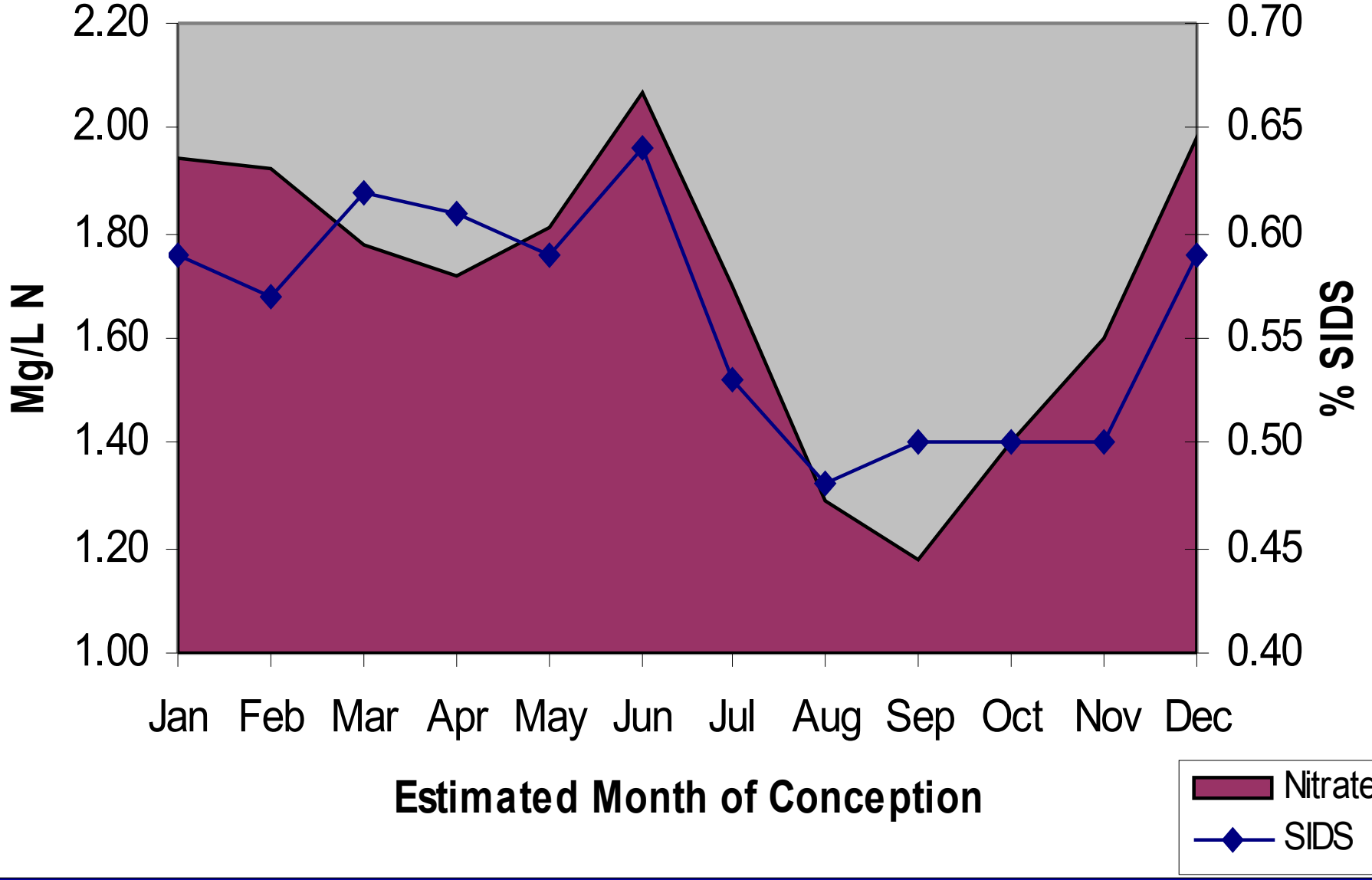
California Preterm Birth Rates are Significantly Associated with County of Residence Pesticide Ranking

Winchester P, Gordon,L, Proctor, C, 2008

Preterm Birth,Spina Bifida and Nitrates 1990-2002



SIDS vs Nitrates US, 1996-2002



Scholastic Achievement and Pesticides

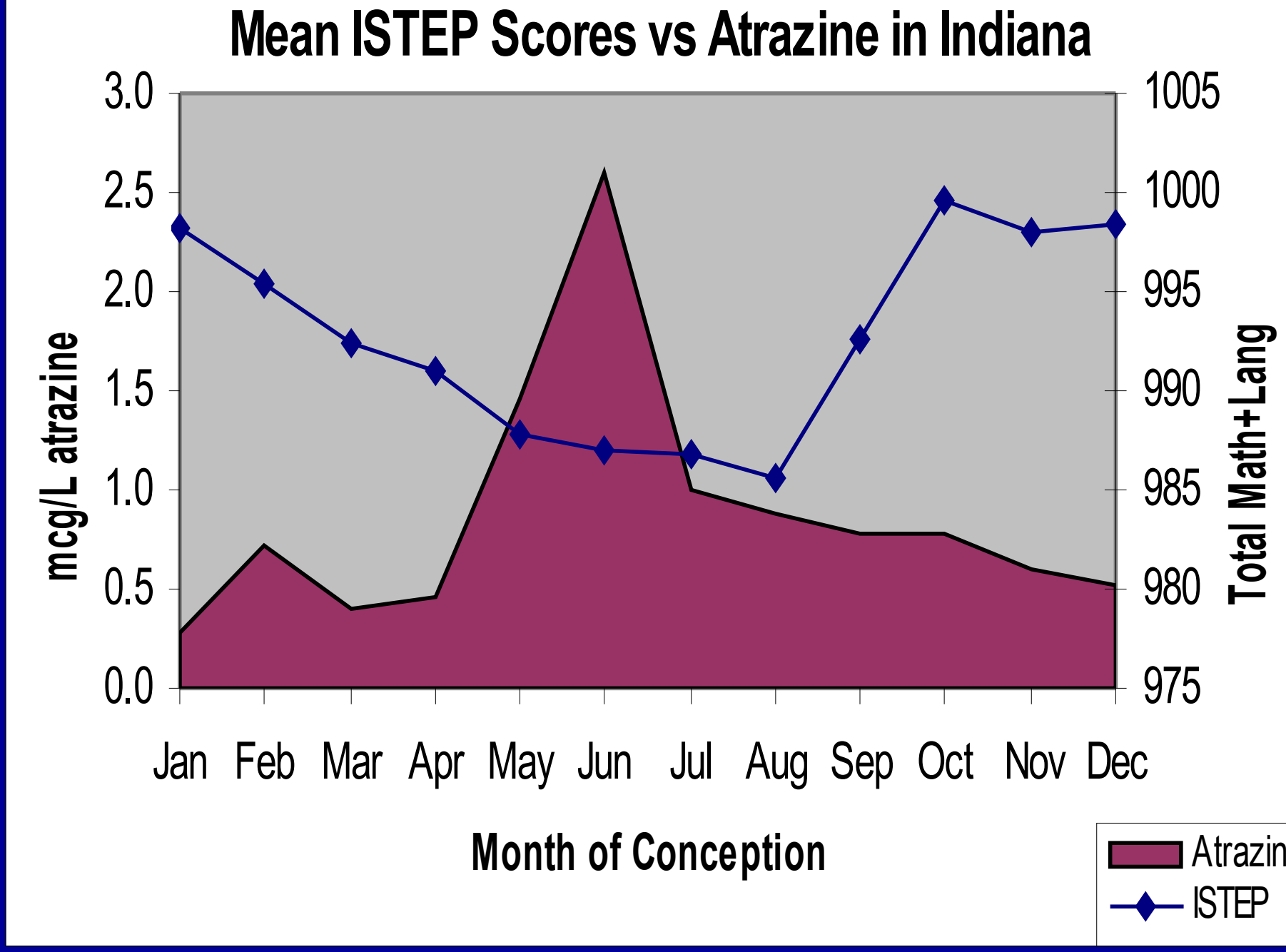
- Maternal thyroid determines cognitive outcome of offspring (esp. 1st trimester)
- Maternal PCBs and Pesticides reduce cognitive performance in offspring

  Jacobson JL, Jacobson SW. 1996. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 335:783-9.

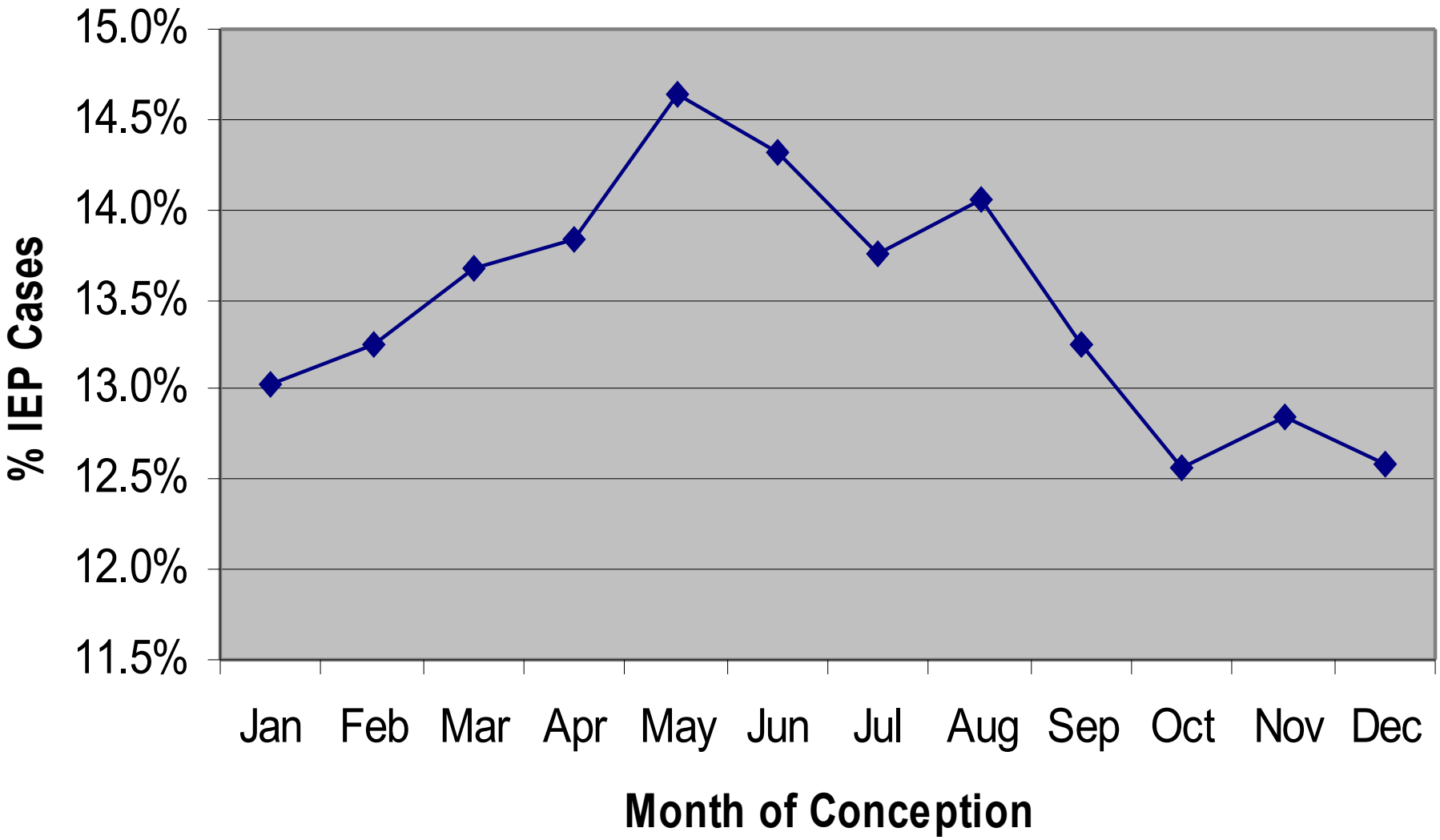
- Maternal PCBs and Pesticides correlate with Maternal thyroid hormone levels

Indiana ISTEP Scores

- We obtained ISTEP scores from Indiana students conceived 1990-2002.
- We used birth dates to calculate months of conception.
- We correlated ISTEP scores with mean atrazine and nitrate concentrations in Indiana surface water 1990-2002


Mean ISTEP Scores vs Atrazine in Indiana
3.0
2.5
2.0
1.5
1.0
0.5
0.0
mcg/L atrazine
1005
1000
995
990
985
980
975
Total Math+Lang
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month of Conception
Atrazine
ISTEP

IEP rate per Month of Conception in Indiana

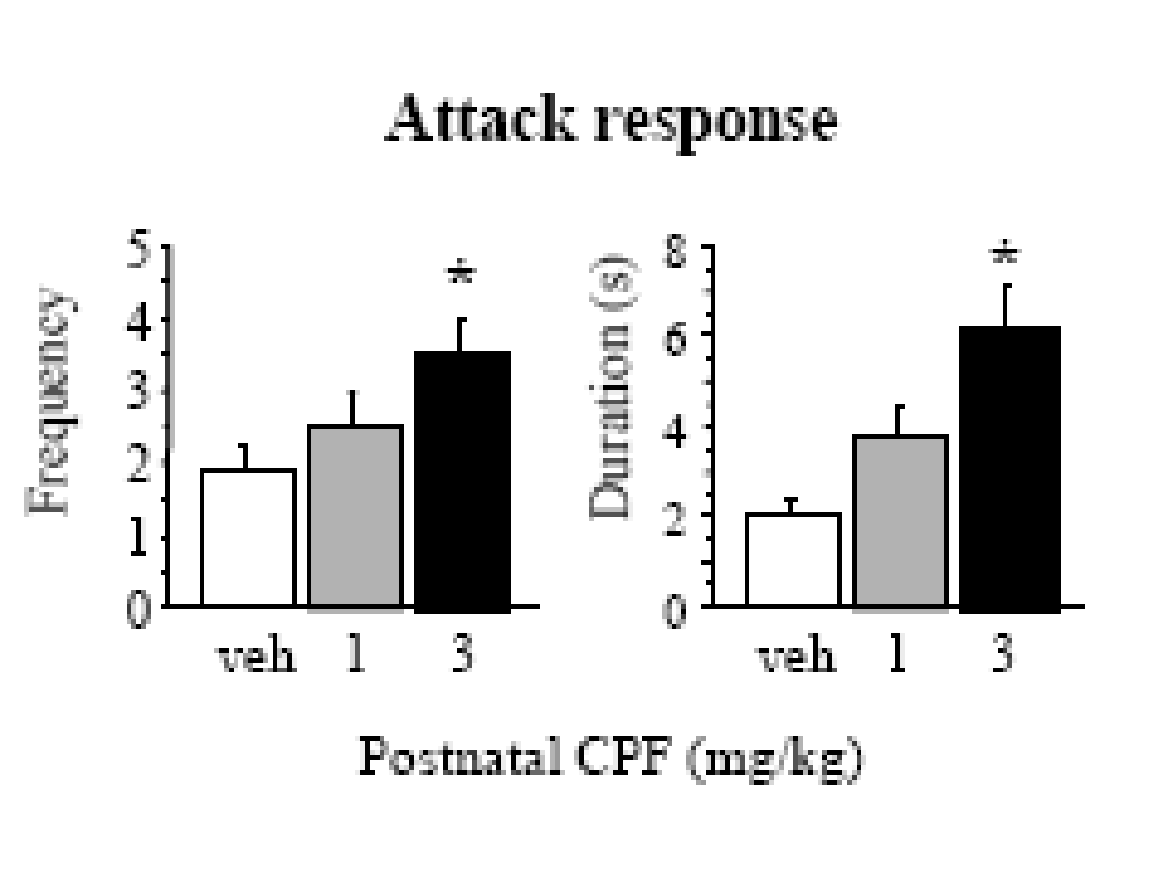


Behaviors Linked to Prenatal Bisphenol A & Pesticides

- Agression Environ Health Perspect. 2003 Feb;111(2):175-8, Pharmacol Biochem Behav. 1999 Dec;64(4):665-72
- Depression
- Learning and memory
- Anxiety
- Maternal behavior
- Sexual identity
- Attention

Male Attack Response & Pesticide Exposure

Toxicological Sciences 2006



Prenatal exposure to PCBs
less masculinized play behavior in boys
more masculinized play behavior in girls.

Effects of Perinatal Exposure to PCBs and Dioxins on Play Behavior in Dutch Children at School Age

Hestien J.I. Vreugdenhil,1 Froukje M. E. Slijper,2 Paul G.H. Mulder,3 and Nynke Weisglas-Kuperus1

Environ Health Perspect 110:A593–A598 (2002).

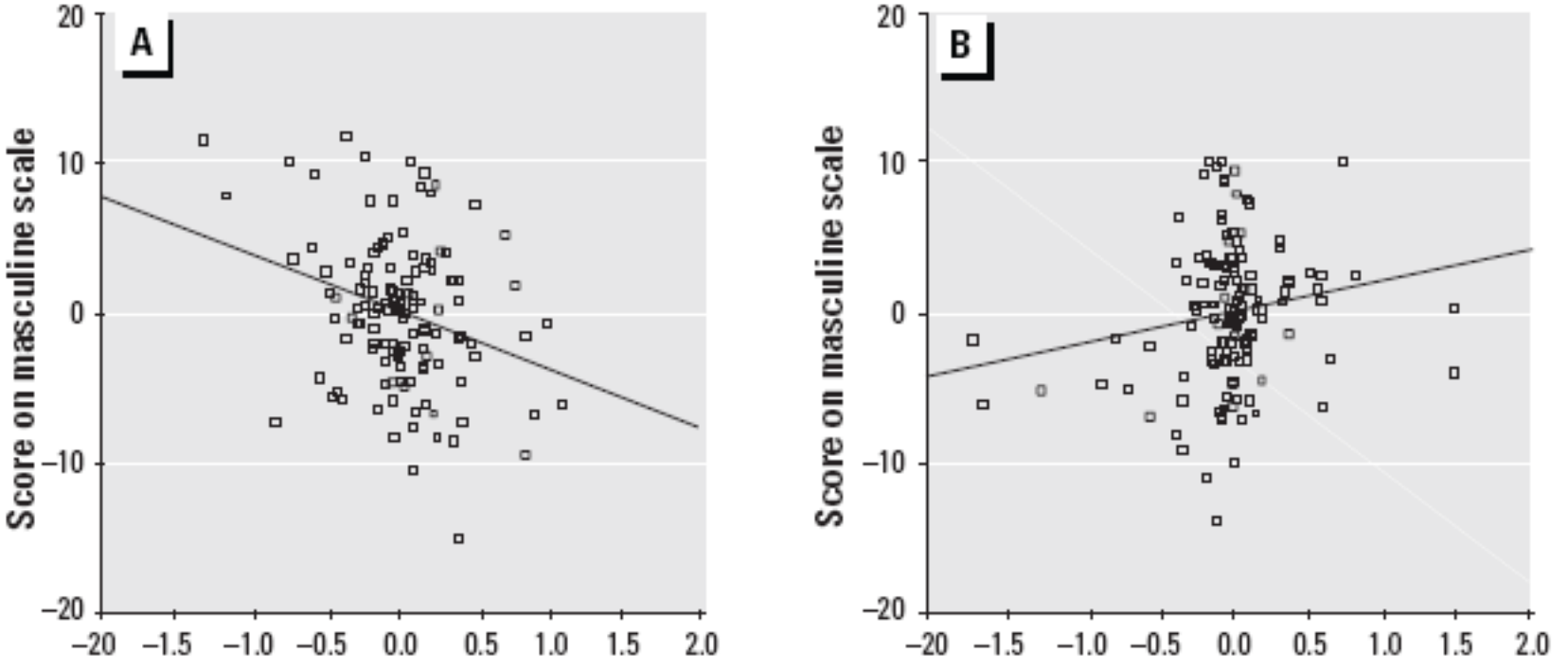


Figure 1. Relation in boys (*A*) (*r* partial = –0.29) and in girls (*B*) (*r* partial = +0.17) between scores on the masculine scale and levels of $\ln\Sigma PCB_{cord}$, adjusted for confounding variables; partial regression plot.

Could Fetal Environment Affect Breast Feeding Ability?

Exposure to a Low Dose of Bisphenol A during Fetal Life or in Adulthood Alters Maternal Behavior in Mice

Paola Palanza,[1] Kembra L. Howdeshell,[2] Stefano Parmigiani,[1] and Frederick S. vom Saal[2]

Environ Health Perspect 110(suppl 3):415–422 (2002).

Fetal BPA; Reduced Nursing, Maternal Behavior

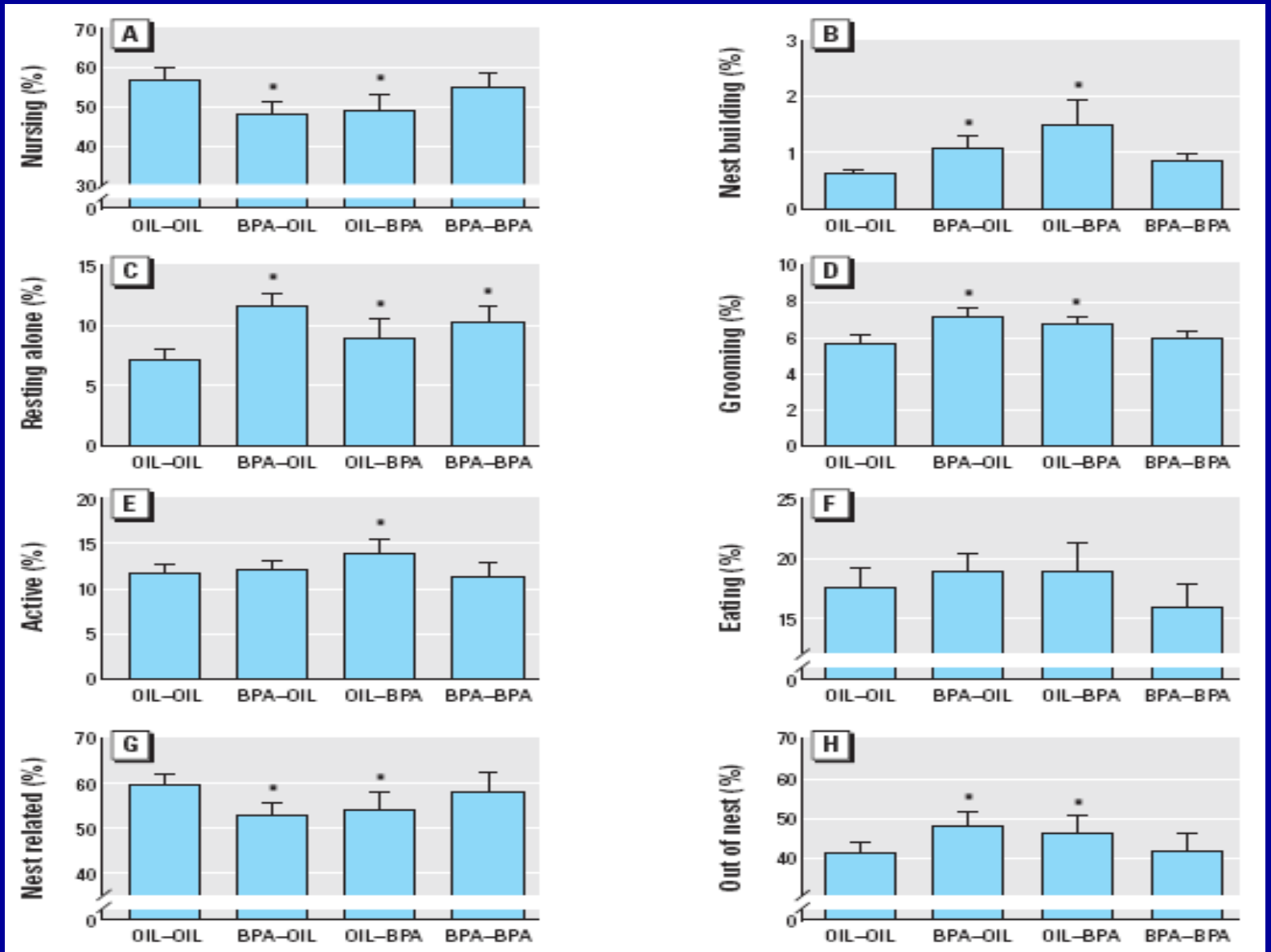
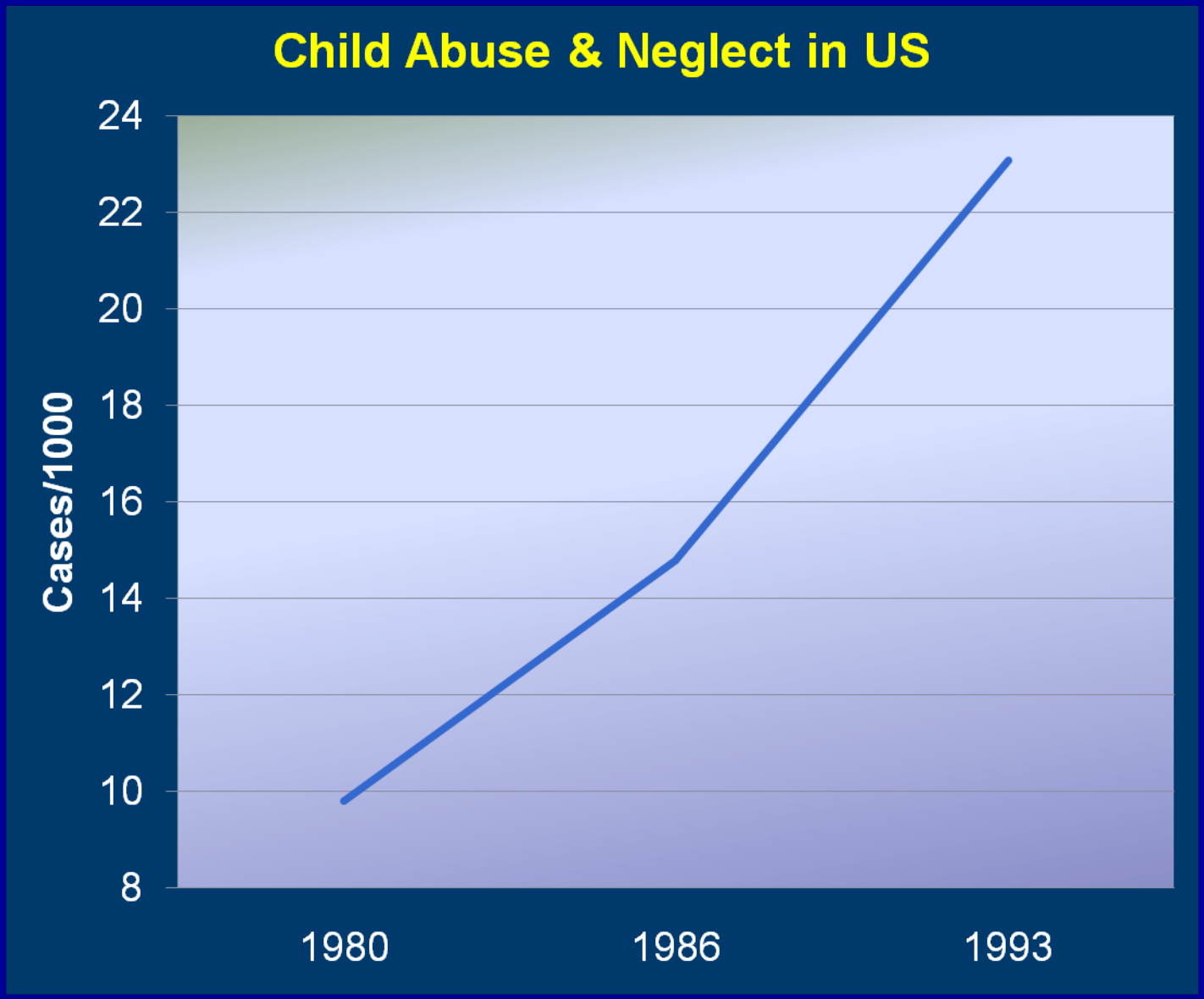


Figure 1. Average percent time (mean ± SE) spent on maternal behavior variables during PNDs 2–15 for dams exposed to 10 µg/kg/day BPA only *in utero* (BPA–OIL), only during gestation (OIL–BPA), or both *in utero* and during gestation (BPA–BPA). *Significantly different from control (OIL–OIL) (Holms *t*-test, $p < 0.05$).

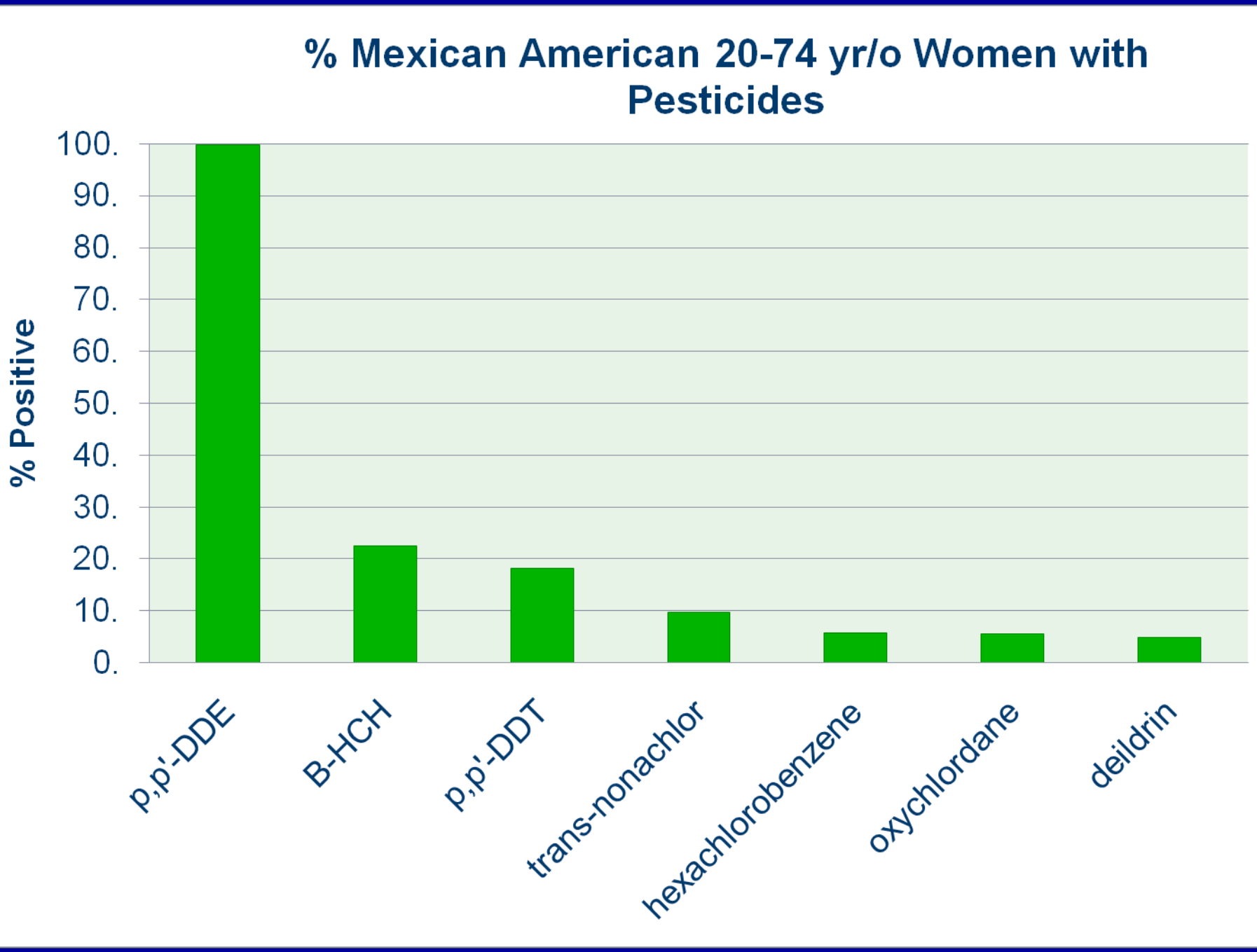
Is the US Experiencing an Epidemic?



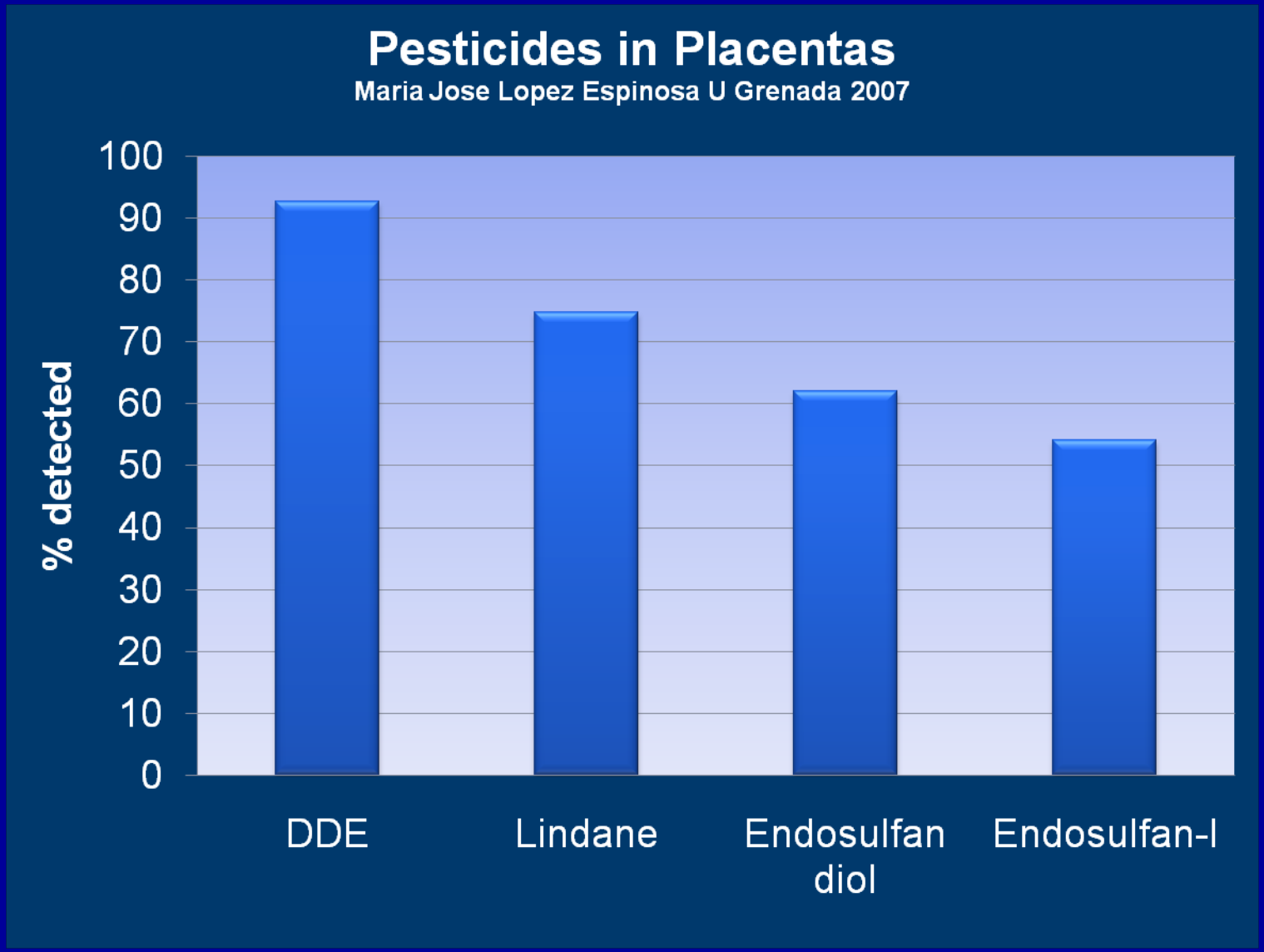
How Prevalent are Pesticide Exposures in Pregnancy?

- 100% of maternal and cord blood samples had Chlorpyrifos, diazinon, or propoxur (Perera, Tang and Whyatt)
- 8 phthalate metabolites detected in 100% of urine samples of women
- 100% of breast milk samples in Indiana had flame retardants (Hites et al).
- 100% Placentas had pesticides Isabel Cerrillo 2004

Mercury in Wisconsin Pregnancies Gliori et al Wisc Med J.2006,105,2


% Mexican American 20-74 yr/o Women with Pesticides
% Positive
100.
90.
80.
70.
60.
50.
40.
30.
20.
10.
0.
p,p'-DDE
B-HCH
p,p'-DDT
trans-nonachlor
hexachlorobenzene
oxychlordane
deildrin

Pesticides in100 % of Placentas



What Adverse Effects Have Been Found? (Perera et al.)

- PAHs/PAH-DNA adducts: , lower birth wt, head circumference, lower developmental scores and developmental delays in young children
- Chlorpyrifos:, lower birth weight, lower developmental scores and developmental delays, ADHD, and other attentional deficits

Risk of Autistic Disorder in Affected Offspring of Mothers With a Glutathione *S*-Transferase P1 Haplotype

Tanishia A. Williams, PhD; Audrey E. Mars, MD; Steven G. Buyske, PhD; Edward S. Stenroos, BS; Rong Wang, MS; Marivic F. Factura-Santiago, MD; George H. Lambert, MD; William G. Johnson, MD

Arch Pediatr Adolesc Med. 2007;161:356-361.

Gene-Environment Interactions

- Polymorphisms of the glutathione *S*-transferase P1 gene (*GSTP1*) act in the mother during pregnancy to contribute to autistic disorder (AD) in her fetus.

GSTP1 A overtransmission suggests mothers risk during pregnancy is the key risk to her child's likelihood of developing Autism.

Influence of Glutathione S-Transferase Polymorphisms on Cognitive Functioning Effects Induced by DDT among Preschoolers

Eva Morales, Jordi Sunyer, Francesc Castro-Giner, Xavier Estivill, Jordi Julvez, Nuria Ribas-Fitó, Maties Torrent, Joan O. Grimalt, and Rafael de Cid

doi:10.1289/ehp.11303 (available at http://dx.doi.org/)

Online 30 July 2008

- children with *GSTP1 Val-105* allele are more at risk of the cognitive functioning effects of early life DDT exposure.

DDT in Cord Blood Lowers 4 y/o Cognitive Scores vs GSTP1 Ile/Val or Val/Val Polymorphisms

	GSTP1 genotype		
	Ile/Ile n=149	Ile/Val or Val/Val n=177	p for interaction
McCarthy areas			
General cognitive	7.13 (6.16) p value=0.25	-8.41 (4.21) p value=0.04	0.05
Perceptual-performance	4.67 (5.75) p value=0.42	-3.81 (4.15) p value=0.36	0.21
Memory	0.90 (6.39) p value= 0.89	-6.75 (4.31) p value=0.12	0.35
Quantitative	8.96 (7.228) p value=0.22	-3.58 (1.46) p value=0.02	0.02
Verbal	0.62 (6.48) p value=0.92	-8.23 (4.30) p value=0.05	0.34
Motor	10.33 (5.62) p value=0.07	2.94 (4.08) p value=0.47	0.36
Executive function	10.17 (6.43) p value=0.12	-10.14 (4.24) p value=0.02	0.01
Working memory	7.36 (6.91) p value=0.29	-2.75 (1.16) p value=0.02	0.02

- DDT ;Oxidative stress, estrogenic
- GSTP1 Ile/Ile antoxidant, protective
- General Cognitive
- Quantitative
- Verbal
- Exec Function
- Working Memory

Polymorphisms in biotransformation enzymes and the risk for recurrent early pregnancy loss

Zusterzee,PL,Nelen,WLD,Roelfs,HMJ,Peters,WHM, Blom,HJ,Steegers, AP

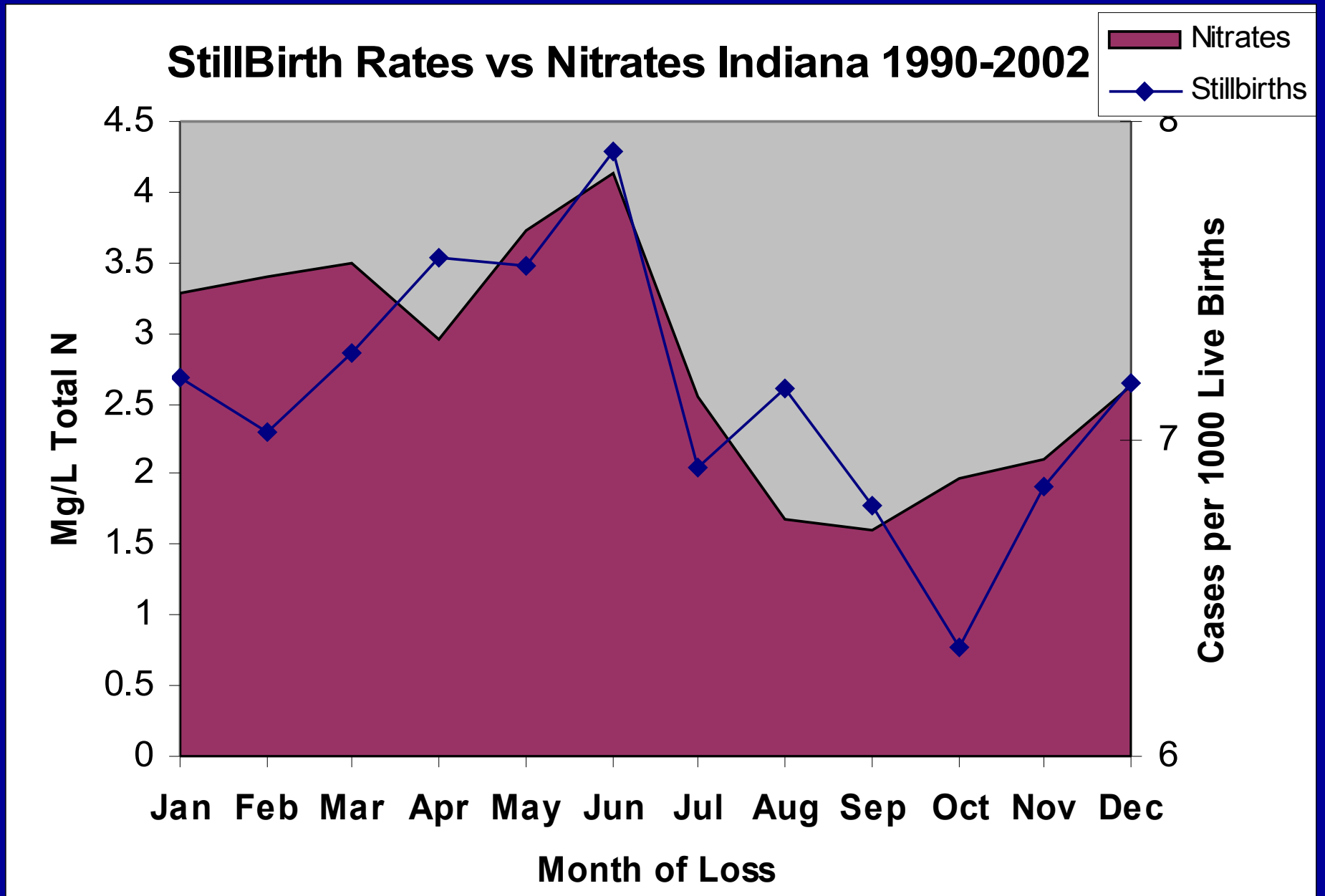
Molecular Human Reproduction vol.6 pp. 474-478,2000

Cytochrome P450 genes and glutathione S-transferase genes needed for detoxification

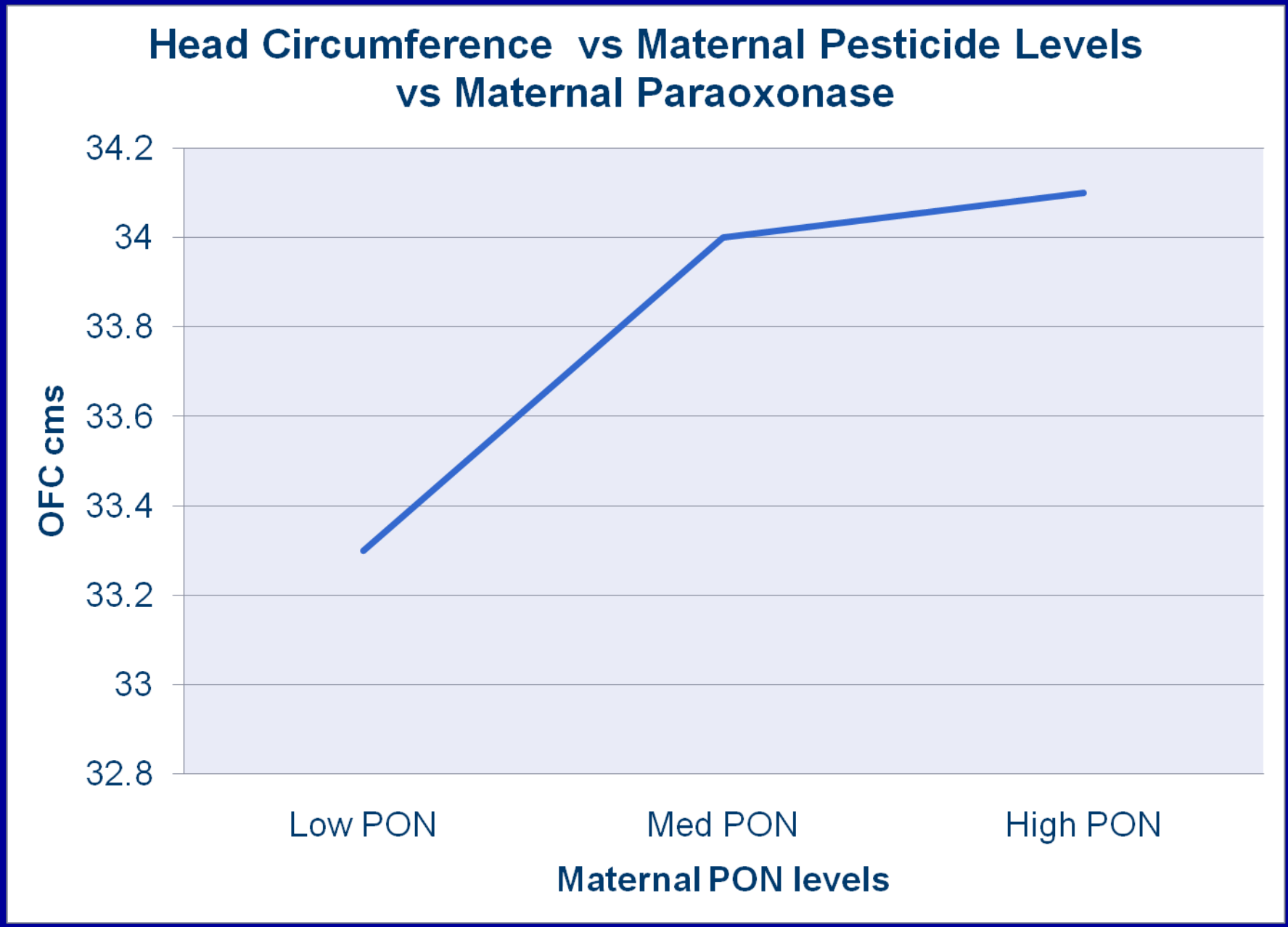
- Glutathione S-transferase P1b-1b more common in women with recurrent early pregnancy loss (12% vs 5% controls) p=.03
- Risk increased for coffee drinkers and smokers.

Conclusions

- Lower GS-t Pi enzyme activity in placenta
- Leads to impaired detoxification
- Early pregnancy loss


StillBirth Rates vs Nitrates Indiana 1990-2002
Nitrates
Stillbirths
Mg/L Total N
Cases per 1000 Live Births
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
8
7
6
Jan
Feb
Mar
Apr
May
Jun
Jul
Aug
Sep
Oct
Nov
Dec
Month of Loss

Pregnancy Pesticide Exposure vs Head Circumference



Do Pesticides In Pregnancy Really Pose That Big a Threat?

- M. Skinner exposed pregnant rats to vinclozolin or methoxychlor
- Evaluated effects on offspring

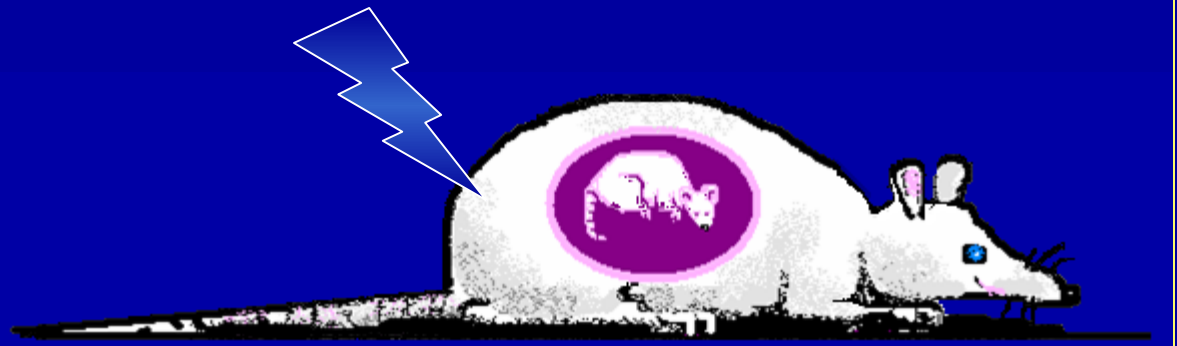
Transgenerational Epigenetic Imprinting of the Male Germline by Endocrine Disruptor Exposure during Gonadal Sex Determination

Hung-Shu Chang, Matthew D. Anway, Stephen S. Rekow, and Michael K. Skinner

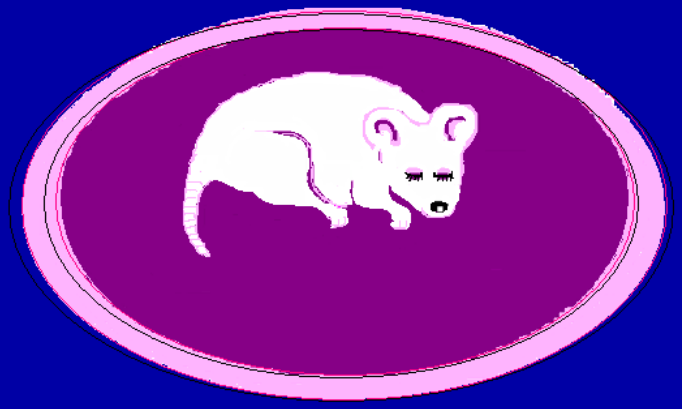
Center for Reproductive Biology, School of Molecular Biosciences, Washington State University, Pullman Washington 99164-4231

Endocrinology 147(12):5524–5541, 2006

Pregnant Rat



Vinclozolin Exposure
(days 8-14)



Offspring

Fetal Exposure: Adult disease

- Low sperm count
- Infertility
- Cancer
- Kidney
- Prostate
- Pregnancy abnormalities
- Immune dysfunction
- High cholesterol
- Accelerated aging

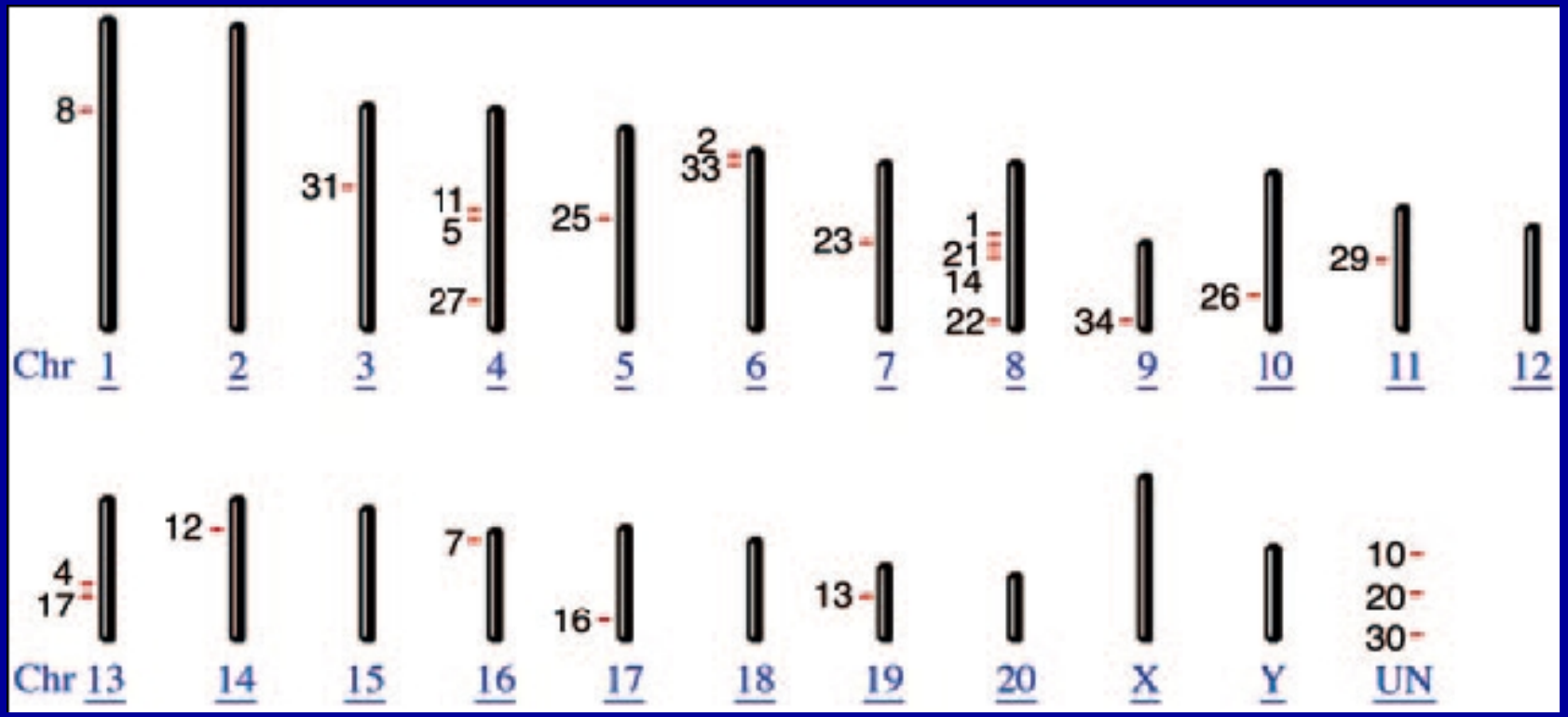
Transgenerational Effects of Fetal Pesticide Exposure

- F1 males mated
- Unexposed F2,F3 and F4 male offspring had same diseases as their fathers (and great grandfathers)

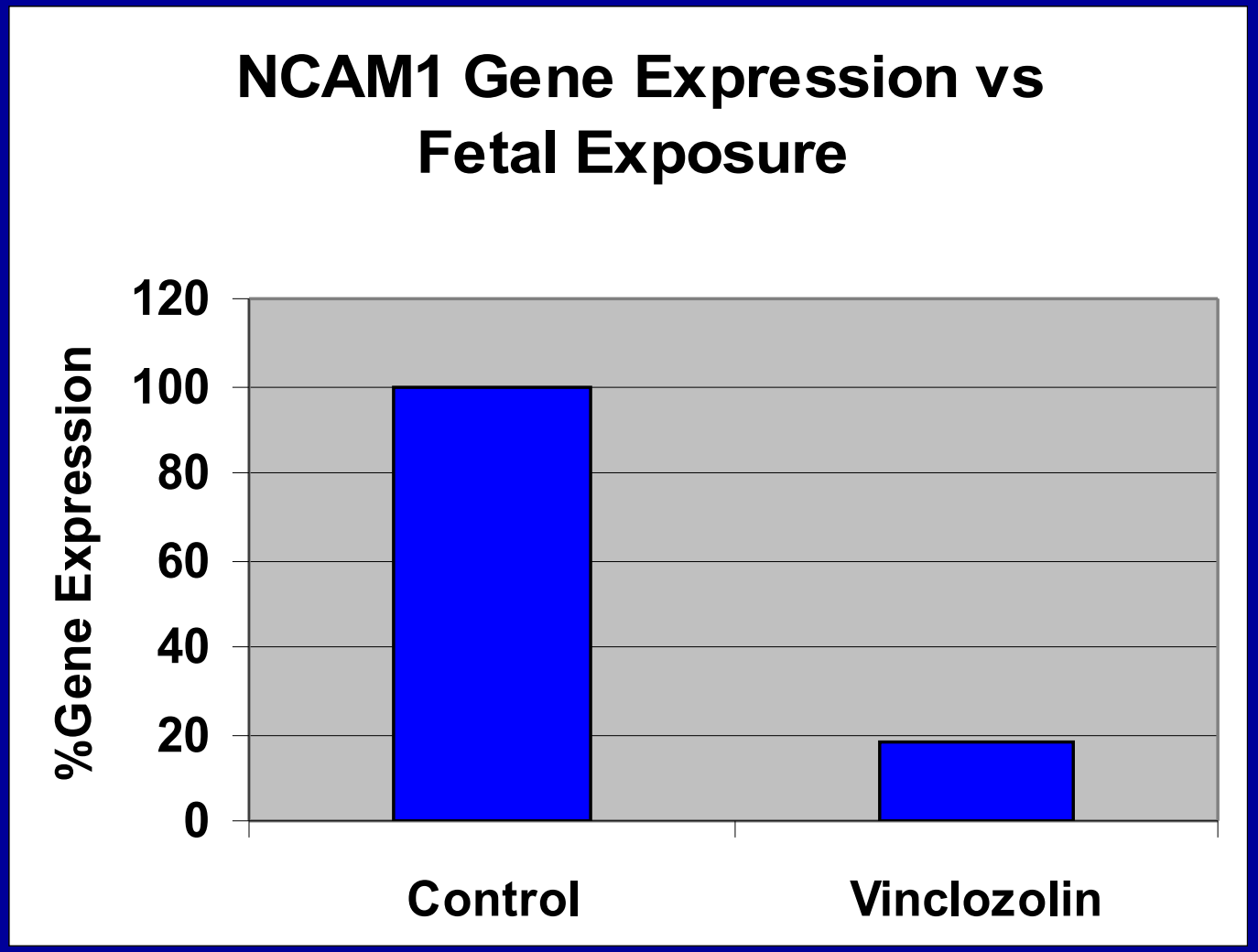
Skinner Found DNA Methylation

- 25 DNA sequences had new methylation sites
- Each sequence altered neighboring DNA
- Altered proteins numbered from hundreds to thousands depending upon the fetal organ
- 954 Prostate. 2008 Jan 25 alterations in prostate, 800 in brain

The chromosome location and physical mapping of each candidate (*numbers*) are indicated for each chromosome (Chr), with those unknown (UN) sequences not mapped indicated.



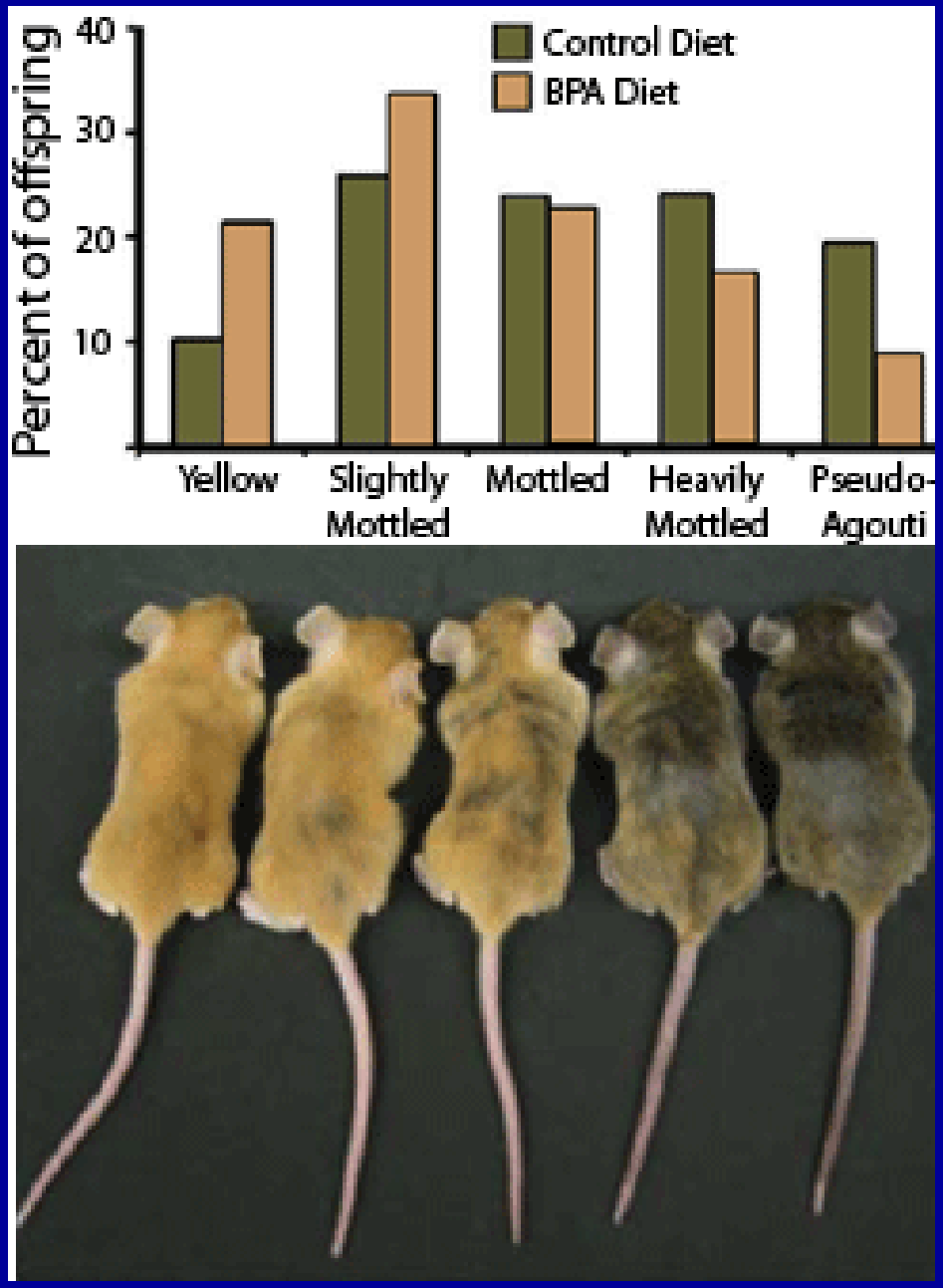
Relative brain expression levels of NCAM1



NCAM1 Gene Related Diseases

- Alzheimers
- Synovial sarcoma
- Schizophrenia
- Mutant-allele-specific amplification (MASA) syndrome
- Neural tube defects
- Various tumor

Agouti-breed mice ordinarily grow into svelte, brown specimens (right). However, when a fetus is exposed to bisphenol A, it can turn into a blond, obese adult (left), showing signs of a gene alteration. Duke Univ. Medical Center



BPA Diet Changed DNA Methylation and Coat Color in Mice

BPA Caused Reduced Methylation of Agouti Gene

- BPA-exposure reduced the percentage of cells with methylation at the nine sites on the Agouti gene by 31%, from 39% methylated in controls to 27% methylated in BPA-exposed ($p = 0.004$).
- The effect of BPA on coat color was on methylation.

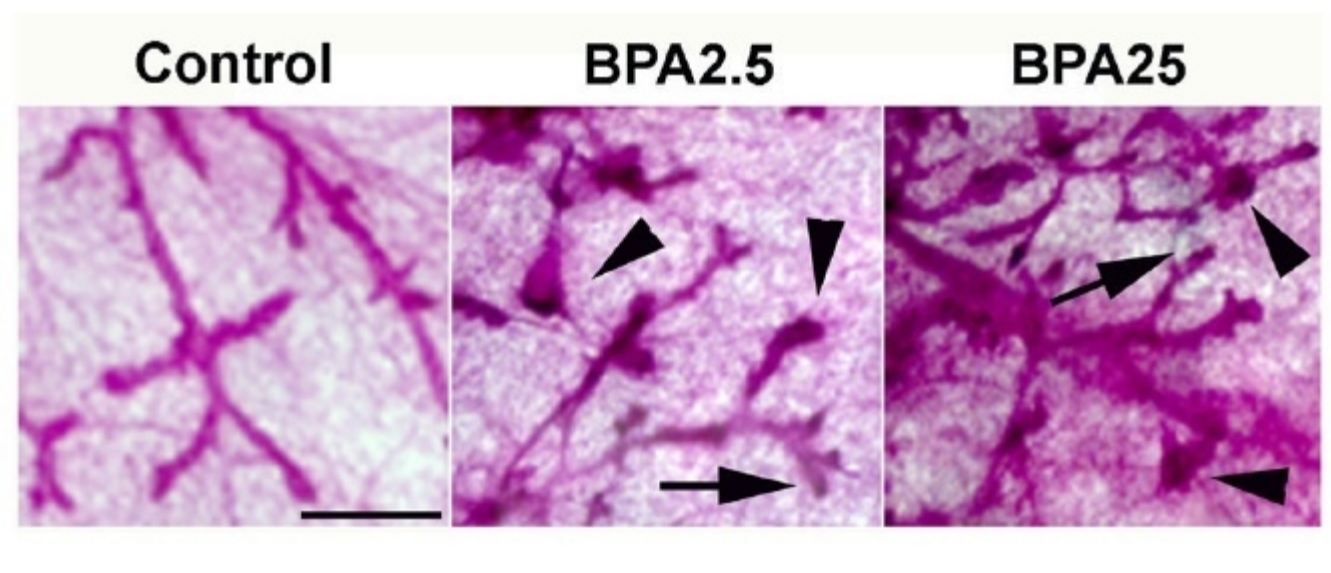
BPA Also Affected Other Genes

- CabpIAP gene BPA-exposed animals had lower methylation rates.
- BPA can cause reduction in methylation on multiple mouse genes.

Induction of mammary gland ductal hyperplasias and carcinoma *in situ following fetal bisphenol A exposure*

Tessa J. Murray, Maricel V. Maffini, Angelo A. Ucci, Carlos Sonnenschein, and Ana M.Soto

Reprod Toxicol. 2007 ; 23(3): 383–390.



Mammary gland whole mounts at PND 95 from control, BPA2.5 and BPA25 groups. The BPAt reated animals developed intraductal hyperplasias, mostly in the terminal ducts (arrowheads).

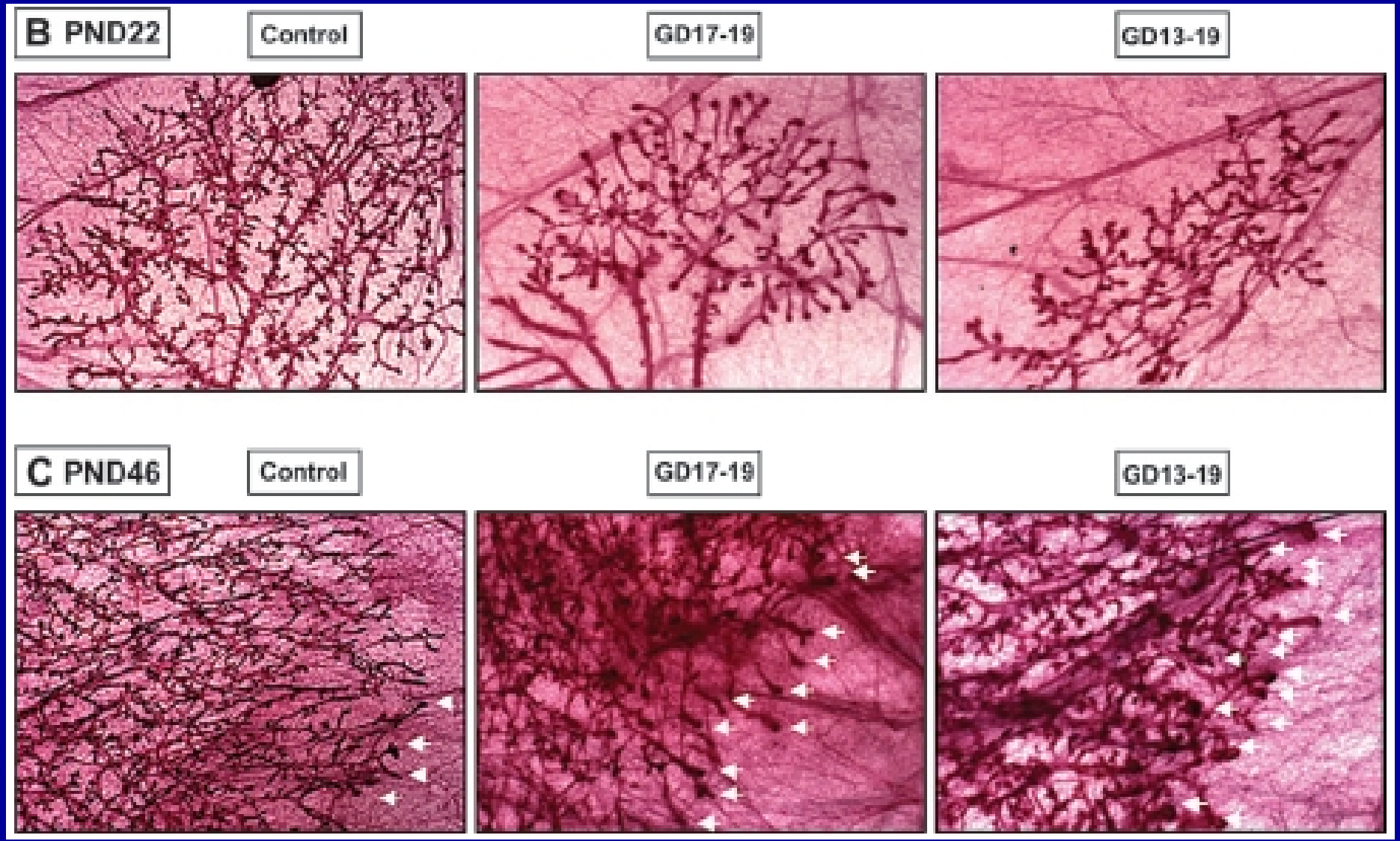
Adverse Effects of Prenatal Exposure to Atrazine During a Critical Period of Mammary Gland Growth

Jennifer L. Rayner,*,† Rolondo R. Enoch,†,2 and Suzanne E. Fenton†,1

TOXICOLOGICAL SCIENCES 87(1), 255–266 (2005)

ATRAZINE exposure during a critical period of fetal Mammary Gland development (GD 17–19), are both delayed MG developmentof the offspring and inadequate nutritional support of F2 offspring, resulting in adverse effects on pup weight gain.

Brief Fetal Atrazine Exposure; Delayed Mammary Gland Development



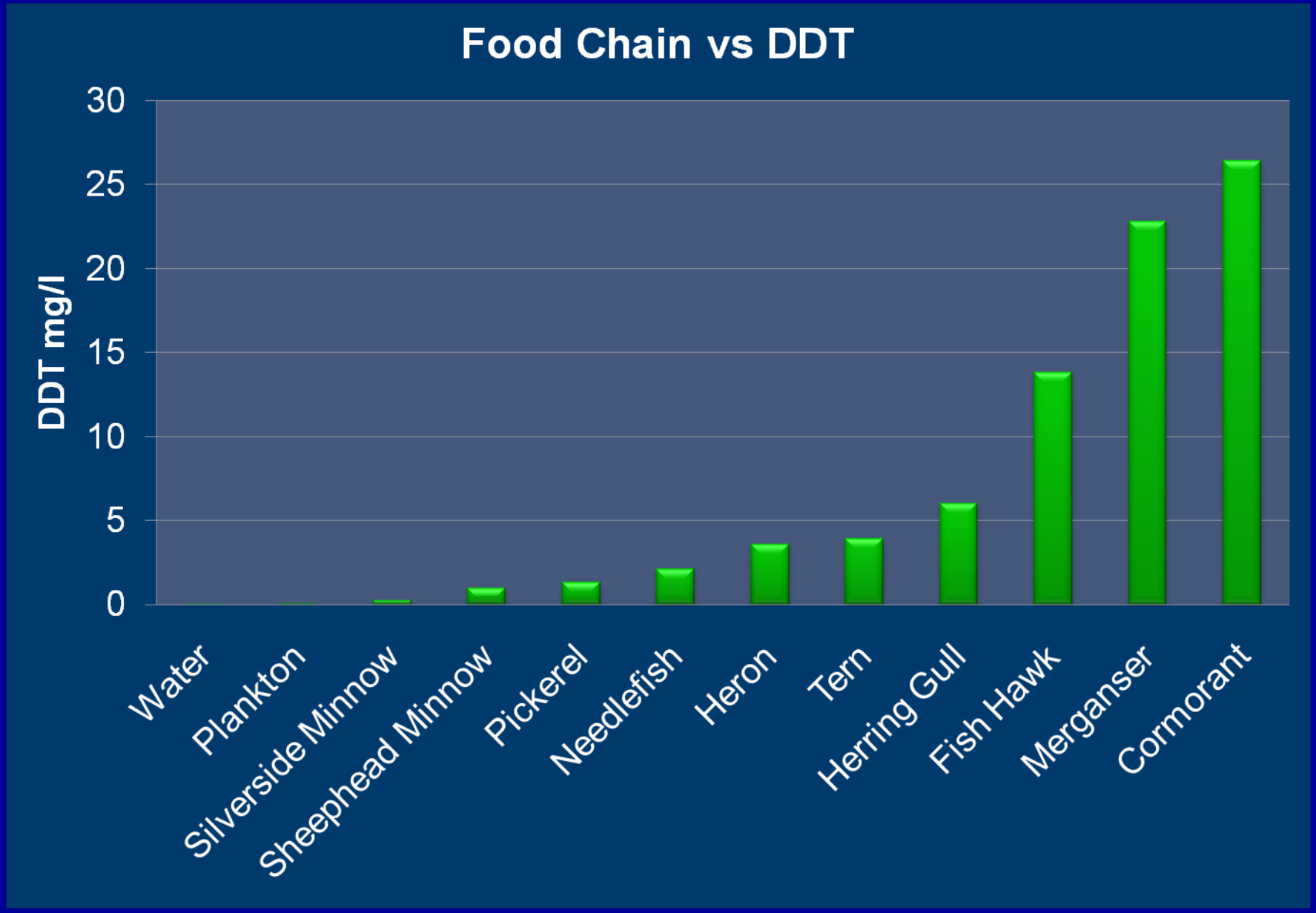
US Body Burden; Pesticides

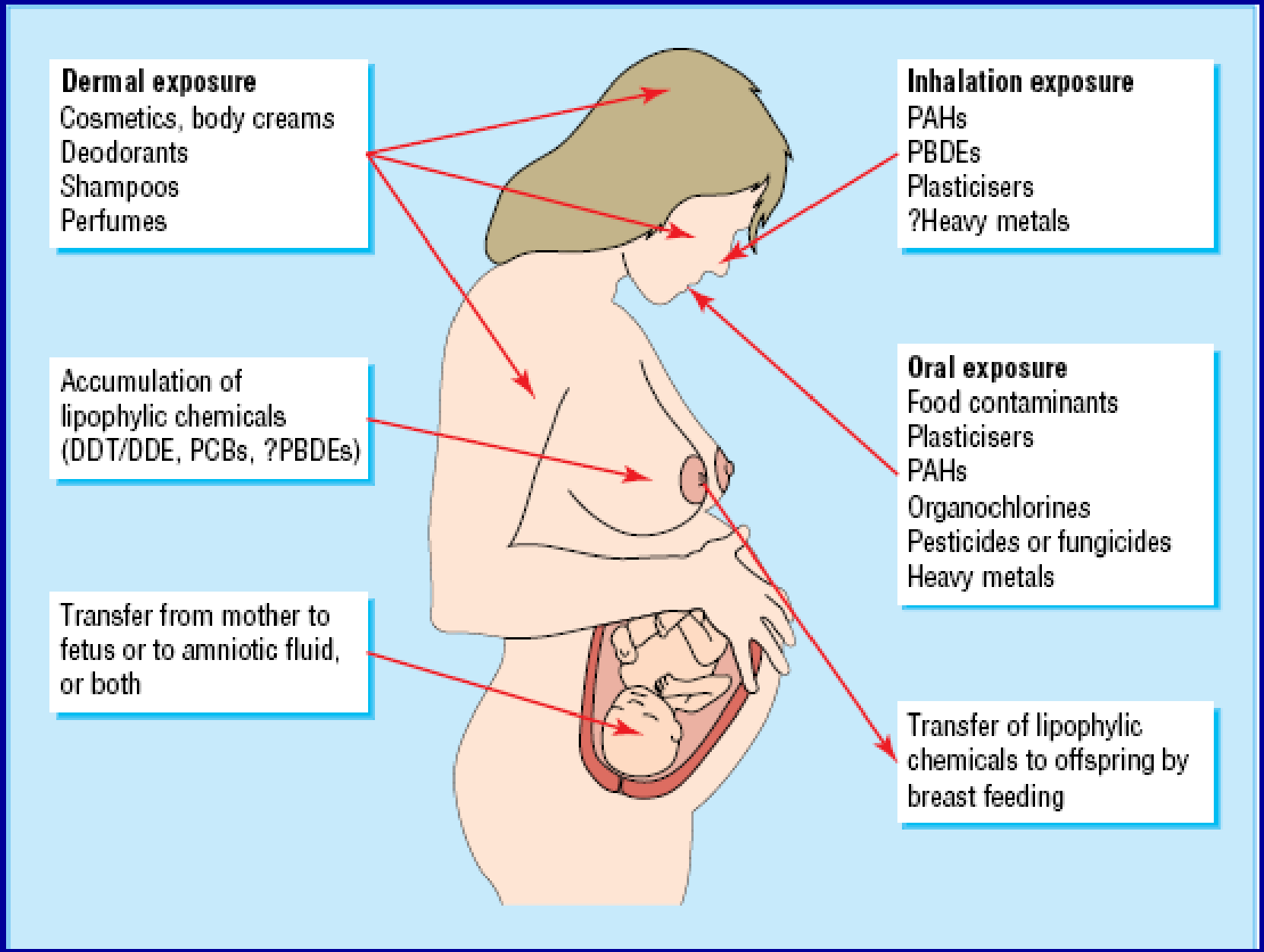
- 97% of US population has pesticides
- 100% breast milk samples in Indiana have Flame retardants
- Pthalates, BPA (BPA was detected in 92.6% *Environ Health Perspect* 116: 39–44 (2008) .
- Mercury,lead, universal
- Nitrates increasing annually
- Benzophenone-3 (sun screen) 96.8% EHP,2008

Toxic Pollution Found In Washingtonians

Toxic Chemicals	Pam Tazioli	Bill Finkbeiner	Karen Bowman	Ann Holmes Redding	Lisa Brown	Laurie Valeriano	Patricia Dawson	Denis Hayes	Allyson Schrier	Deb Abrahamson
PFCs ("Teflon chemicals")	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PBDEs (toxic flame retardants)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Phthalates (plasticizers and fragrance carriers)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Pesticides		✓		✓	✓		✓		✓	✓
DDT (banned pesticide)	✓		✓	✓	✓		✓	✓	✓	✓
PCBs (banned industrial coolant)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Mercury	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Lead			✓							
Arsenic	✓		✓		✓		✓	✓		

Bioconcentration of Persistent Pesticides




Dermal exposure
Cosmetics, body creams
Deodorants
Shampoos
Perfumes
Inhalation exposure
PAHs
PBDEs
Plasticisers
?Heavy metals
Accumulation of lipophylic chemicals (DDT/DDE, PCBs, ?PBDEs)
Oral exposure
Food contaminants
Plasticisers
PAHs
Organochlorines
Pesticides or fungicides
Heavy metals
Transfer from mother to fetus or to amniotic fluid, or both
Transfer of lipophylic chemicals to offspring by breast feeding

Ten Babies: Cord Blood Test Results

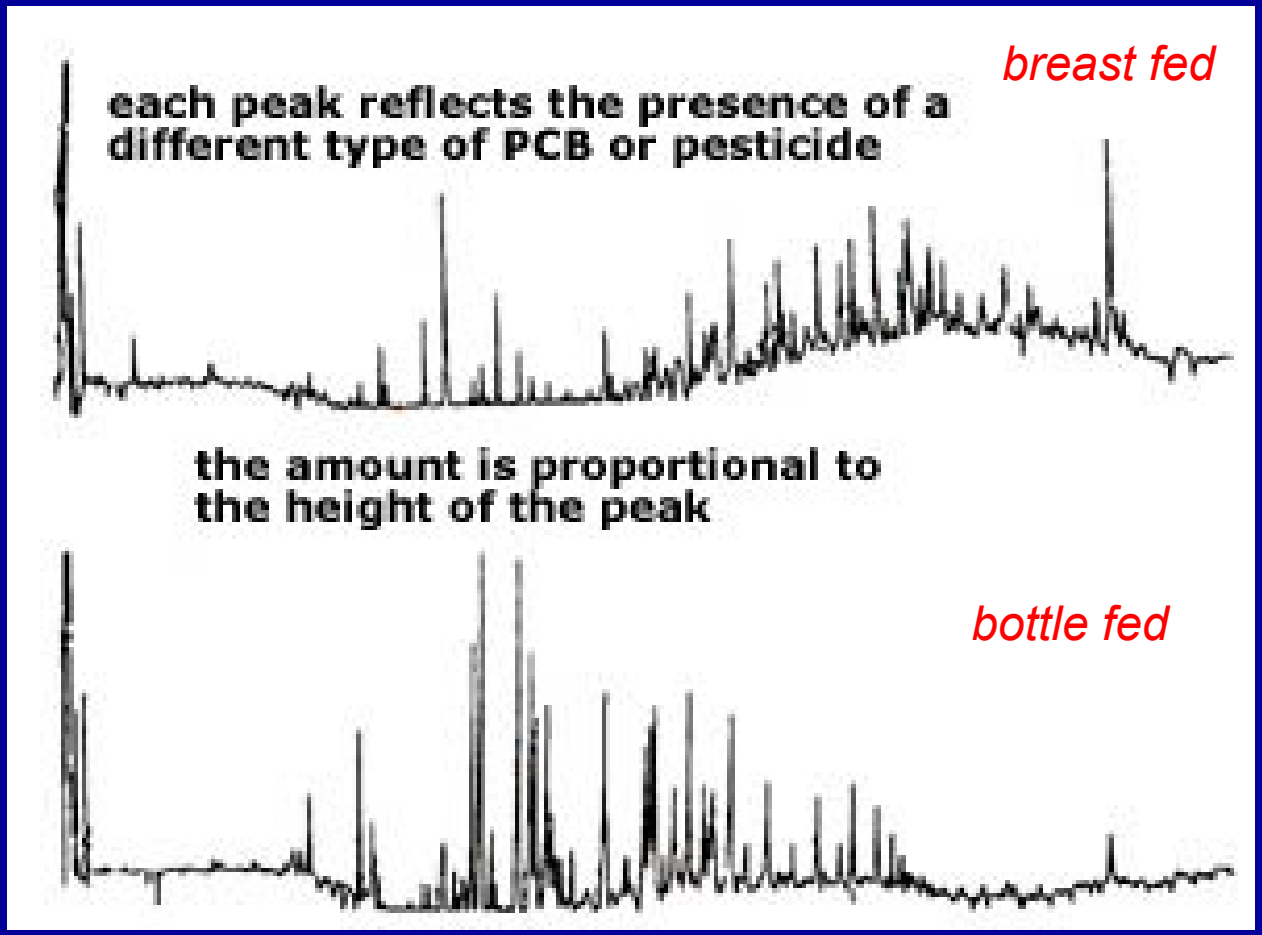
Babies born in August - September 2004 in U.S. Hospitals
Source of cord blood: Red Cross

Number of chemicals detected: 287 out of 413

Bisphenol A and Phthalates

Potent Estrogens in Plastic

Contaminants in Breast and Bottle-Fed Babies

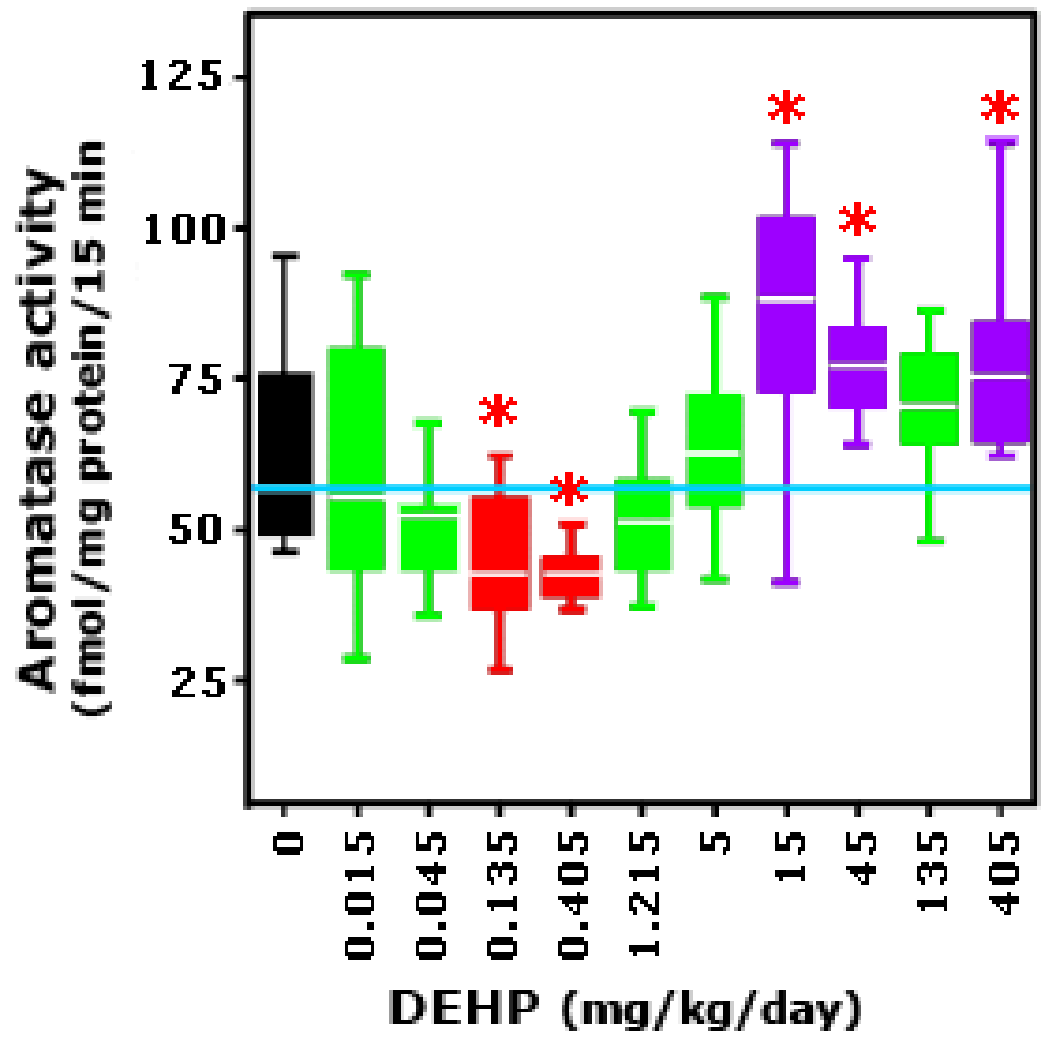


gas chromatographs of baby urine obtained from the diapers of two infants at 1 yr of age.

Bush *et al*. 1990

More than 85,000 synthetic chemicals have been introduced in the last 50 years for industrial, farming, and other uses, yet more than 90% of them have not been tested for their effects on human health. Biomonitoring studies have detected more than 200 toxic substances in breast milk.(3

Phthalate Endocrine Effects Opposite at Low vs High Doses



Aromatase, converts testosterone to estrogen in pregnancy

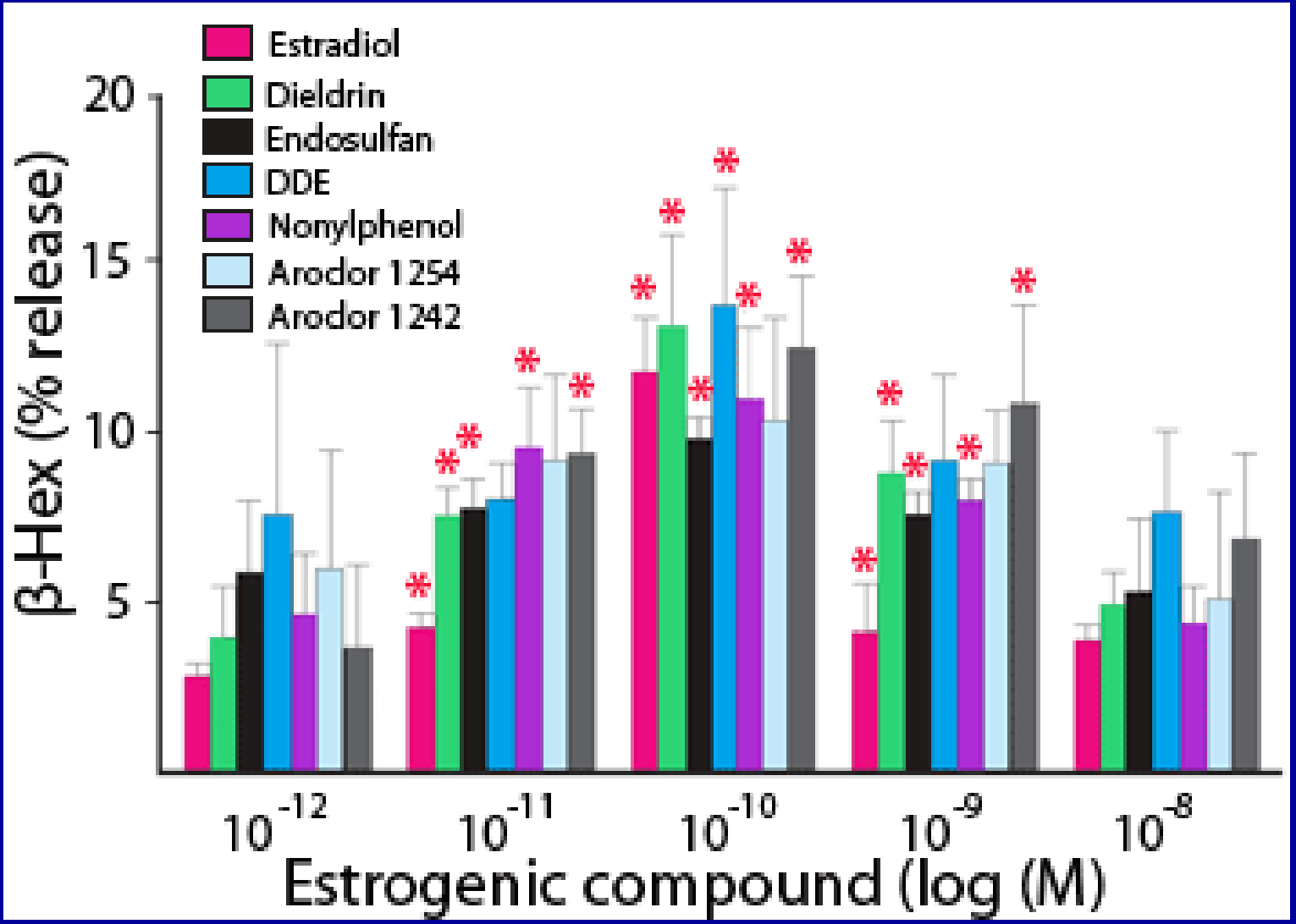
Estrogen early in life is necessary to masculinize the brain of male mammals.

Regulatory tests for DEHP would not have gone below 5mg/kg/day

would have *missed* the aromatase suppression at lower levels.

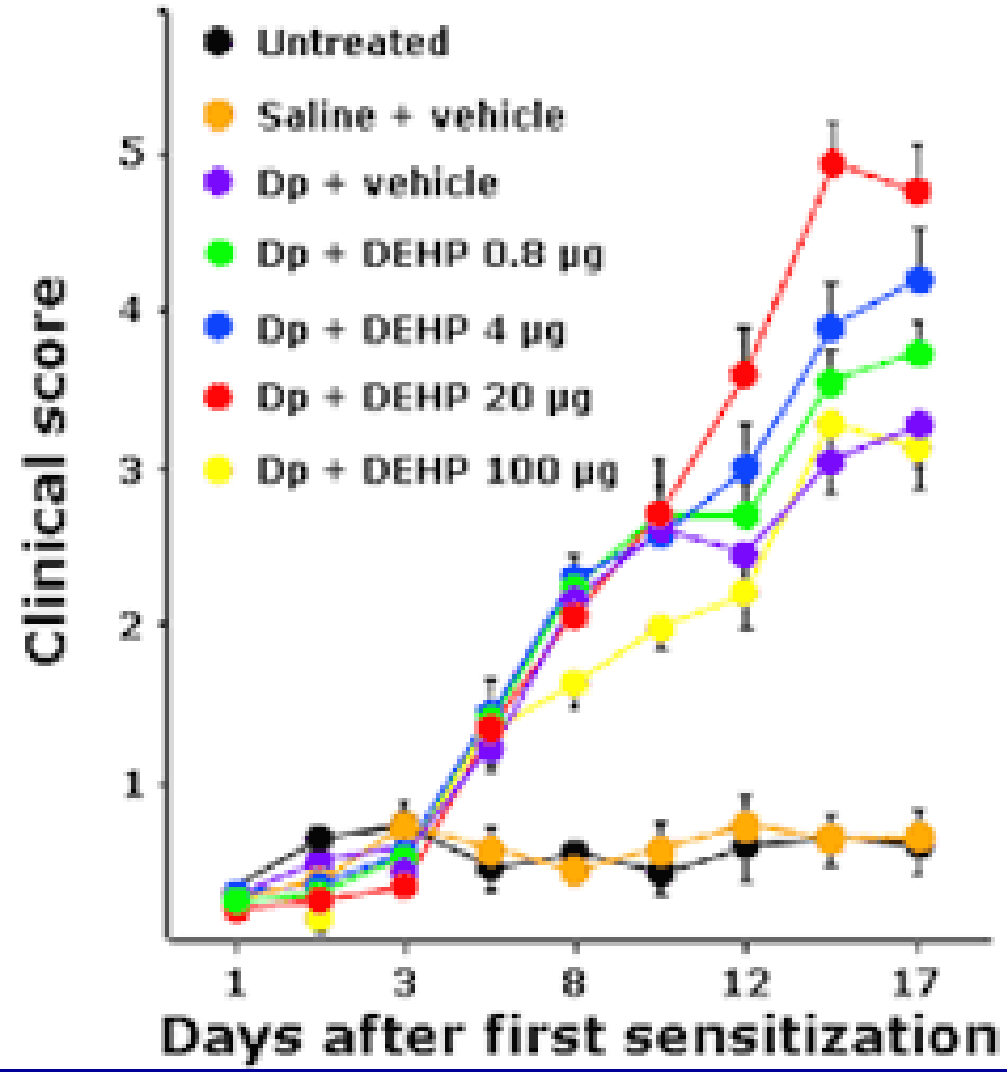
Andrade *et al*. 2006

Pesticides Effects on Histamine Release from Mast Cells Narita *et al*



Phthalates vs Allergic Reaction

Takano *et al*.

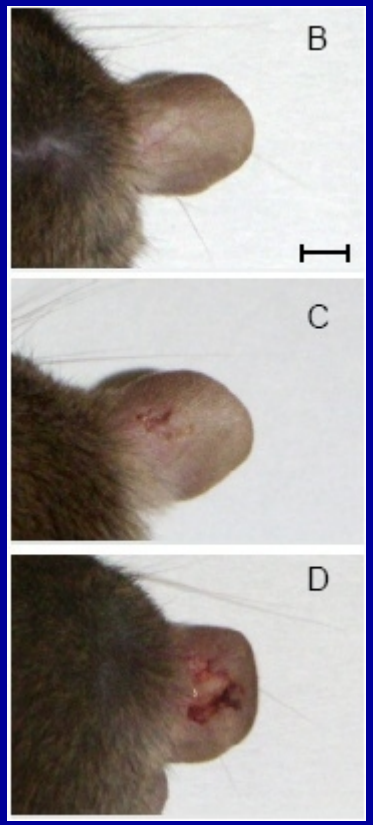


Effects of Maternal Exposure to Di-(2-ethylhexyl) Phthalate during Fetal and/or Neonatal Periods on Atopic Dermatitis in Male Offspring

Rie Yanagisawa, Hirohisa Takano, Ken-ichiro Inoue, Eiko Koike, Kaori Sadakane, Takamichi Ichinose

doi:10.1289/ehp.11191 (available at http://dx.doi.org/)

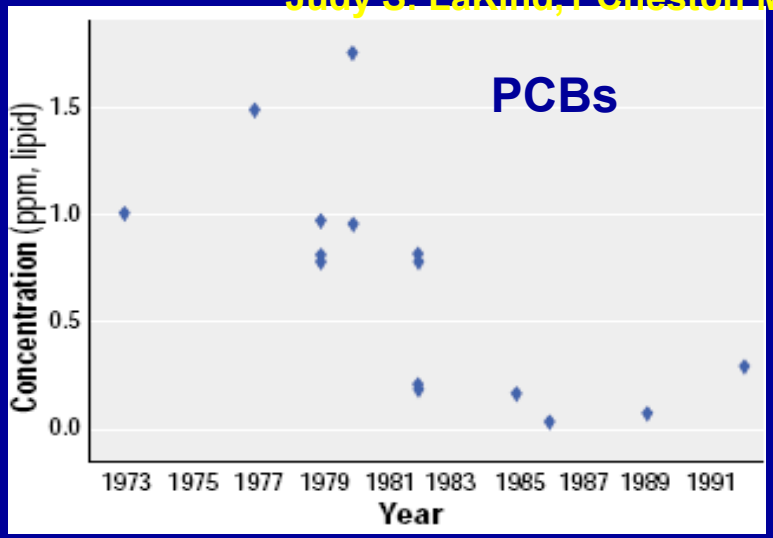
Online 9 April 2008

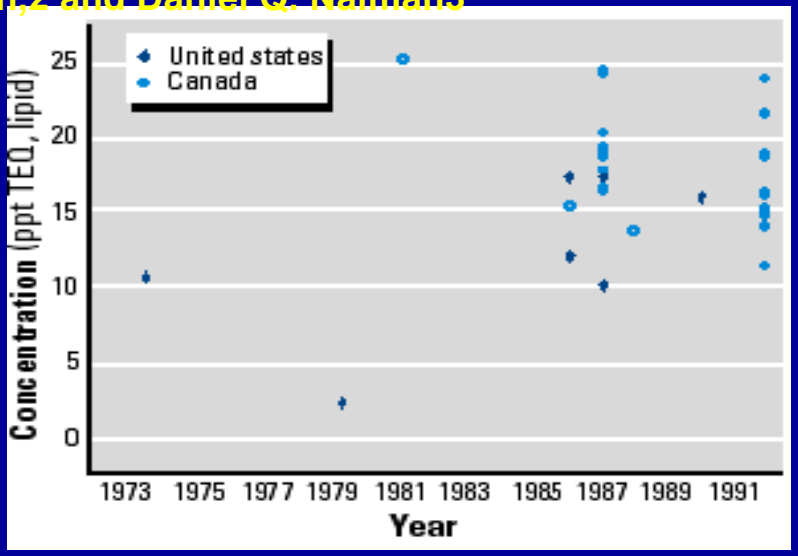


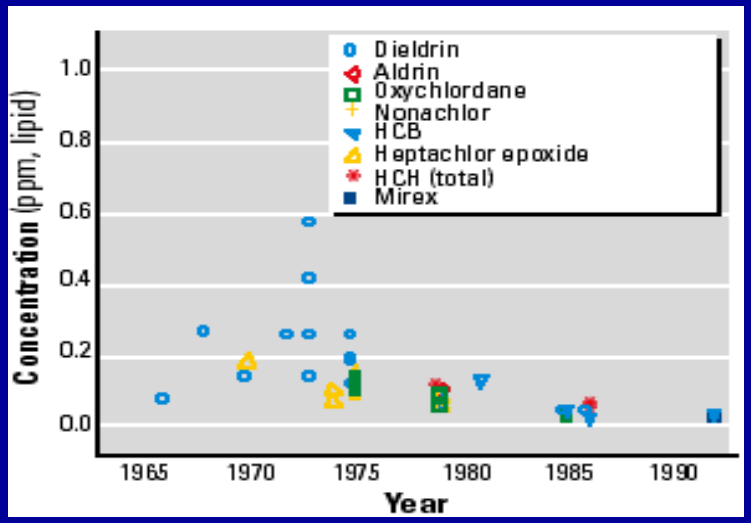
Infant Exposure to Chemicals in Breast Milk in the United States: What We Need to Learn From a Breast Milk Monitoring Program

Environ Health Perspect 109:75–88 (2001).

Judy S. LaKind,1 Cheston M. Berlin,2 and Daniel Q. Naiman3

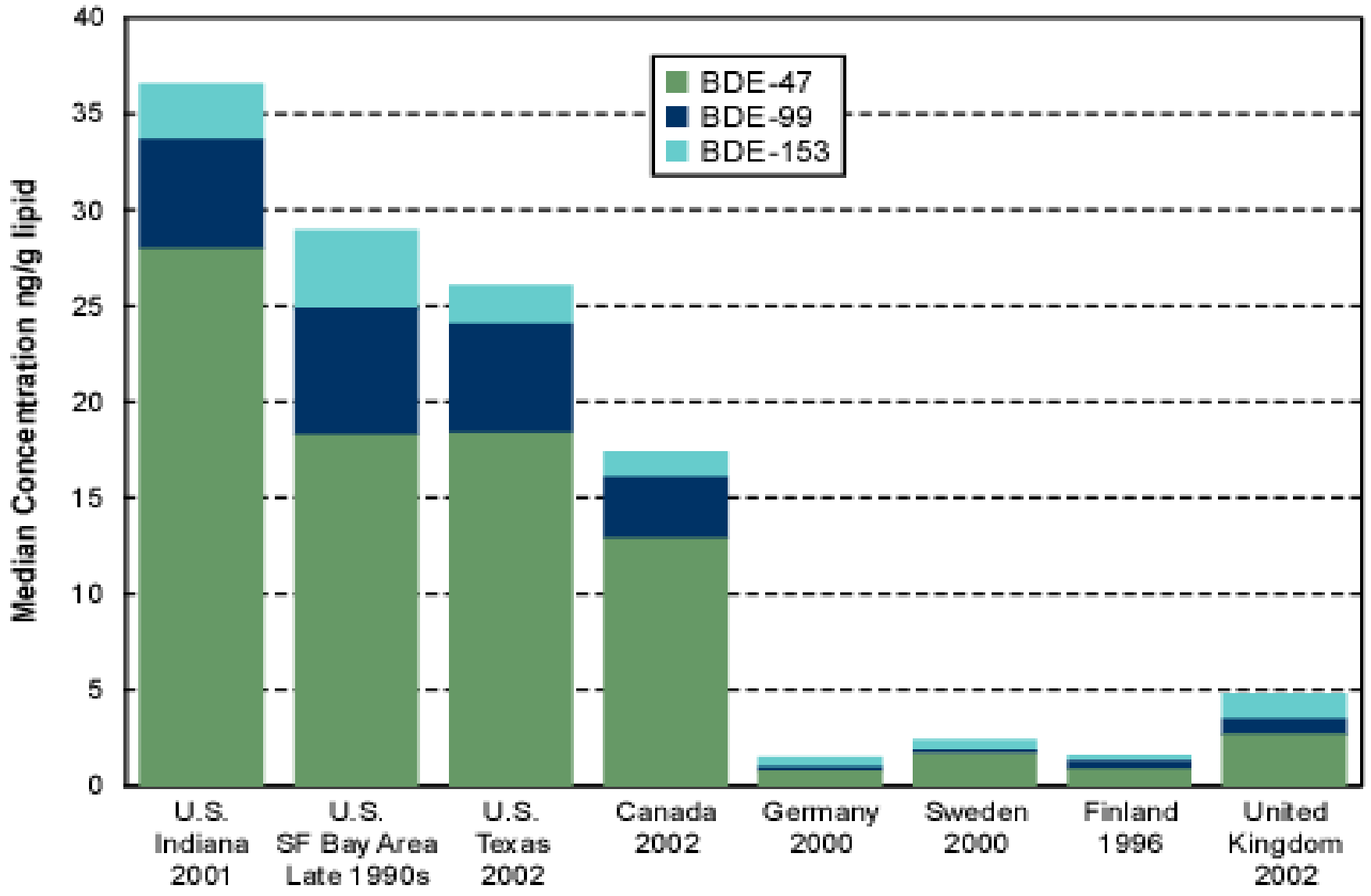






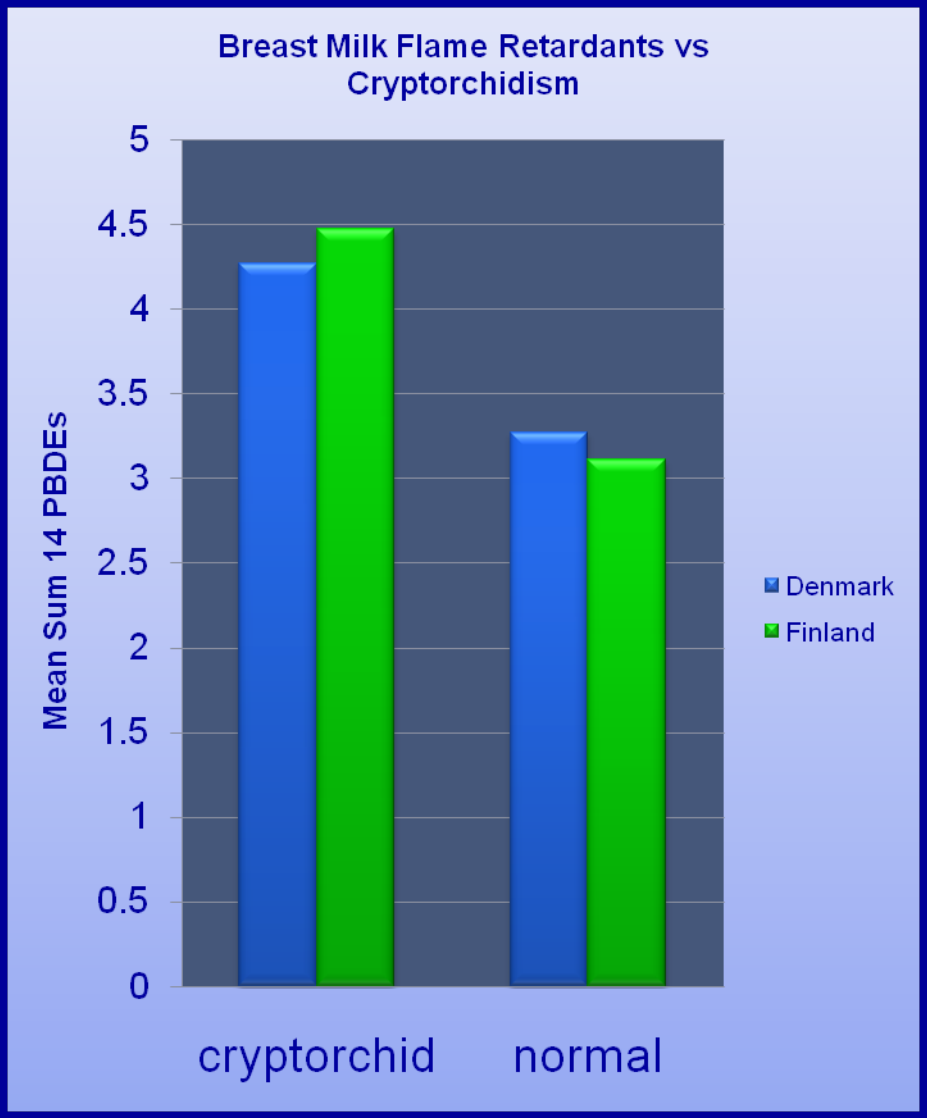
More than 85,000 synthetic chemicals have been introduced in the last 50 years for industrial, farming, and other uses, yet more than 90% of them have not been tested for their effects on human health. Biomonitoring studies have detected more than 200 toxic substances in breast milk.

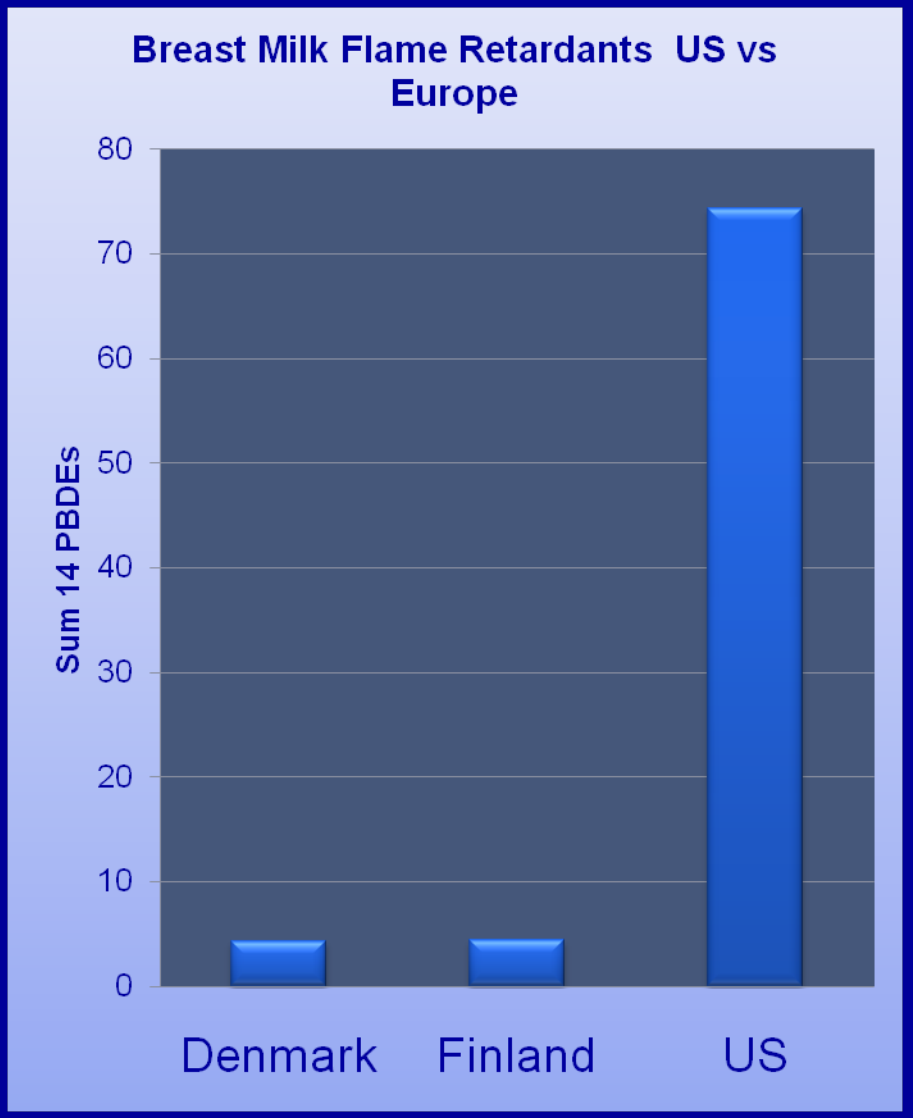
PBDEs Breast Milk and Fat Samples Around the World



Source: Figure 3 in Schecter et al (EHP, August 2003), Table 1 in Mazdai et al (EHP, July 2003), and Table 1 in Kalantzi et al (EHP, July 2004)

Flame Retardants in Mom's Breast Milk & Undescended Testes in Sons





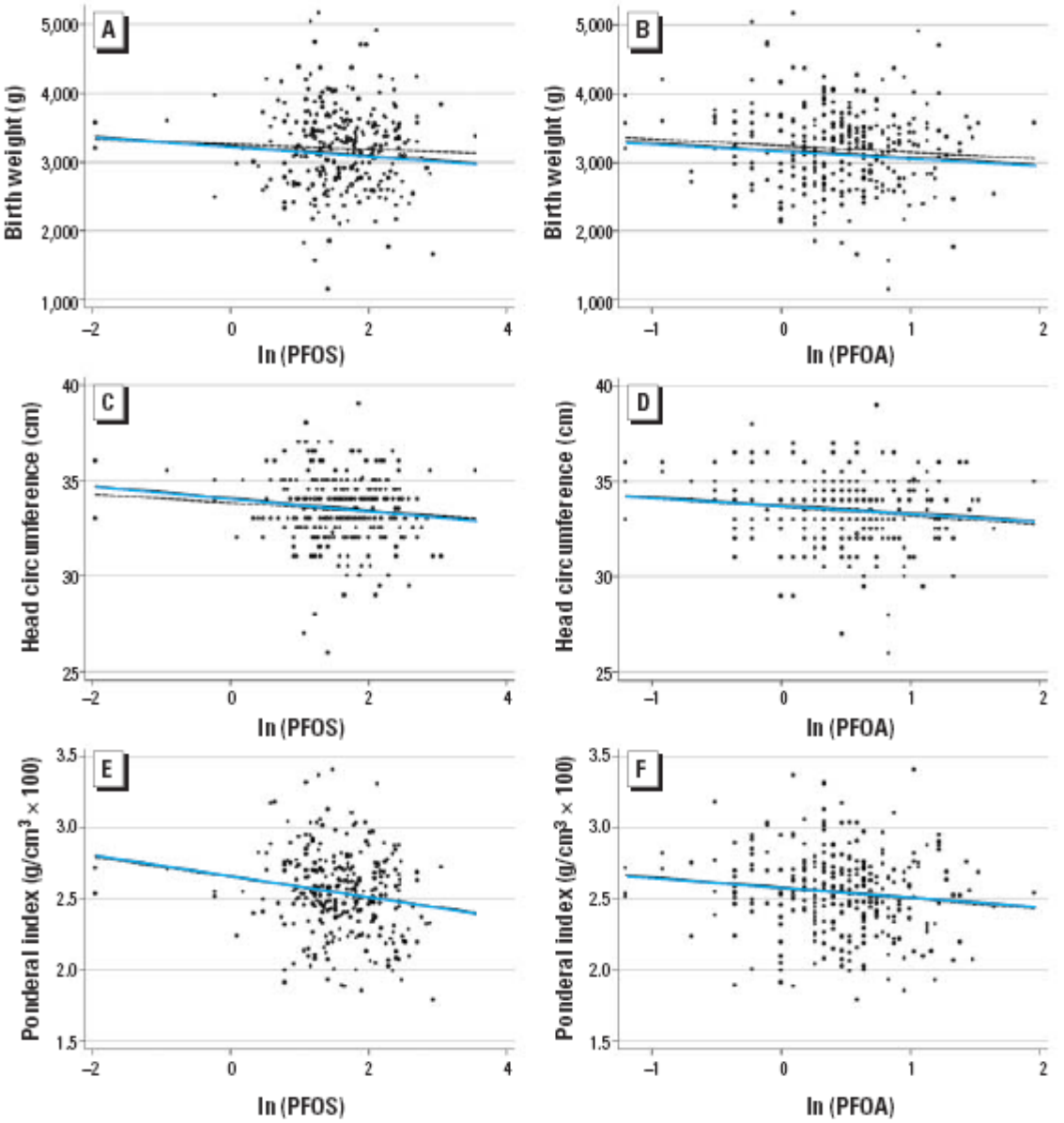


Figure 1. Birth weight (*A*, *B*), head circumference (*C*, *D*), and ponderal index (*E*, *F*) versus ln(PFOS) and ln(PFOA) concentrations, before and after adjustment for potential confounders. The black dotted lines denote the predicted fit from a simple linear regression model. The blue solid lines denote the predicted fit from the fully adjusted multivariate regression model. Corresponding regression coefficients are presented in Table 3.

Teflon Cord Blood Levels & Birth Weight & Head Circumference

Benjamin J. Apelberg,1 Frank R. Witter,2 Julie B. Herbstman,3 Antonia M. Calafat,4 Rolf U. Halden

Larry L. Needham,4 and Lynn R. Goldman

EHP 2007

In-Utero Arsenic and Altered Gene Expression

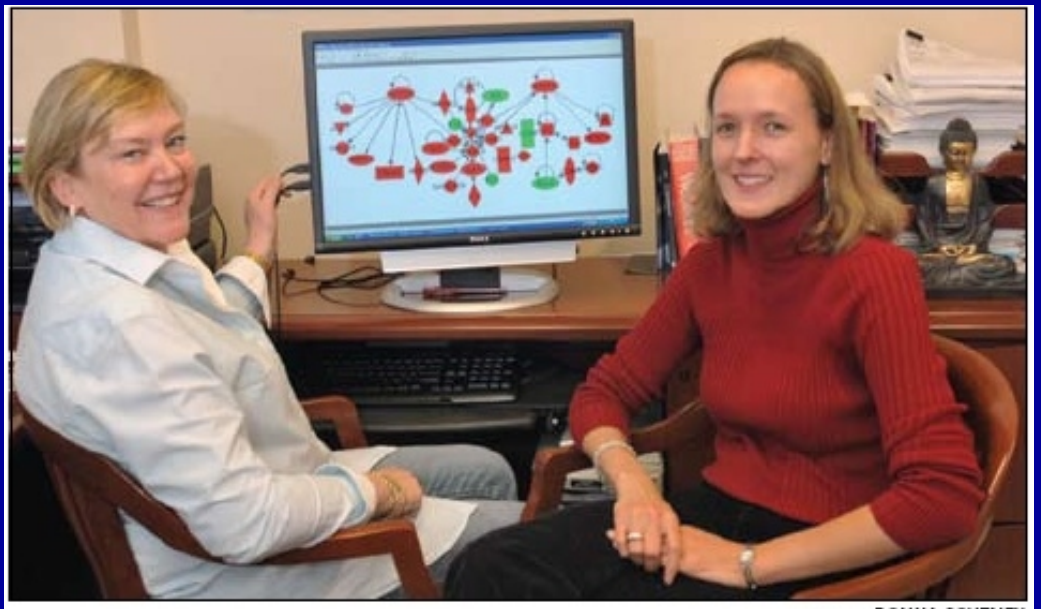


PHOTO / DONNA COVENEY

Leona Samson, left, and Rebecca Fry have found that prenatal exposure to arsenic leads to alarming changes in the activity of genes of newborn babies. Samson is the director of MIT's Center for Environmental Health Sciences (CEHS) and the American Cancer Society Professor in the Departments of Biological Engineering and Biology. Fry is assistant scientific director of CEHS.

Shown in her Bangkok office, CRI Vice President for Research Mathuros Ruchirawat, Ph.D., posed at her computer as colleague Panida Navasumrit, Ph.D., an investigator in the CRI Laboratory of Environmental Toxicology, joined her for this photograph.

Fetal Origins of Adult Diseases and Arsenic Exposure

- The children of mothers whose water supplies were contaminated with arsenic during their pregnancies harbored gene expression changes that may lead to cancer and other diseases later in life (Bypass ,Angina Heart disease, Heart attack, High blood pressure, Stroke, Circulatory problems, Type 2 diabetes mellitus, Depression)
- 32 mothers and their children in a province of Thailand that experienced heavy arsenic contamination from tin mining. Similar levels of arsenic are also found in many other regions, including the U.S. southwest and New Hampshire.

Methods/Results

- Cord Blood from babies whose mothers were exposed to arsenic during their pregnancy. Arsenic exposure was independently determined by analyzing toenail clippings.
- Patterns of gene expression were compared for exposed and unexposed pregnancies.
- Gene expression from 11 genes were found to predict arsenic exposure
- Most genes were associated with inflammation

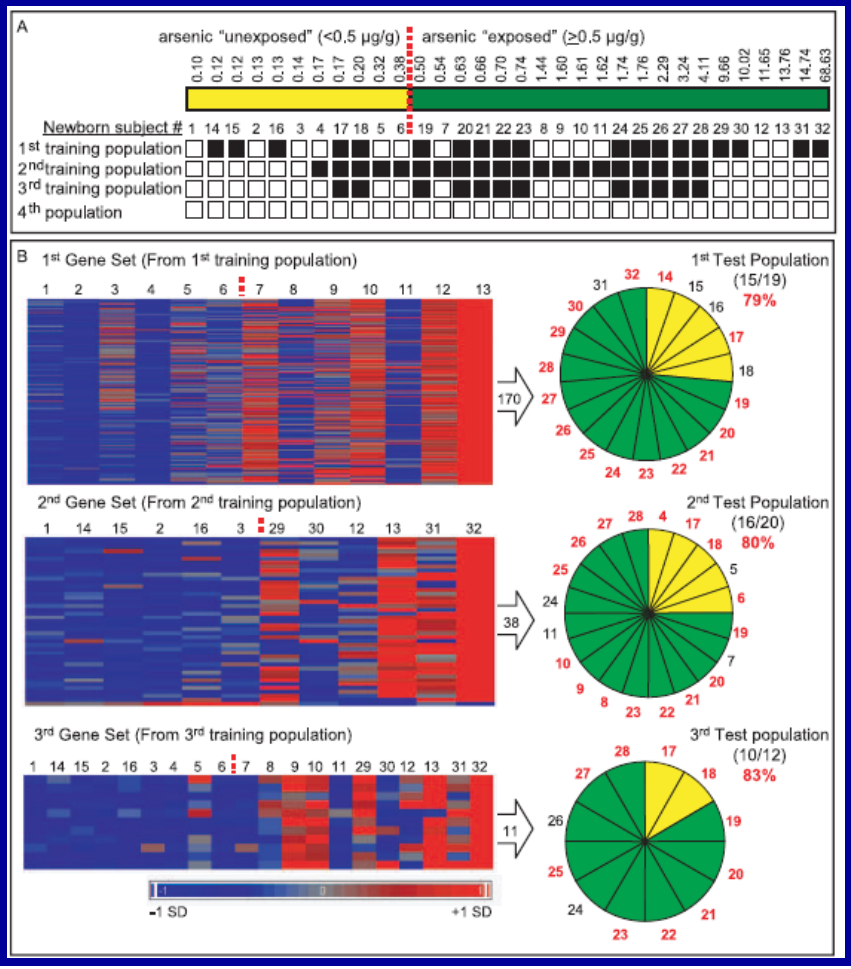


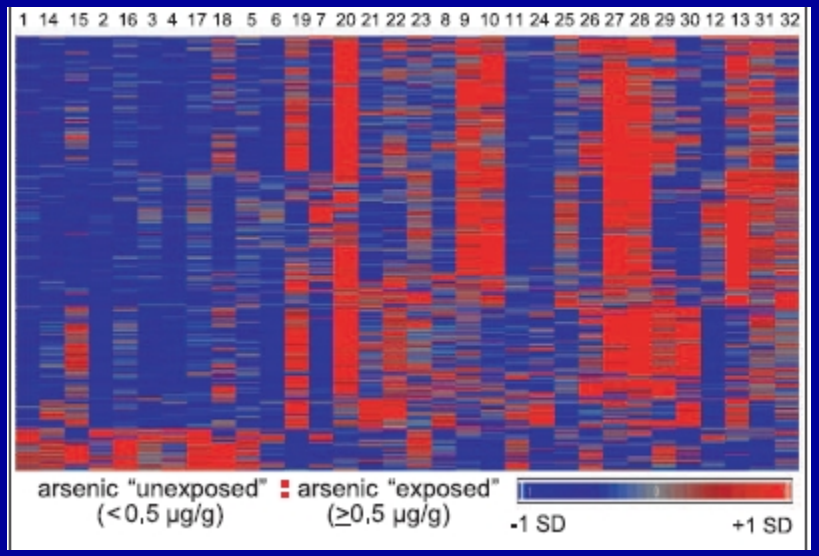
Figure 1. Gene Expression Signatures Predict Arsenic Exposure in Test Populations

(A) A population of newborns (subjects 1–32) born to mothers with varying levels of arsenic exposure was used to establish arsenic-associated gene expression signatures. Arsenic exposure levels were determined by maternal toenail arsenic concentration (µg/g). Babies born to unexposed (yellow) or arsenic-exposed mothers (green) were classified based on WHO guidelines with the cut point demarcated by the red dotted line. Subjects used in the populations to establish arsenic-associated gene sets are indicated with a white box. For two-class prediction, those subjects not included in the training population comprise the test population and are indicated with a black box.

(B) Three arsenic expression signatures (gene sets) were derived from populations spanning the range of arsenic exposure (first gene set), at the extremes of exposure (second gene set), or a combined population of the previous two (third gene set). To be included in the gene set, the transcript had to not only be differentially expressed (on average) between the exposed and unexposed groups, but also display a significant trend across increasing arsenic exposure levels. Expression values are mean centered with high relative expression indicated in red and low relative expression indicated in blue. The three derived gene sets (170 genes, 38 genes, or 11 genes) were used to predict prenatal arsenic exposure in test populations where correct classification is indicated by a red number.

doi:10.1371/journal.pgen.0030207.g001

Protein transcripts changed by Prenatal Arsenic Exposure



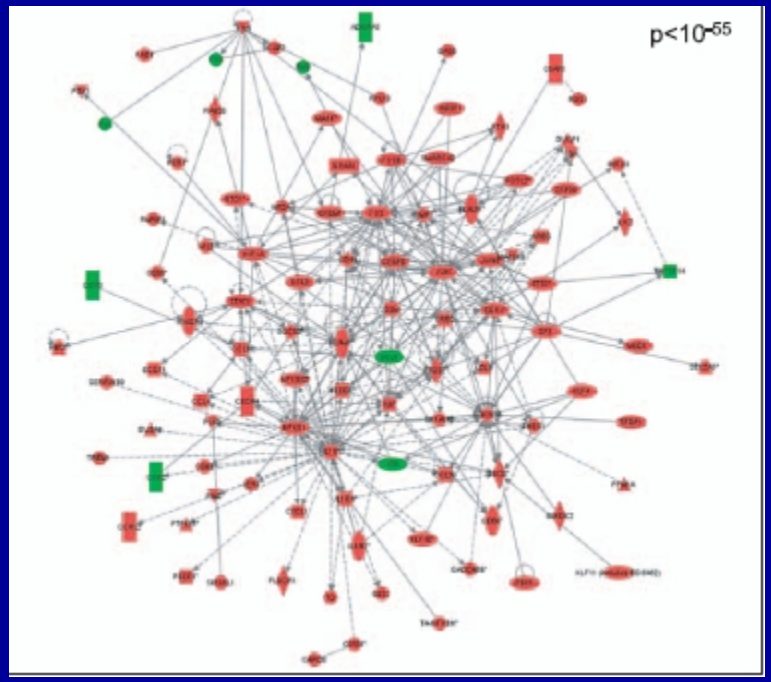


Figure 2. Prenatal Arsenic Exposure Results in Robust Genome-Wide Changes

(A) Heat map of the 447 differentially expressed genes identified between two newborn populations, those born to unexposed or arsenic exposed mothers. The cut point of exposure is indicated with a red dotted line. Unlike Figure 1, the differentially expressed transcripts did not have to display a significant trend with increasing arsenic exposure. Expression values are mean centered with high relative expression indicated in red and low relative expression indicated in blue.

(B) The 285 arsenic-modulated gene products existing in the Ingenuity database were analyzed for significant enrichment of molecular interactions. A significant ($p < 10^{-55}$) interactome containing 105 arsenic-modulated gene products was identified. Proteins in red represent arsenic-induced transcripts, proteins in green represent arsenic-repressed transcripts.

doi:10.1371/journal.pgen.0030207.g002

Potential Gene Biomarkers of Prenatal Arsenic Exposure

Gene	Description
CXCL1	chemokine (C-X-C motif) ligand 1
DUSP1	dual specificity phosphatase 1
EGR1	early growth response 1
IER2	immediate early response 2
JUNB	jun B proto-oncogene
MIRN21	microRNA 21
OSM	oncostatin M
PTGS2	prostaglandin-endoperoxide synthase 2
RNF149	ring finger protein 149
SFRS5	splicing factor
SOC3	suppressor of cytokine signaling 3

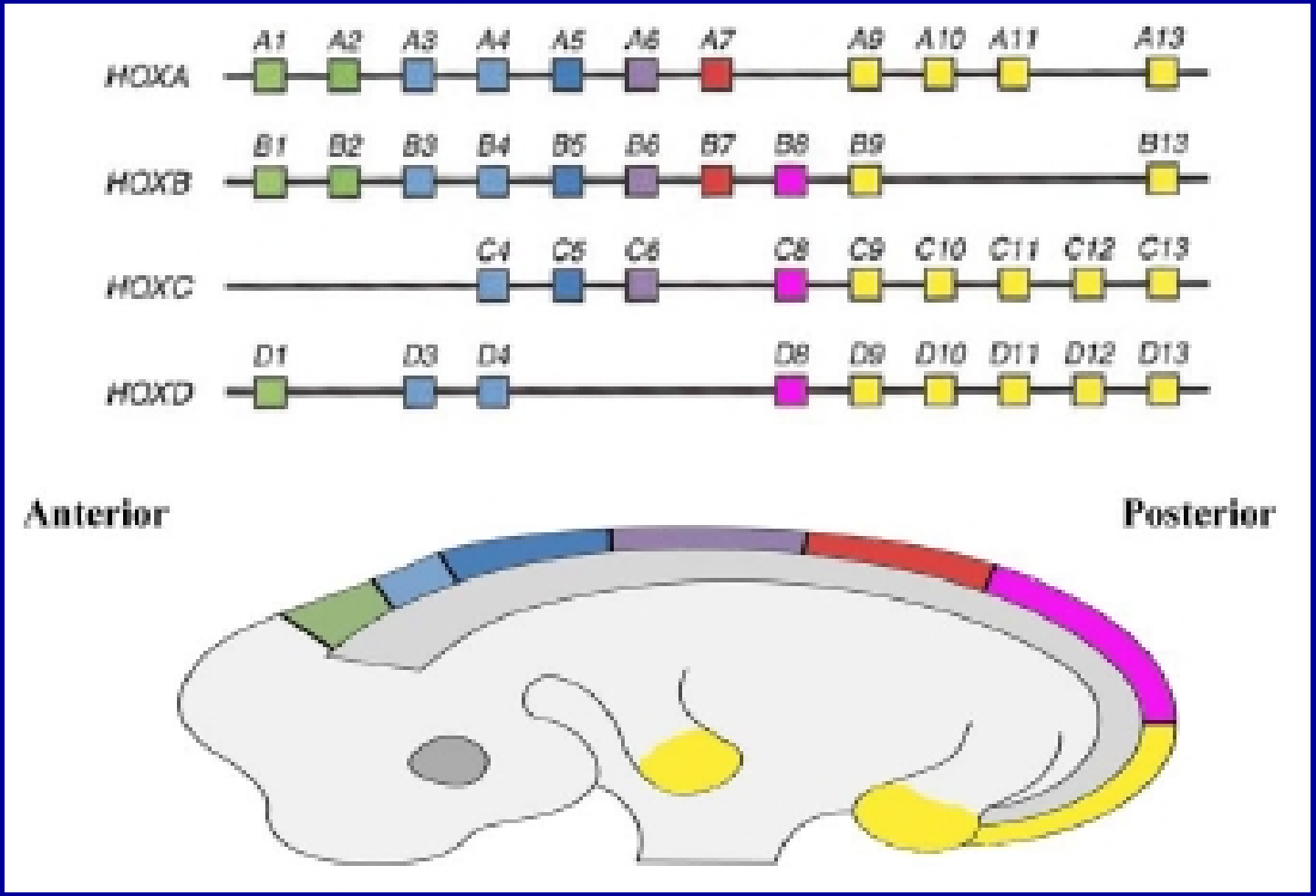
Arsenic exposure results in activation of an integrated network of pathways involving NF-kB, inflammation, cell proliferation, stress, and apoptosis.

SRF	Serum response factor
NF-kB	Nuclear factor-κB
MTF-1	Metal transcription factor

DES; the accidental endocrine disruptor human experiment

- vaginal and cervical clear-cell adenocarcinoma and genital tract abnormalities, earlier onset of menopause
- spontaneous abortions, ectopic pregnancies, and preterm deliveries
- abnormalities of men's urogenital systems ;epididymal cysts, undescended testes, and small testes. testicular cancer
- hypospadias in third-generation men
- a 15-year-old girl with small cell carcinoma of the ovary whose maternal grandmother had been taking DES while she was pregnant with the patient's mother. Although this is an anecdotal case, the rarity of this disorder suggests that DES exposure could have a trans-generational effect.

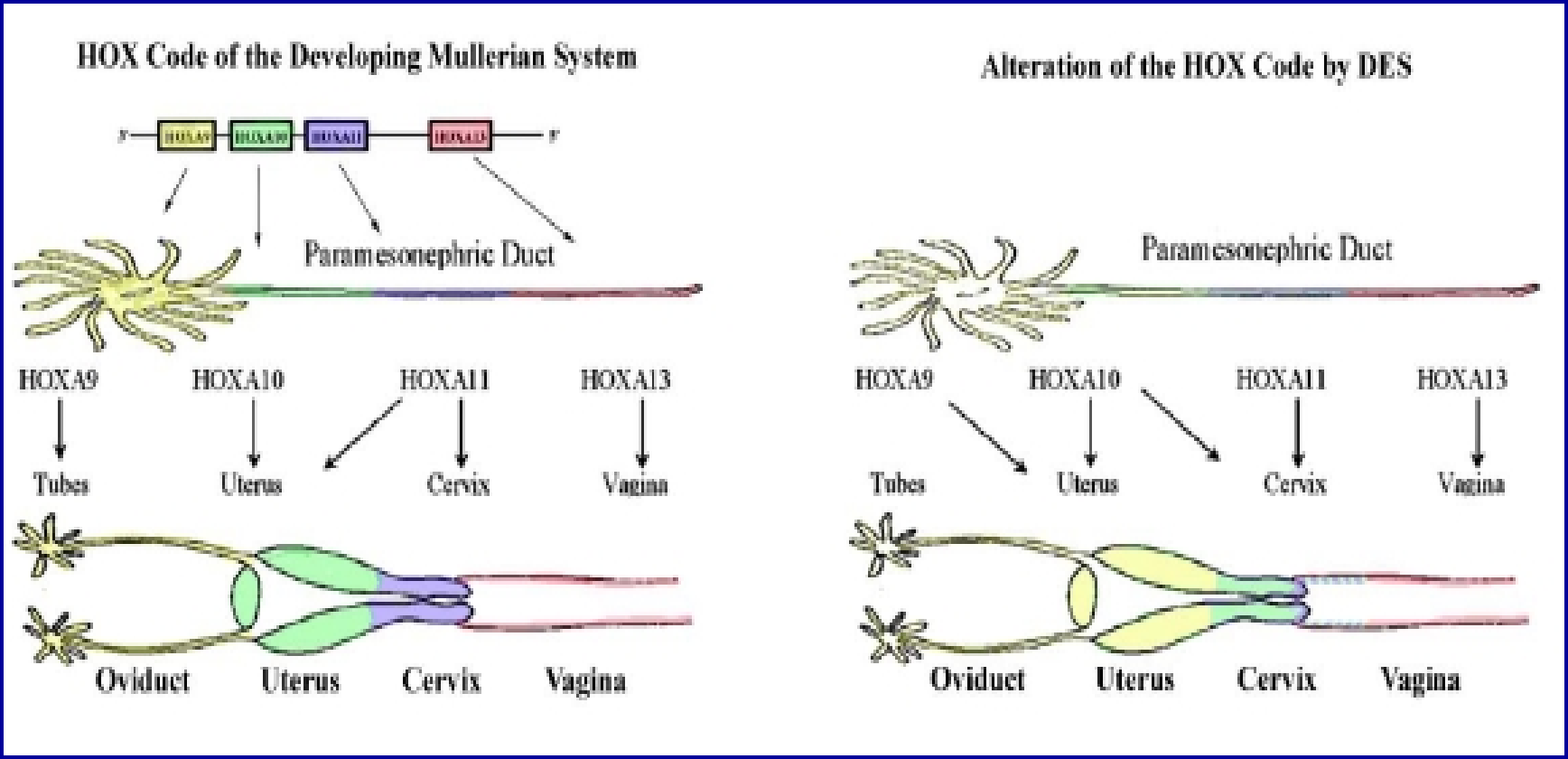
HOX Genes Control Embryological Axis Development



Sex Hormones Regulate HOX

- retinoic acid regulates the more 3', anterior and earlier expressed HOX genes
- the sex steroids estradiol and progesterone regulate more 5', posterior and later expressed HOX genes.
- Aberrations in endocrine control mechanisms lead to developmental anomalies.

How DES affects HOX Gene Expression



Methoxychlor Disrupts Uterine Hoxa10 Gene Expression

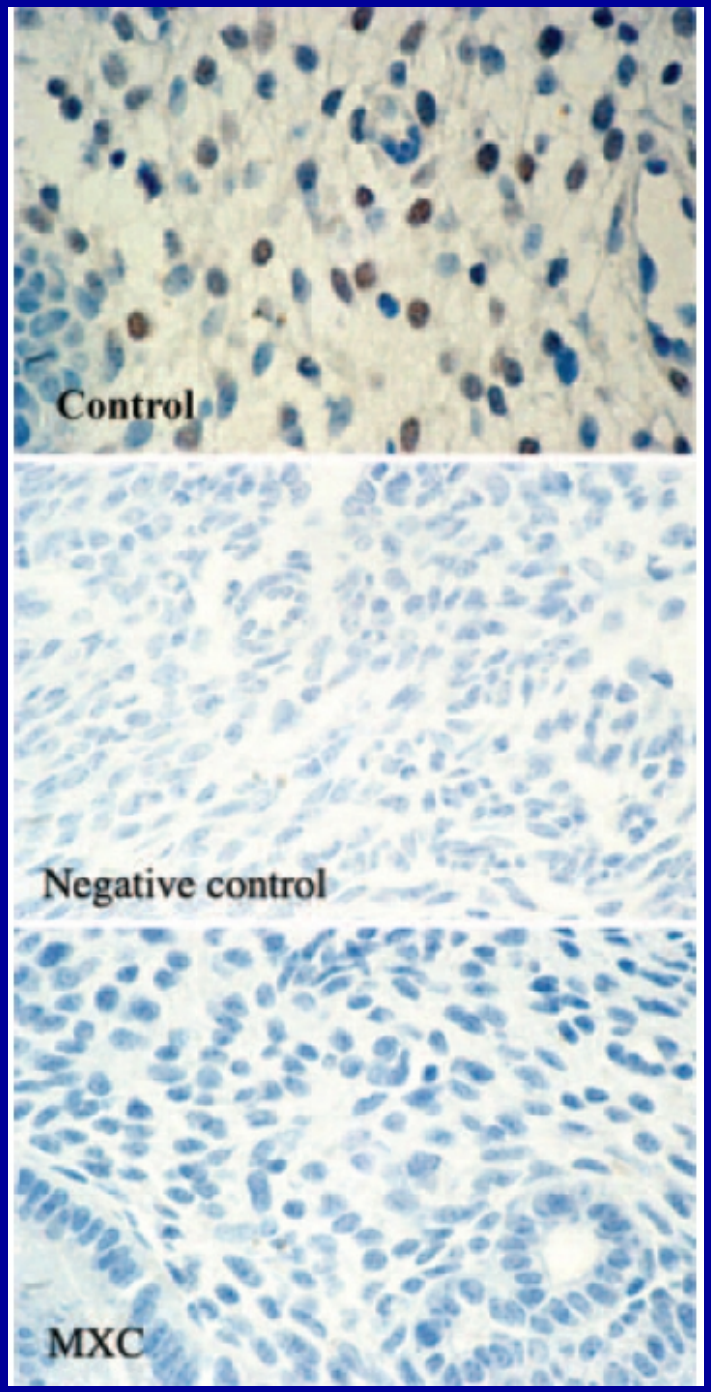
X. Fei, H. Chung, and H. S. Taylor

Endocrinology, August 1, 2005; 146(8): 3445 - 3451

DES,Methoxychlor, and Pregnancy

- **Hoxa10 is an estrogen-regulated gene that is an essential mediator of the decidual responseand necessary for pregnancy.**
- **MXC inhibited the expression of Hoxa10, a gene necessary for uterine development and function**
- **One common mechanism by which endocrine disrupting chemicals produce lasting reproductive tract defects is through permanentalteration of developmental gene expression**

Neonatal MXC exposure results in decreased Hoxa10 expression,



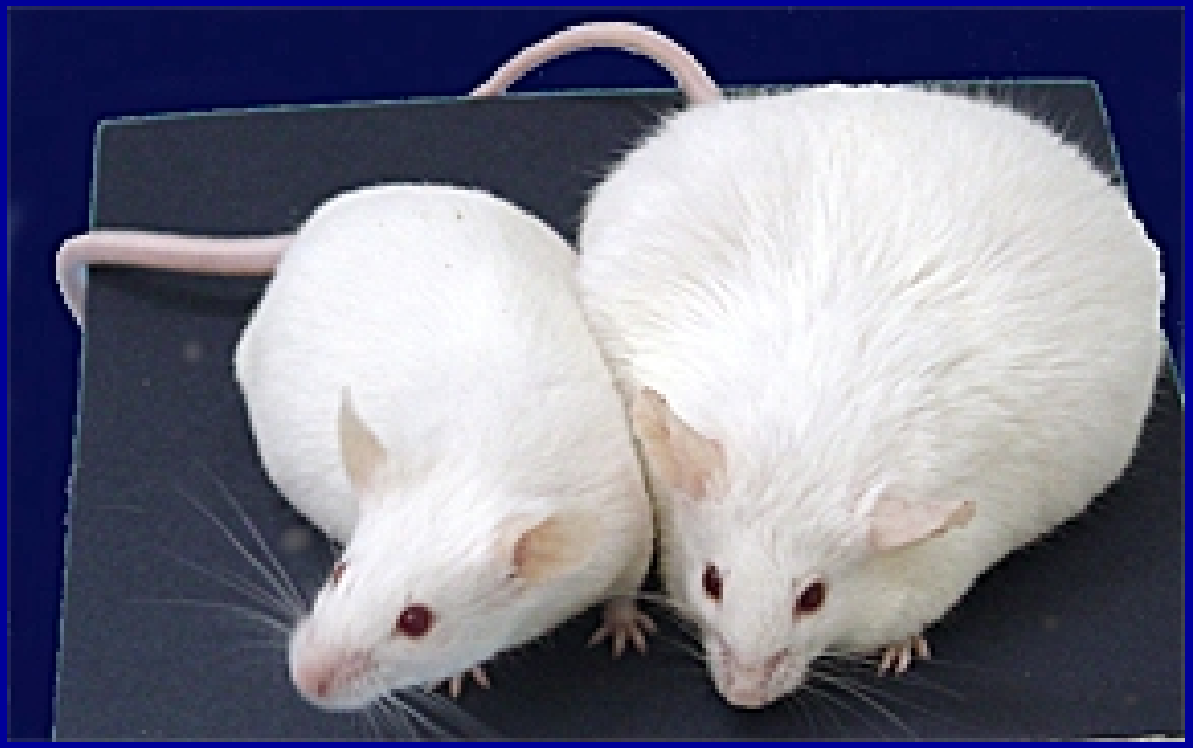
Neonatal MXC exposure decreases Hoxa10 expression in the adult.

Methoxychlor Stimulates Estrogen-Responsive Messenger Ribonucleic Acids in Mouse Uterus through a Non-Estrogen Receptor and Non-Erβ Mechanism

Endocrinology, 146: 3445-3451
(August 2005)

DES in Pregnancy

Newbold, RR, E Padilla-Banks, RJ Snyder and WN Jefferson. 2005. **Developmental Exposure to Estrogenic Compounds and Obesity**. *Birth Defects Research (Part A) 73:478–480*



The mouse on the right was exposed to 1 ppb DES in the womb, on days 9-16 during pregnancy; control animal on left.
Photo courtesy of Retha Newbold

Prior experiments by Newbold show that DES at levels 10x to 100x that used in this experiment produce weight loss in adulthood.

Conclusions

- Pesticides and plasticizers are in 97% of us
- Human fetus is most vulnerable
- Two mammalian models have proven that pesticides and plasticizers can alter DNA methylation
- Causing adult diseases ranging from cancer, kidney, prostate, immune,obesity,cholesterol and diabetes
- If this is happening in humans we need to know now!

Conclusion: Ask for More

- Count the babies
- Measure the water (in June)
- Connect the Dots; (ISTEP scores+birth certificates, Maternal exposures and adult diseases. Fetal deaths with LMPs.)
- Your grandmother's pesticide exposure may still linger in your child's genome
- The harvest may have a cost measured in preterm births, miscarriages, stillbirths, birth defects and lower academic achievement, cancer, diabetes,life-span

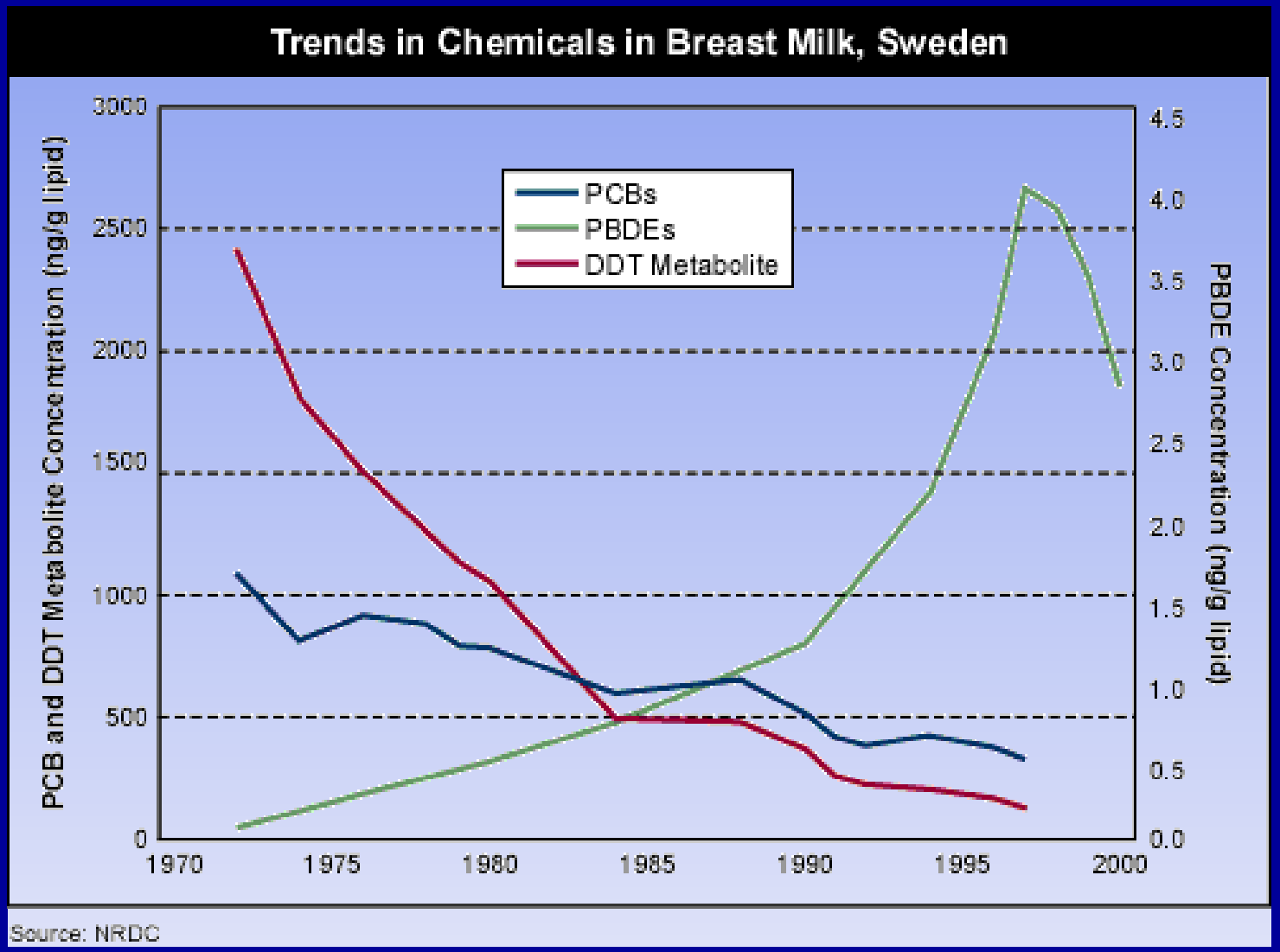
MARION COUNTY HEALTH DEPARTMENT & INDIANAPOLIS HEALTHY BABIES PRESENT

Harvesting a Safe Environment During Pregnancy

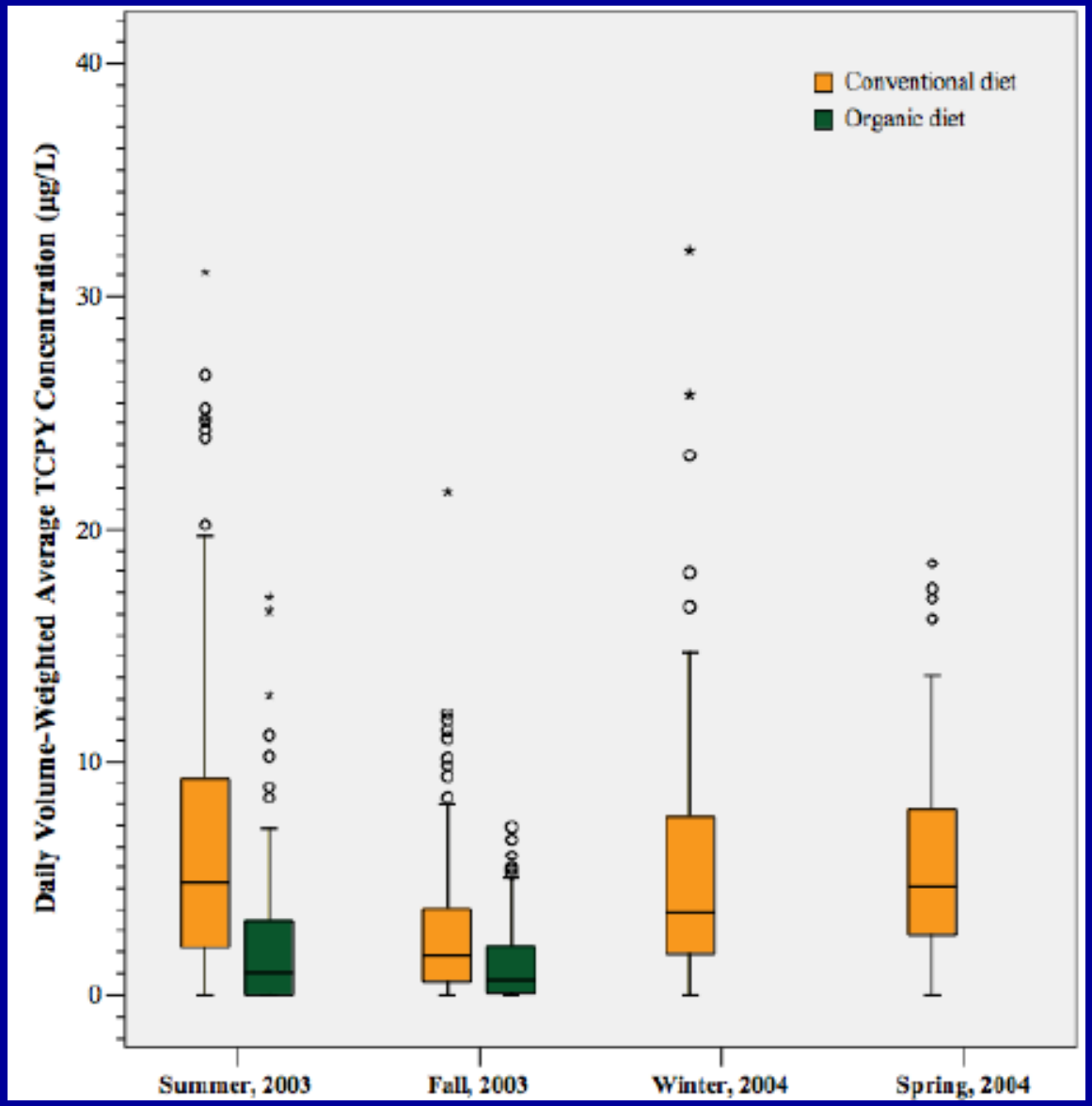
Before the Corn Harvest Came the Pesticides and Nitrates

Some Good News

- Organic diets reduce exposure
- Smoking rates and serum cotinine levels are declining
- Lead levels are declining
- After banning some organochlorine pesticides Sweden has seen decreases in non-hodgkins lymphoma.
- EPA could make a difference if they stood up to Dow, Monsanto, Syngenta and the US Senate

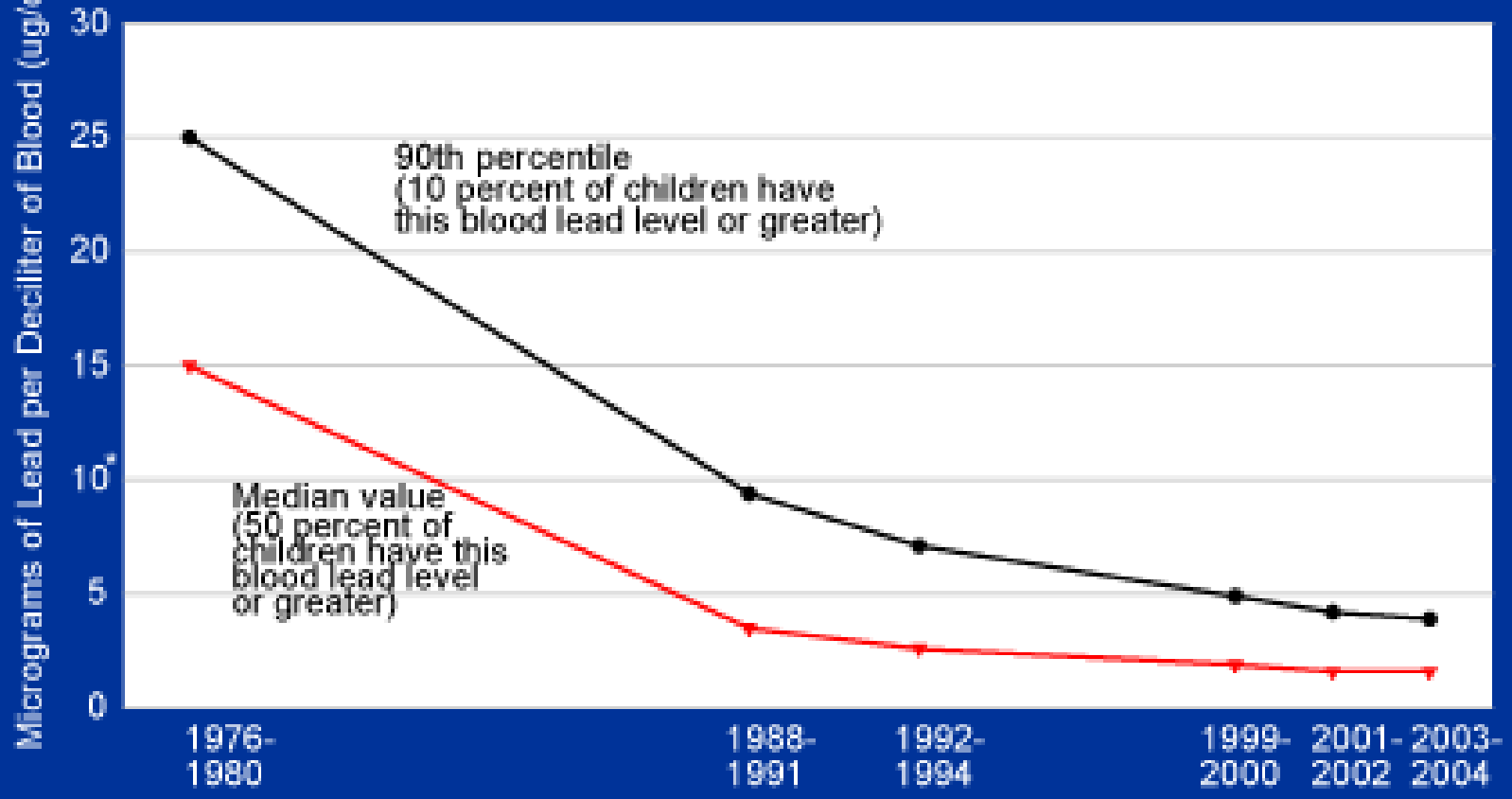

Trends in Chemicals in Breast Milk, Sweden
PCB and DDT Metabolite Concentration (ng/g lipid)
PBDE Concentration (ng/g lipid)
PCBs
PBDEs
DDT Metabolite
3000
2500
2000
1500
1000
500
0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1970
1975
1980
1985
1990
1995
2000
Source: NRDC

Organic Vegetables Lower Pesticides in Children



Measure B1

Concentrations of lead in blood of children ages 5 and under



SOURCE: U.S. EPA. America's Children and the Environment. www.epa.gov/envirohealth/children

DATA: Centers for Disease Control and Prevention, National Center for Health Statistics, National Health and Nutrition Examination Survey

* 10 µg of blood lead has been identified by CDC as elevated, which indicates need for intervention. There is no demonstrated safe concentration of lead in blood. Adverse effects may occur at lower concentrations.

Murder vs Childhood Lead

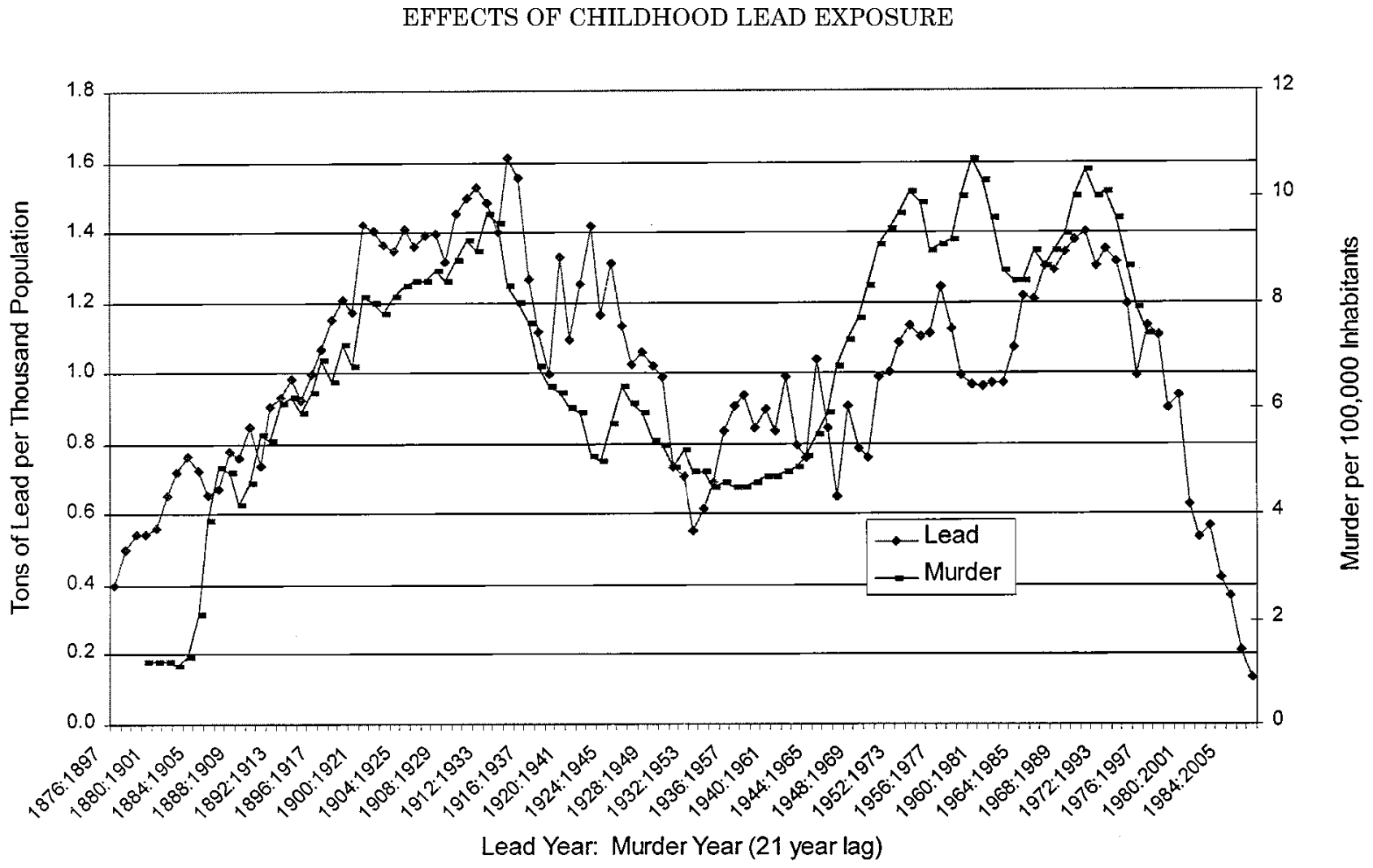


FIG. 12. Gasoline and white lead versus murder.

Unwed Pregnancies vs Lead

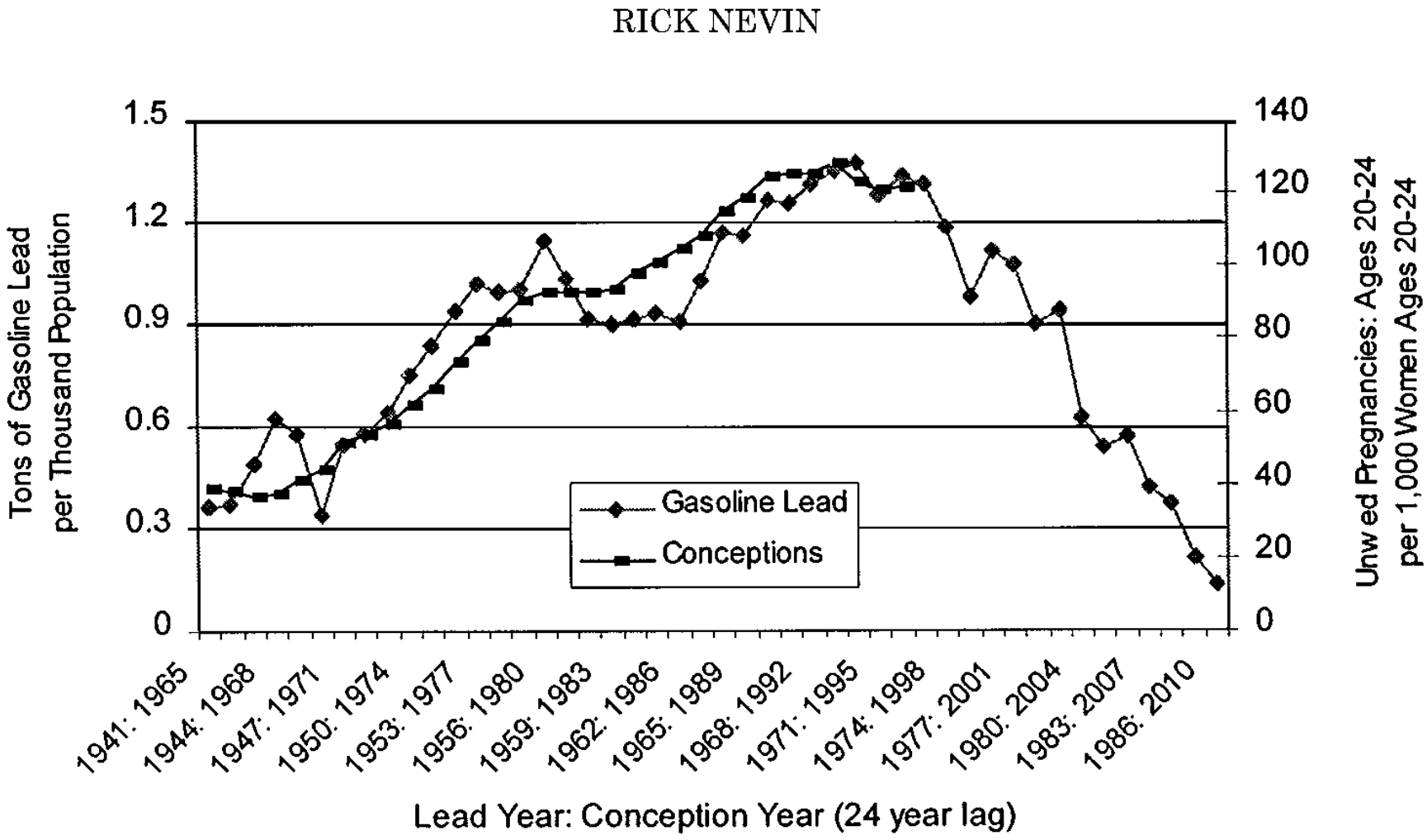
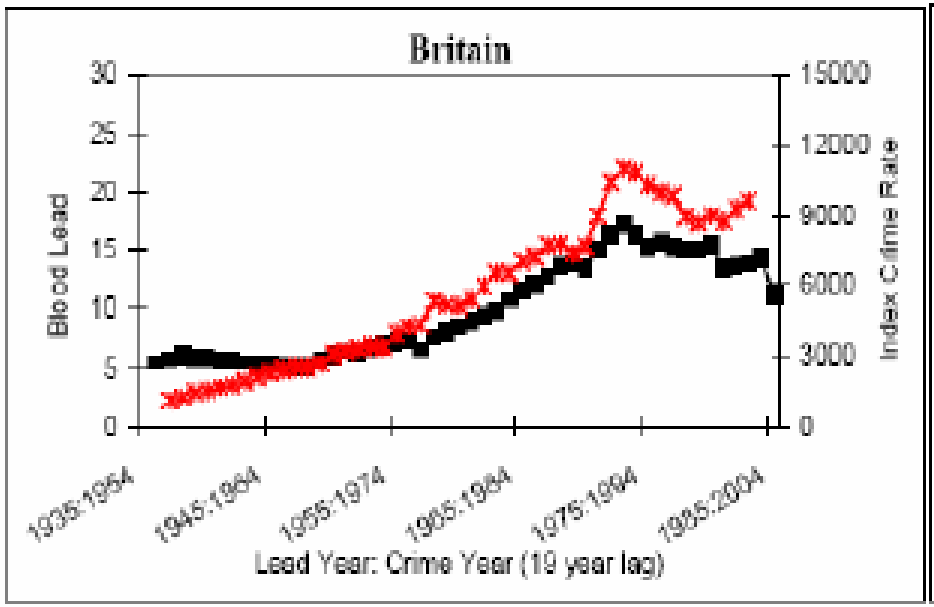
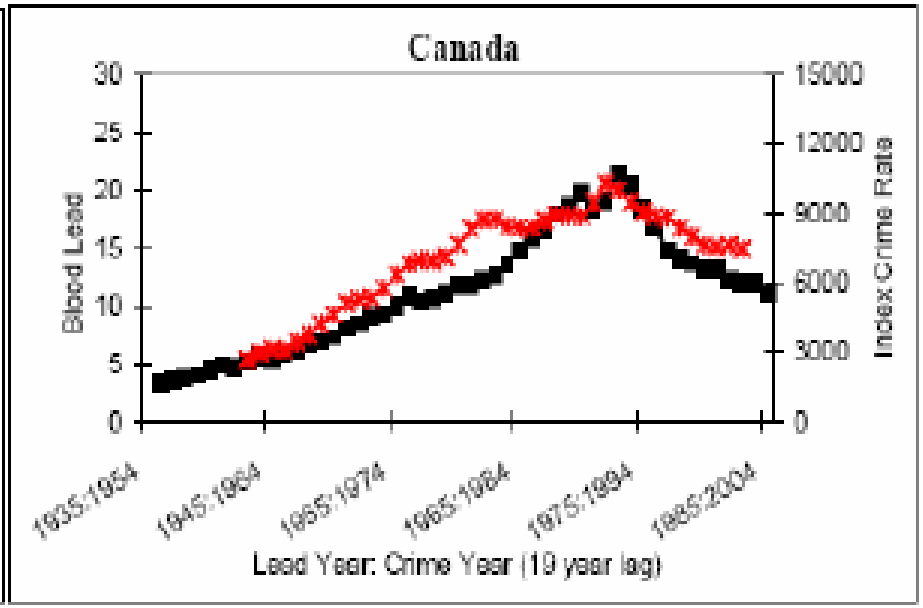
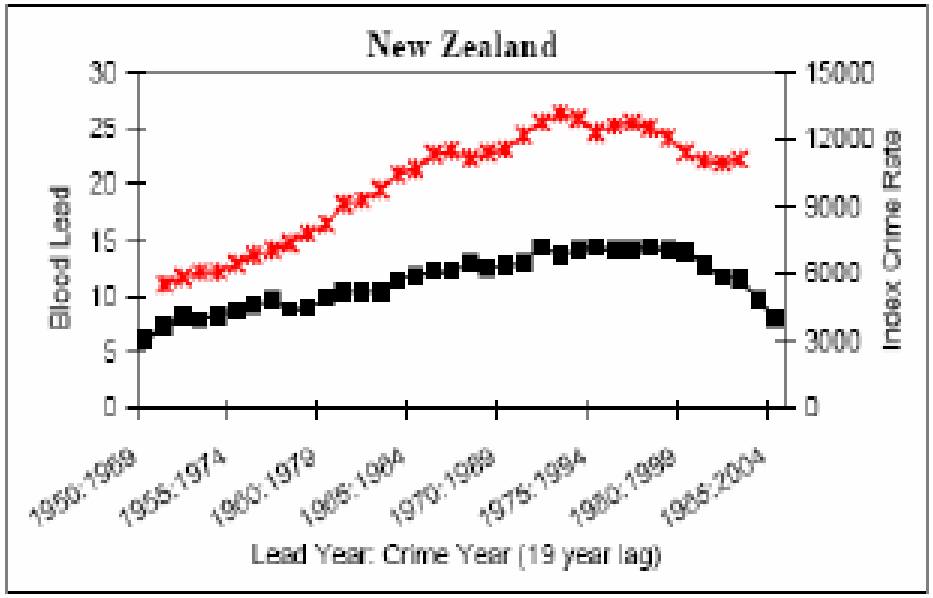


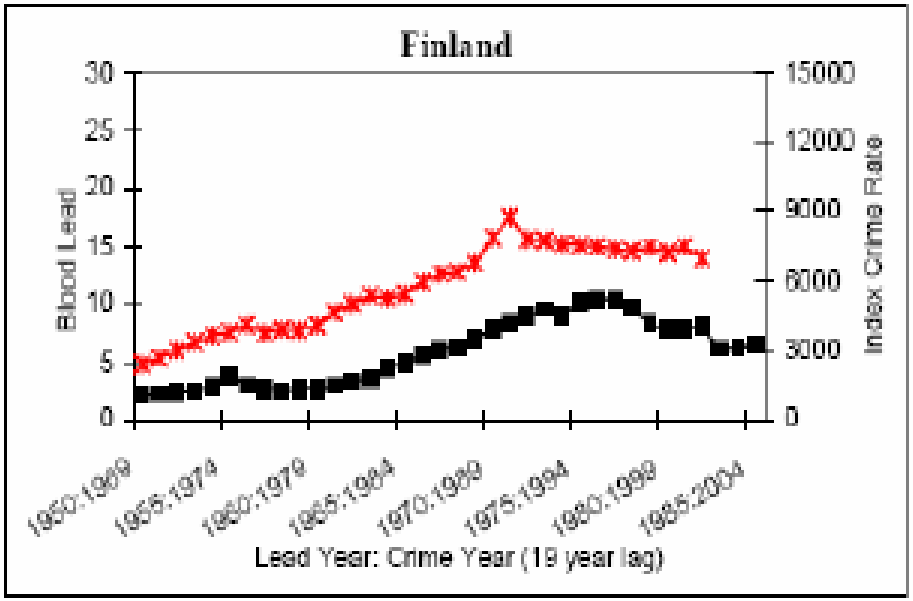
FIG. 6. Gasoline lead versus unwed pregnancies: ages 20–24.

Preschool Blood Lead vs. Broadly Defined Index Crime with a 19-Year Lag



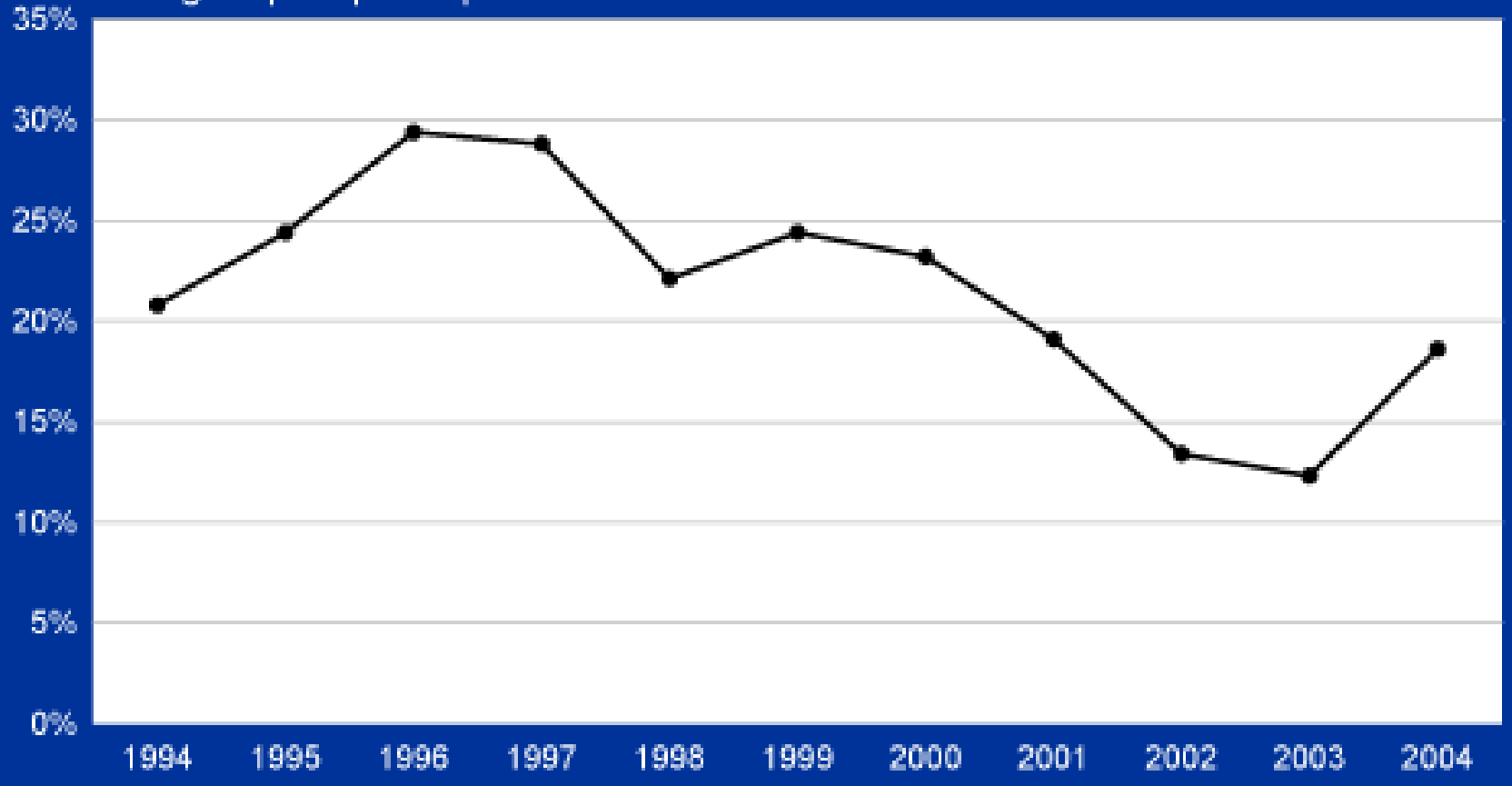






Measure E8

Percentage of fruits, vegetables, and grains with detectable residues of organophosphate pesticides



SOURCE: U.S. EPA. America's Children and the Environment. www.epa.gov/envirohealth/children

DATA: U.S. Department of Agriculture, Pesticide Data Program

Do We Have the Political Will to Decrease Contaminants?

Former migrant worker Francisca Herrera holds her son Carlos Candelario in the family's trailer in Florida City.
Palm Beach Post file photo