Atrazine Induced Epigenetic Transgenerational Inheritance of Disease, Lean Phenotype and Sperm Epimutation Pathology Biomarkers

Margaux McBirney,Stephanie E. King,Michelle Pappalardo,Elizabeth Houser,Margaret Unkefer,Eric Nilsson,Ingrid Sadler-Riggleman,Daniel Beck

Paul Winchester,Michael K. Skinner

PLOS ONE Manuscript
submitted Aug 18, 2017

Does Atrazine Imprint Our Babies?

- Atrazine is the most commonly found pesticide in US water systems.
- Atrazine is the second most commonly used Herbicide (weed killer) (glyphosate is 1st)
- Atrazine is a known endocrine disruptor (capable of turning male frogs into hermaphrodites at concentrations seen in drinking water)

What Harm Could a Little Atrazine in Your Water Cause?

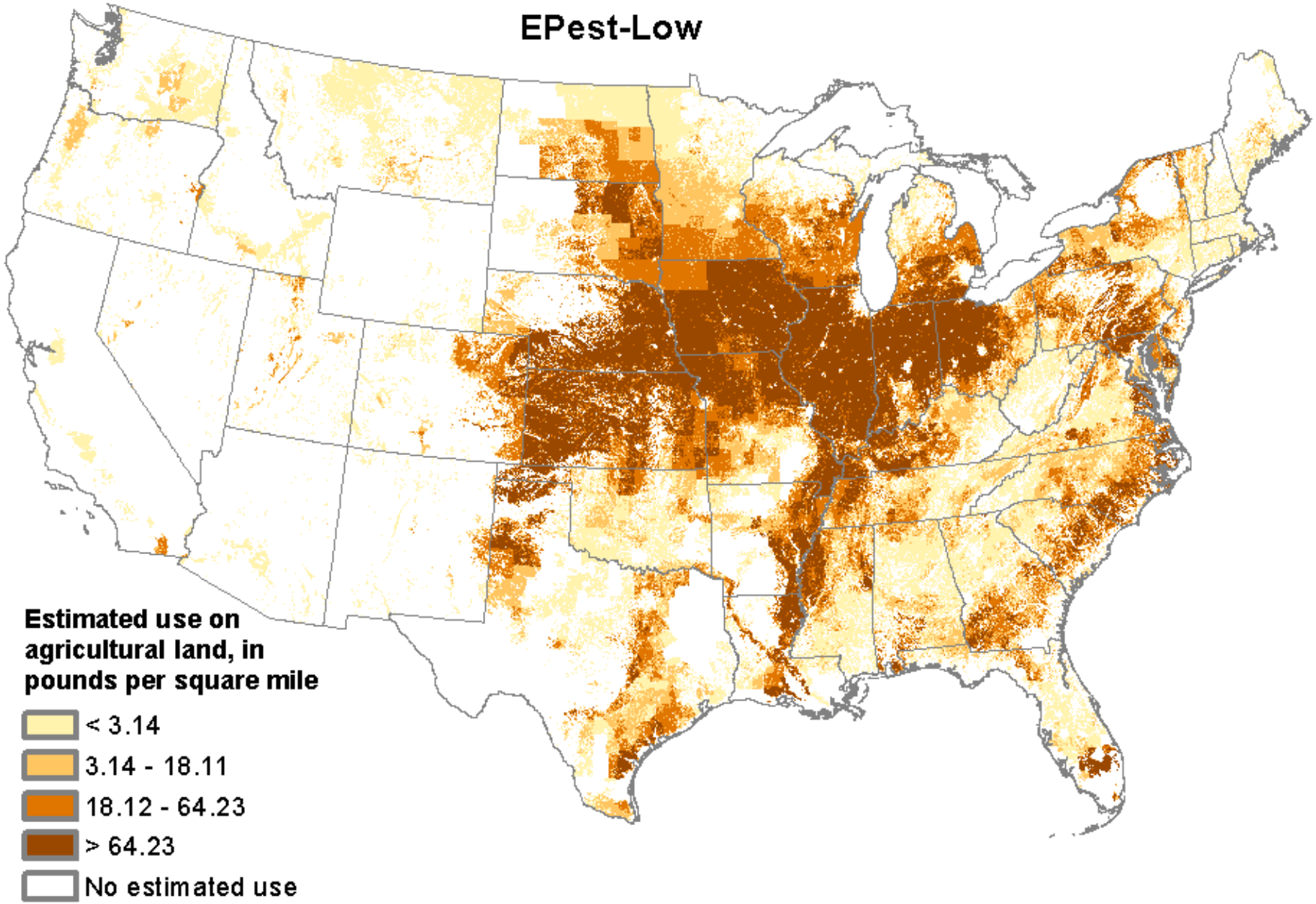
- Mike Skinner's lab has shown that very low doses of pesticide exposure in fetal life..
- Can induce DNA "imprints" called DNA methylation.
- Even though the exposed fetus looks normal at birth (free of illness or disease)
- They develop adult diseases.
- Their offspring also develop adult diseases.
- Skinner discovered a new mechanism of inheritance called transgenerational epigenetic inheritence. He also found that environmental exposures can induce "heritable" disease. This was thought to be impossible in classical theories of genetics,evolution and origin of disease.
- Epigenetic disruption is not used by EPA to evaluate safety.

Why Study Atrazine?

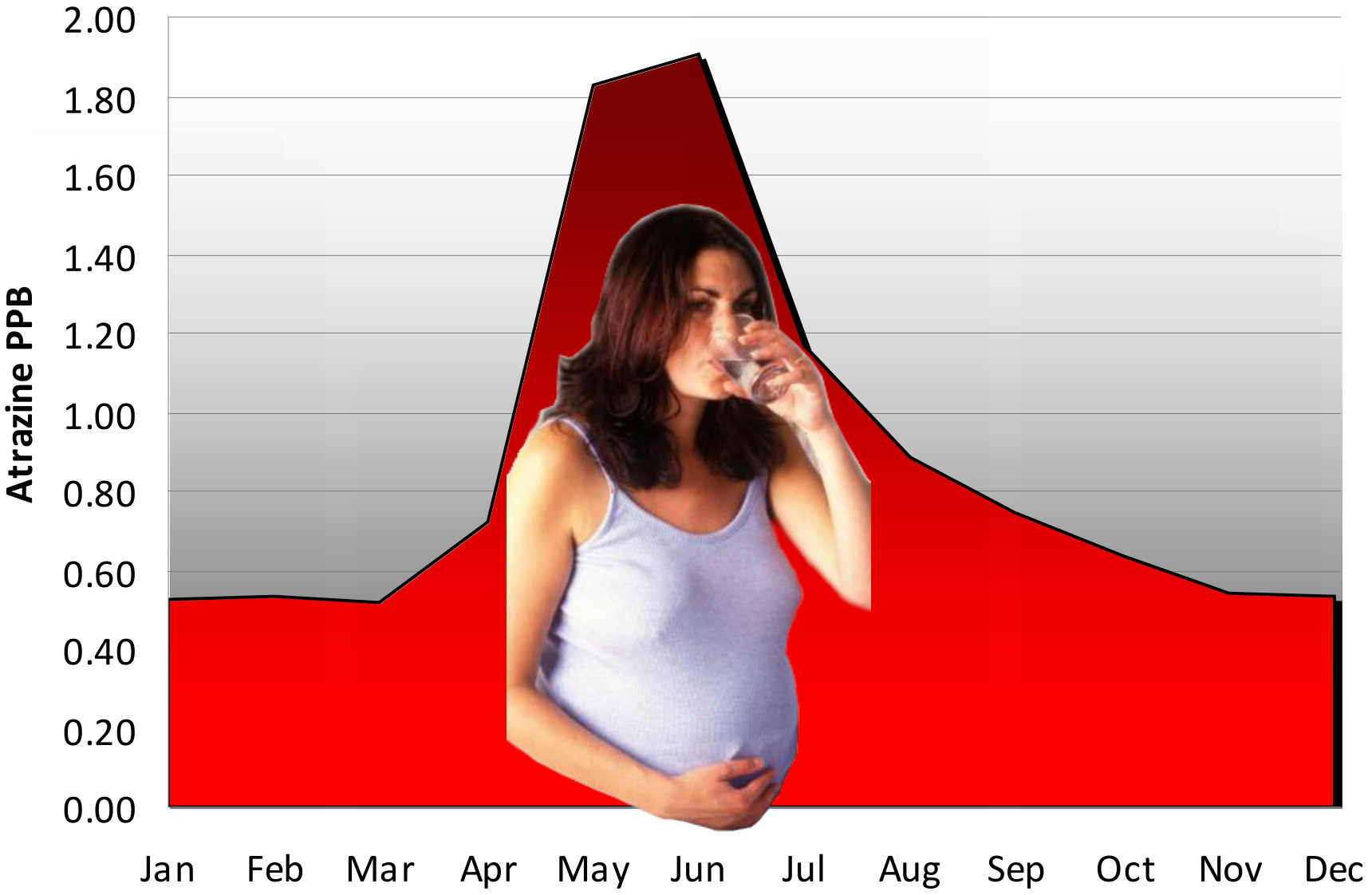
- None of current use pesticides have been tested for epigenetic safety.
- If chemical exposures are occurring in utero there may be unmeasured and potentially multigenerational risks to our children.
- Peak atrazine levels have been linked with preterm birth, birth defects and even low fertility rates in IVF pregnancies.
- No one has yet measured pregnant women or tested whether atrazine (in a rodent model) could create multigenerational disease through epigenetic mechanisms.

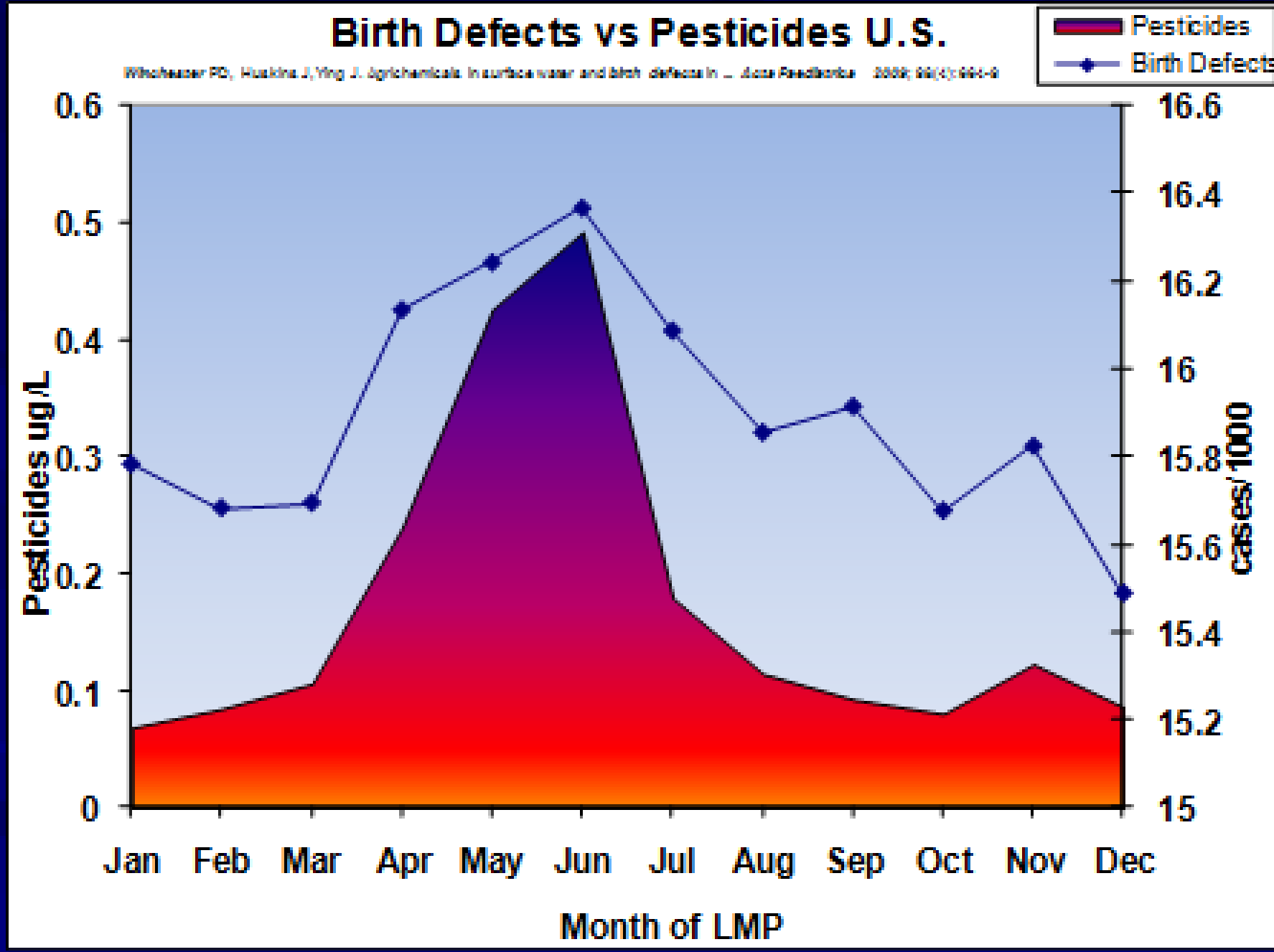
Estimated Agricultural Use for Atrazine , 2014 (Preliminary)

EPest-Low



Atrazine in Drinking Water 2003-2008




Birth Defects vs Pesticides U.S.
Pesticides
Birth Defects
0.6
0.5
0.4
0.3
0.2
0.1
0
Pesticides ug/L
16.6
16.4
16.2
16
15.8
15.6
15.4
15.2
15
cases/1000
Jan
Feb
Mar
Apr
May
Jun
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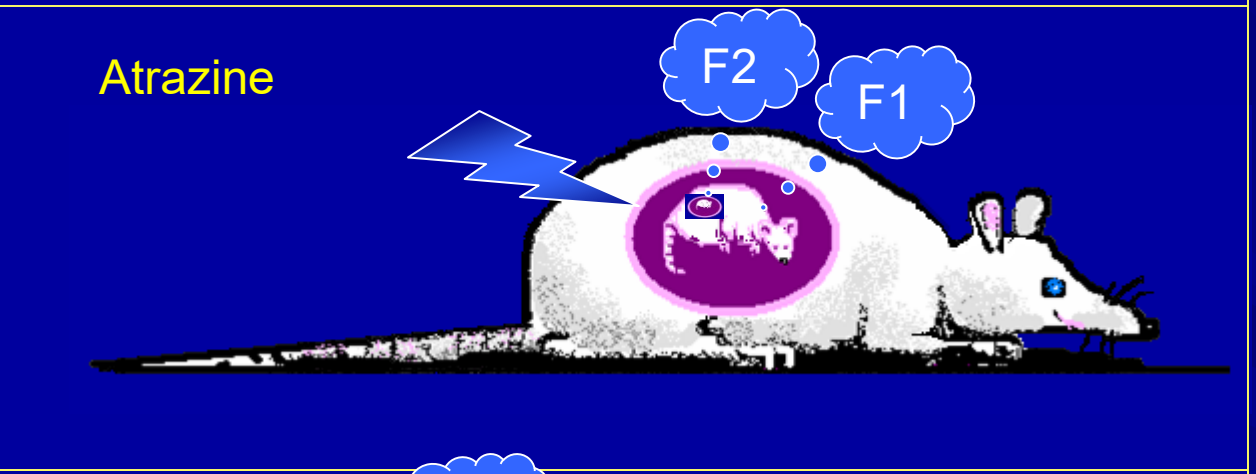
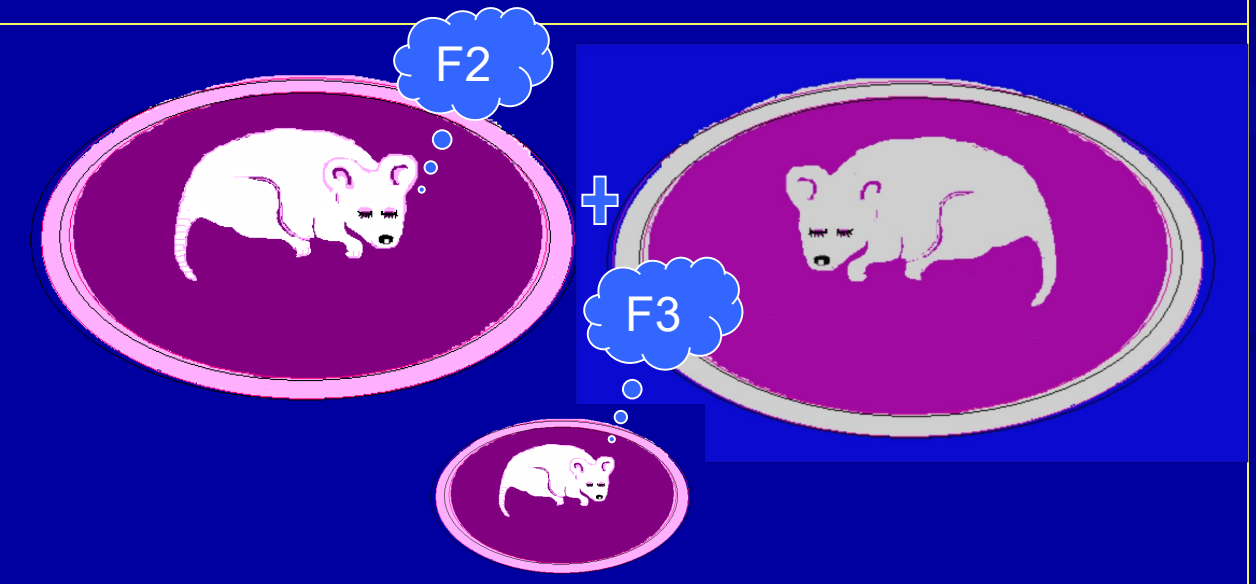
Oct
Nov
Dec
Month of LMP





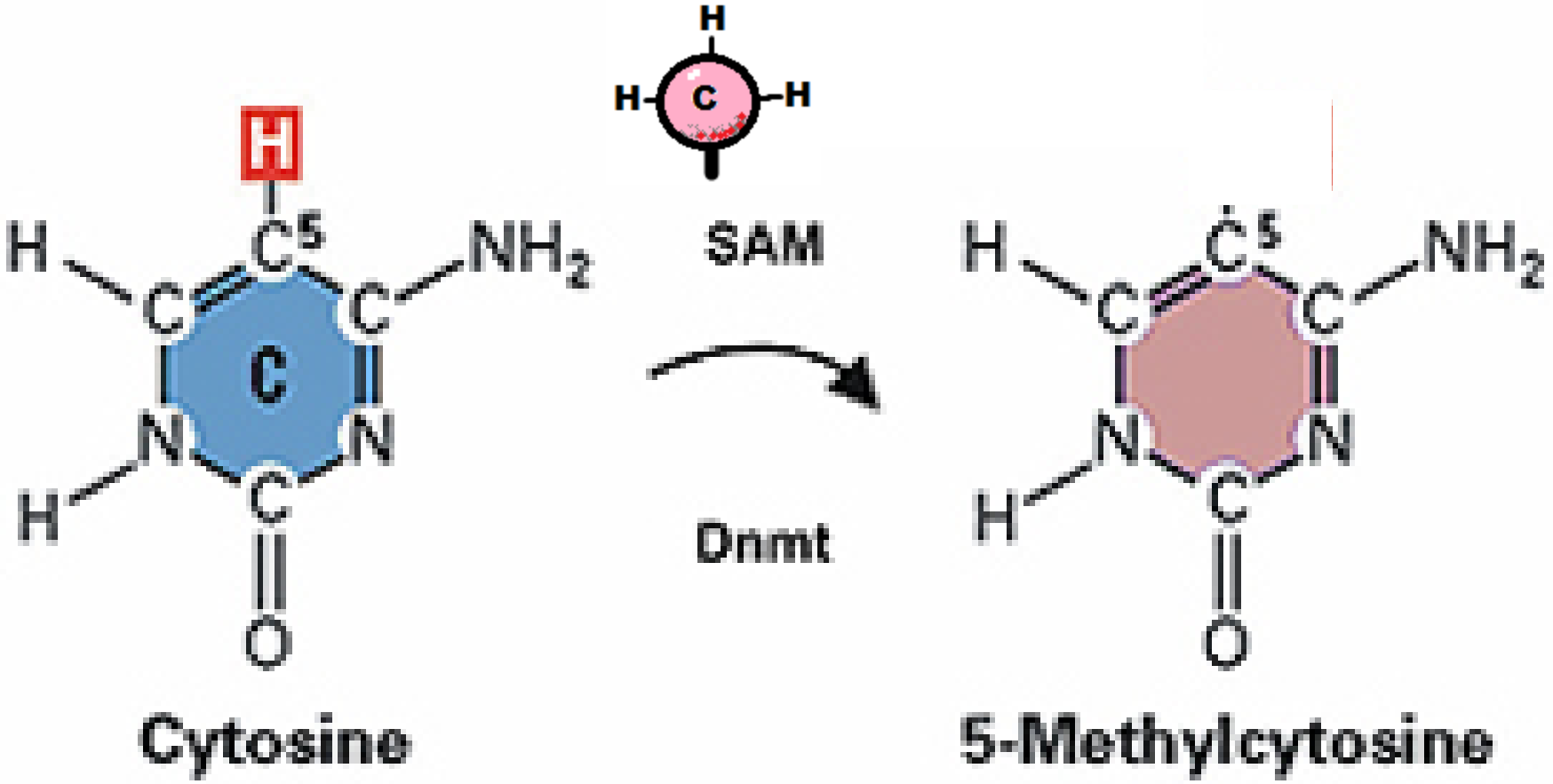
Pregnant Rat

Atrazine Exposure

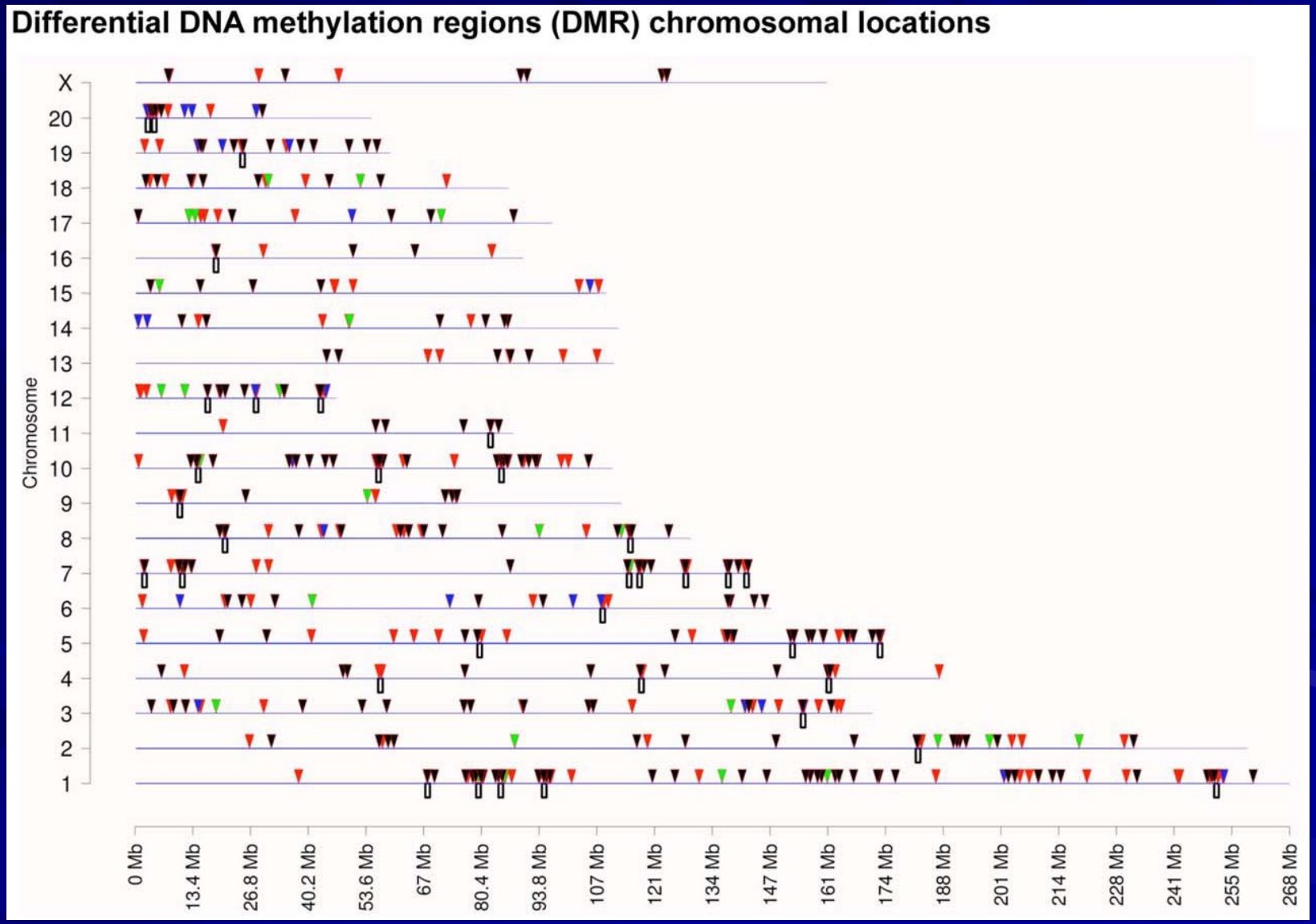
(PC days 8-14)

Offspring

DNA Methylation



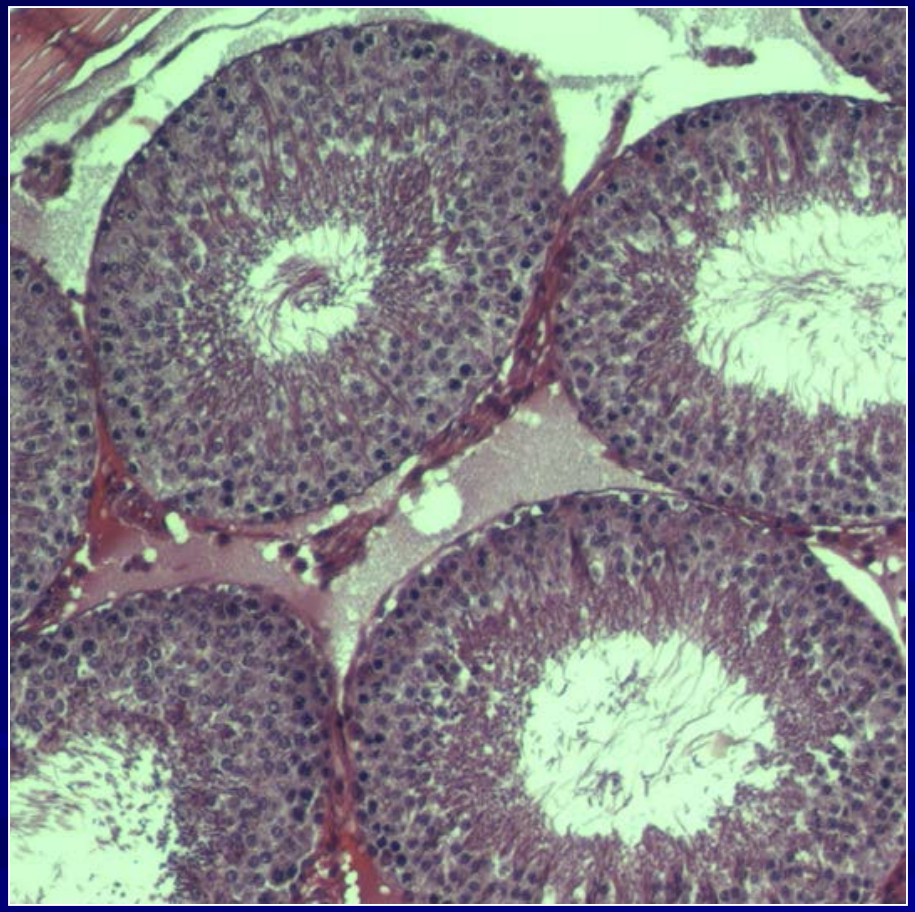
Contaminants Produced DNA Methylation Changes.



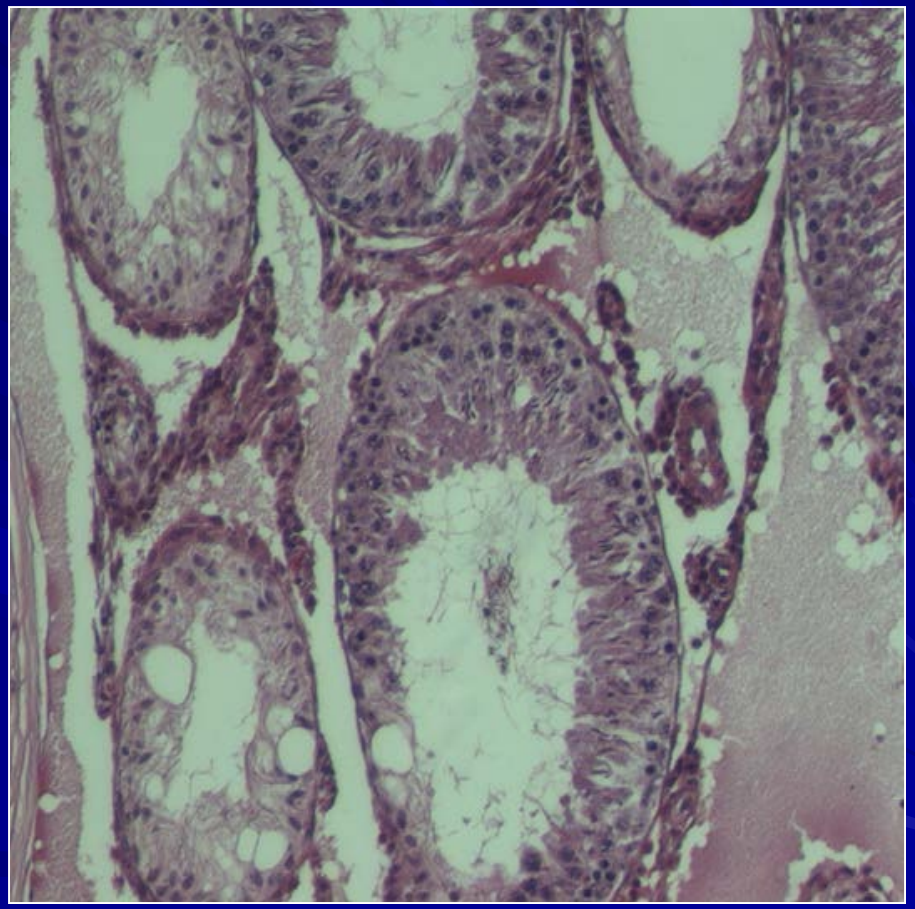
Atrazine Results

- F1: Weighed less than controls.
- F2: Testis disease, Breast Cancer (both males & females), Lower Weight.
- F3: Testis Disease,
- F3:Premature Puberty
- F3: "Skinny" Phenotype,
- F3: 50% with Multiple Diseases.
- F3: Fearless Risk Taking Males

Testicular Disease

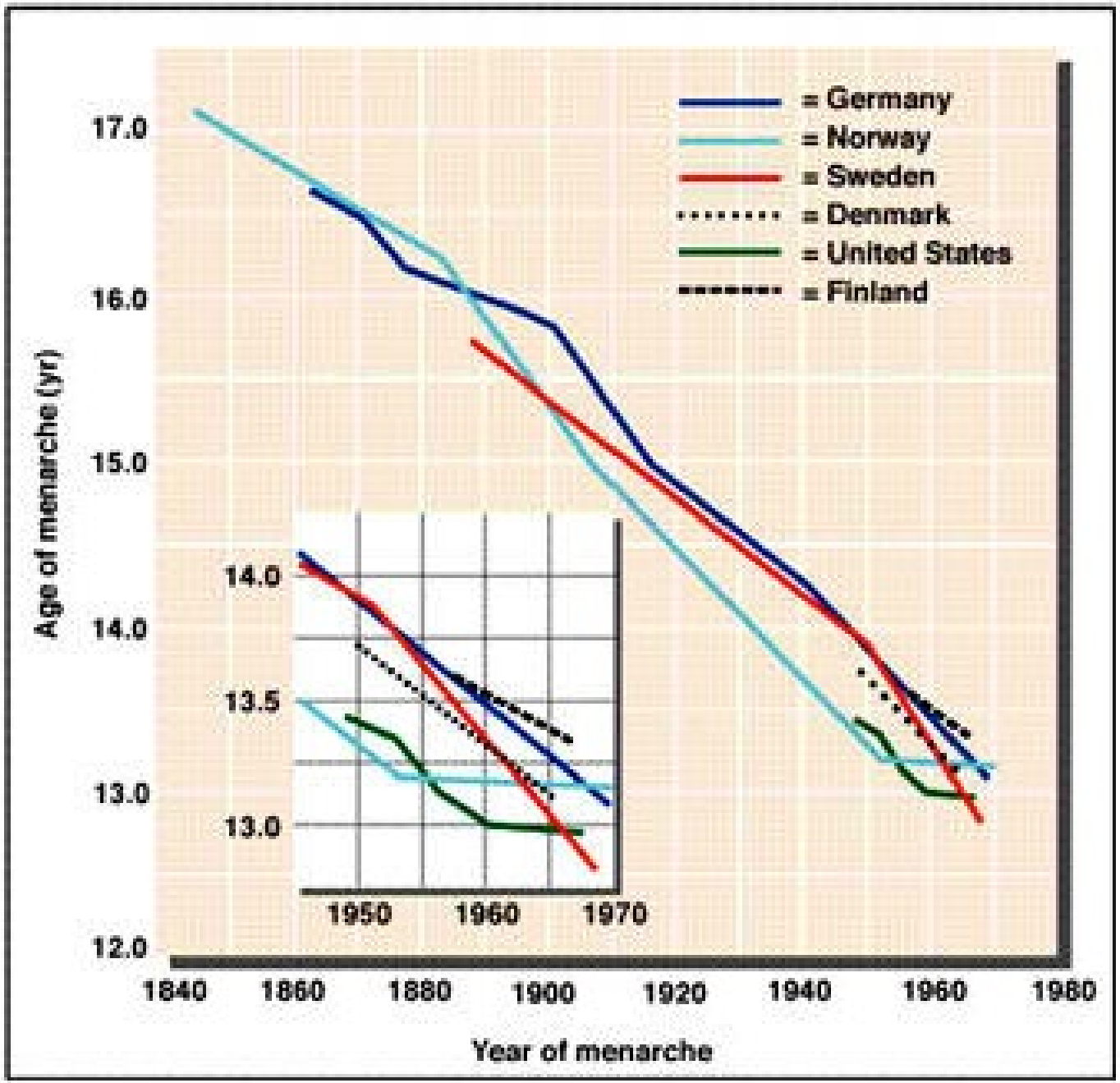


F3 Control testis:
Normal seminiferous tubules

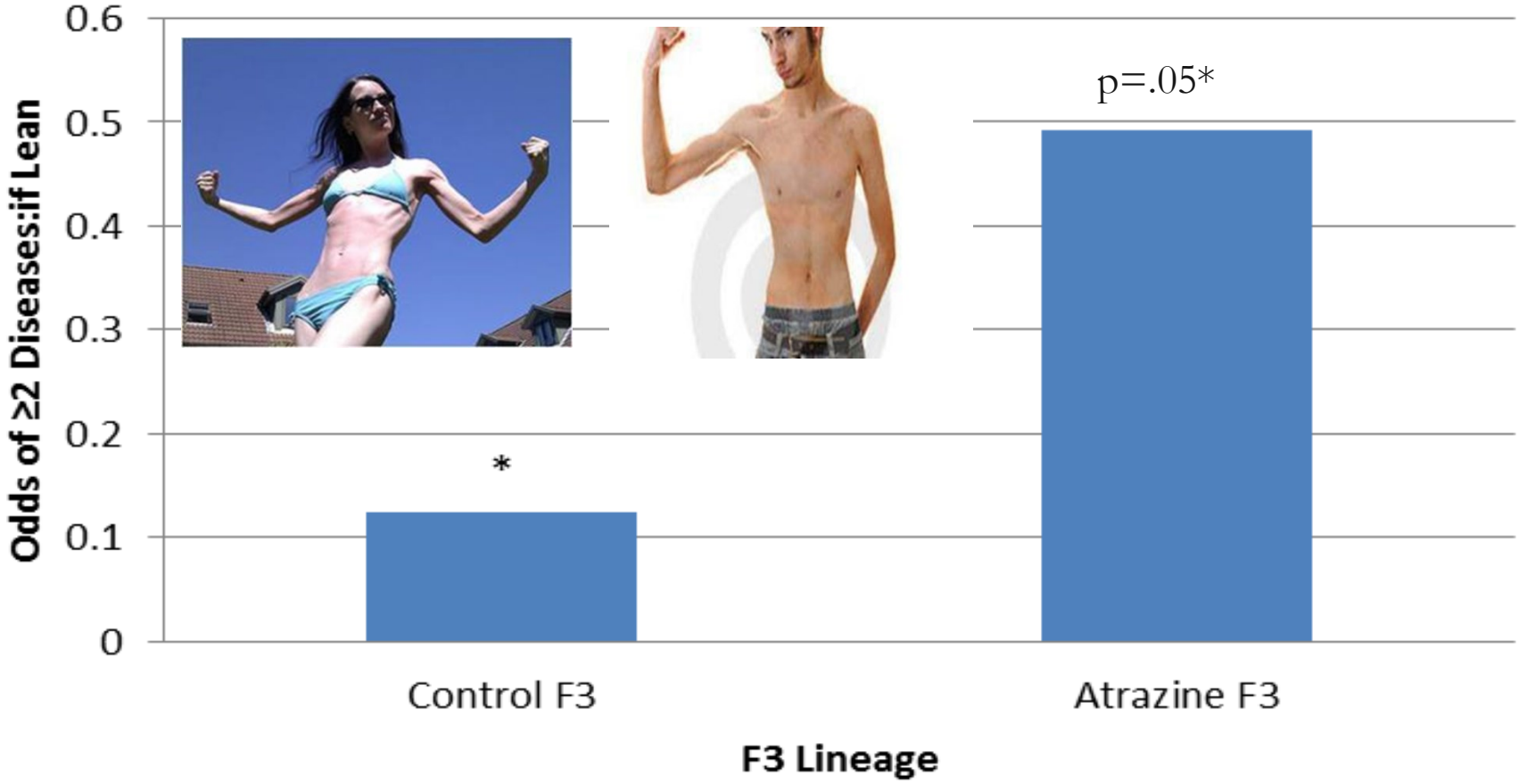


F3 Atrazine testis:
Seminiferous tubule atrophy and vacuoles

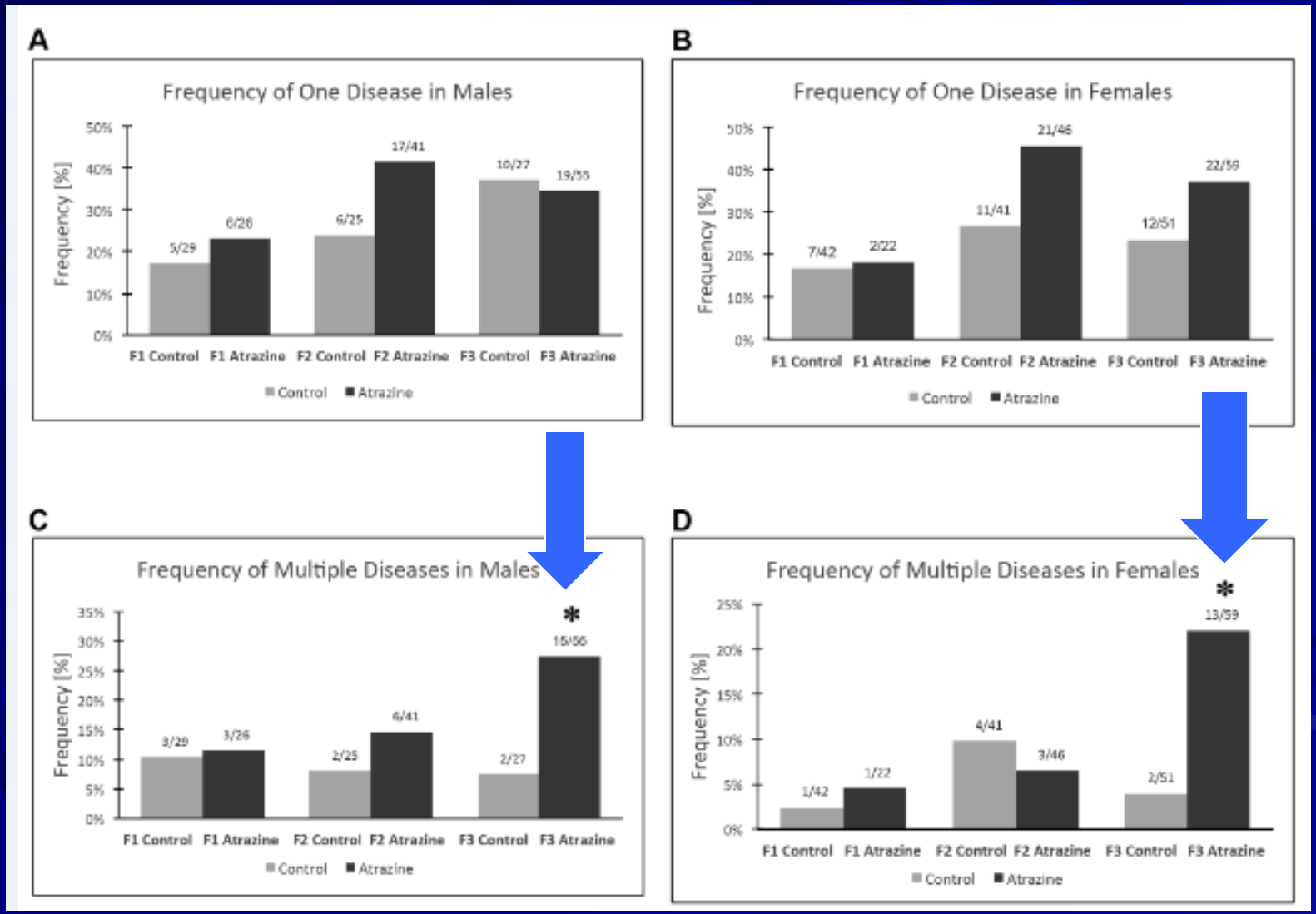
dolescence, 4e. Copyright © 1996. McGraw-Hill Companies, Inc. All Rights Reserved.



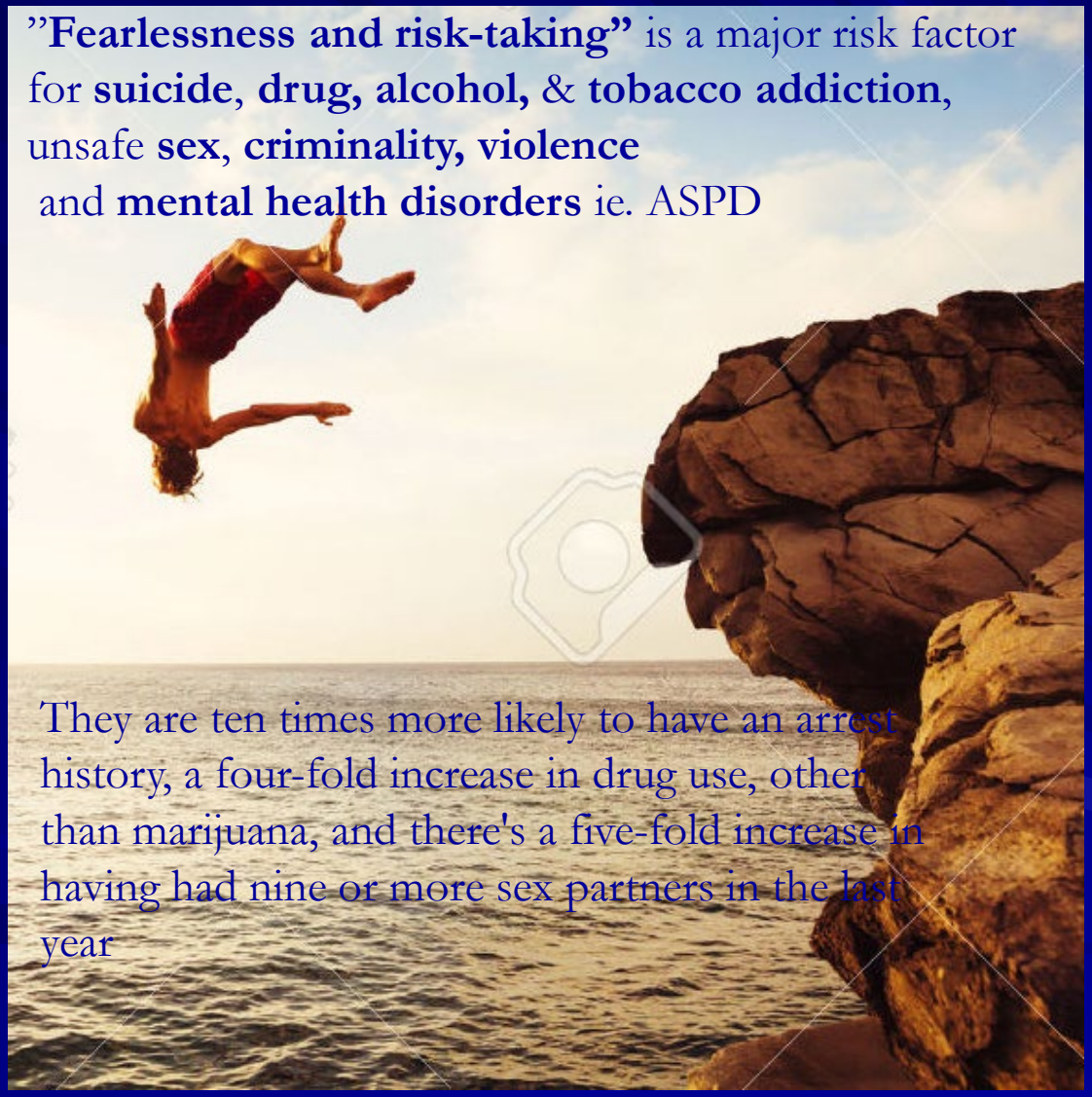
Price for Being "Skinny"



More Multiple Disease in F3



Reduced Anxiety and Higher Risk Taking



Summary

- Atrazine: Not Toxic by EPA standards even after low dose exposure in pregnancy.
- Atrazine: imprints fetal DNA, creates disease in 2nd and 3rd generation offspring.
- Worst effects: infertility, proness to multiple diseases, probable behavioral problems.

Conclusions

- Environmental pesticides used on an industrial scale are now part of our epigenome.
- The diseases they cause in animals are now epidemic in humans.
- Lack of funding prevents us from answering industry critics (with epigenetic studies) who insist that we are safe.

Thank You Gerber Foundation!

Those who contemplate beauty in the earth will find reserves of strength that will endure as long as life lasts! ***Rachel Carson***

END

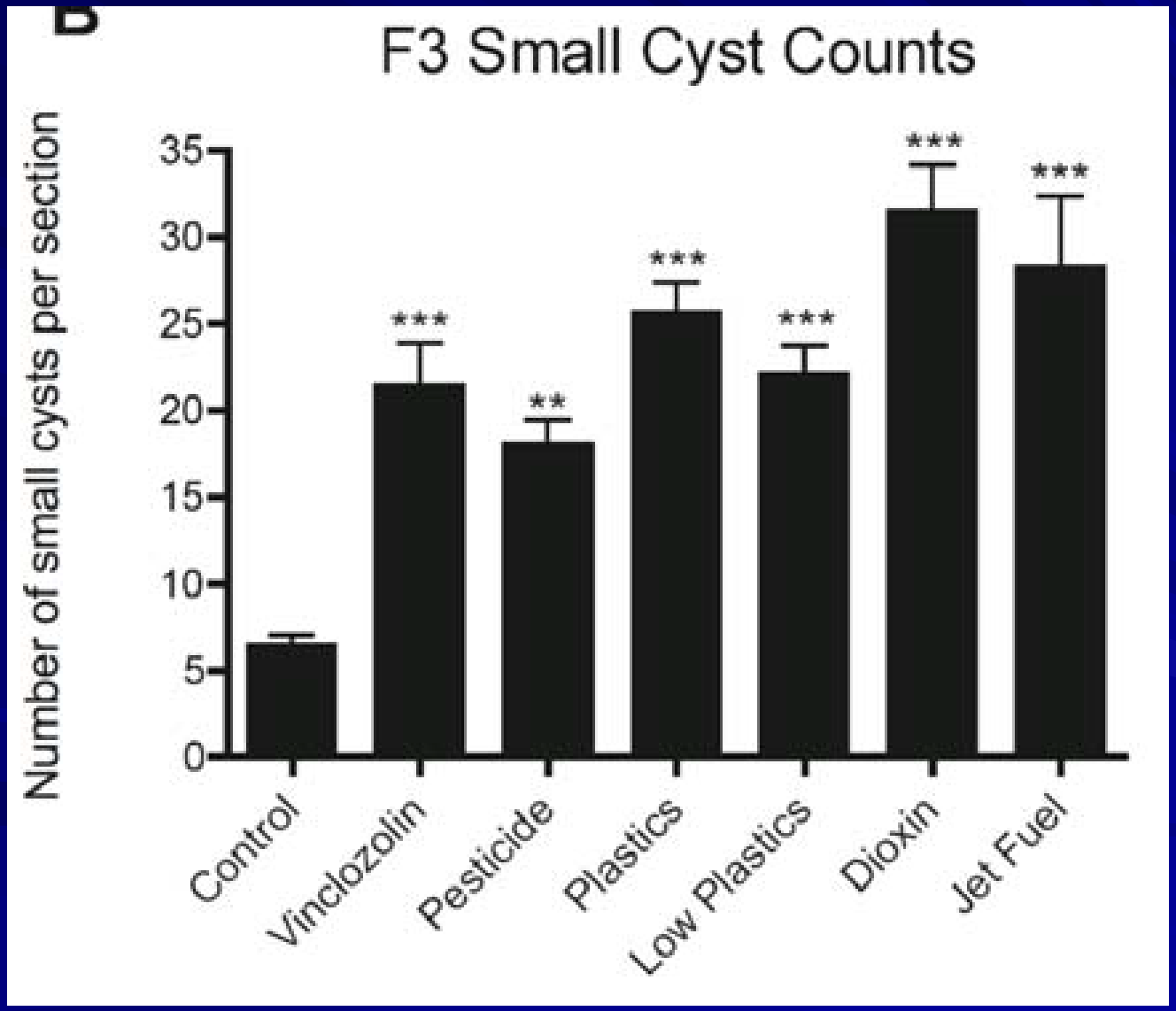
Paul Winchester MA (Michigan), MD

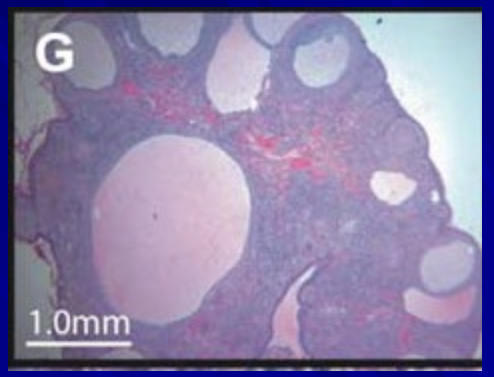
Clinical Professor Pediatrics Indiana University School of Medicine,Director NICU,St.Francis Hospital, Indianapolis, Indiana

Supplemental Slides

- More Skinner Data
- More Public Health Data
- More Glyphosate Data

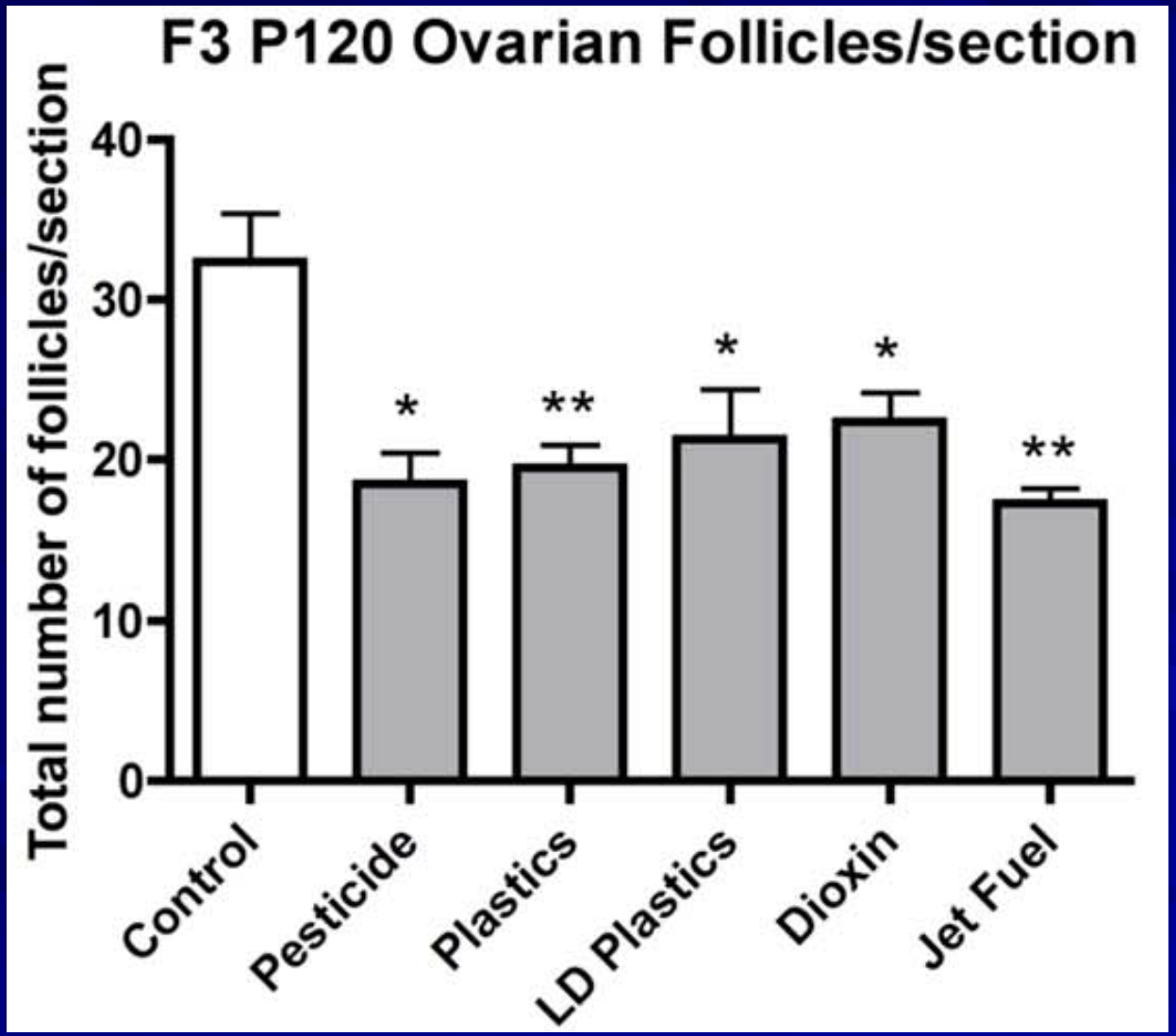
Polycystic Ovarian Disease

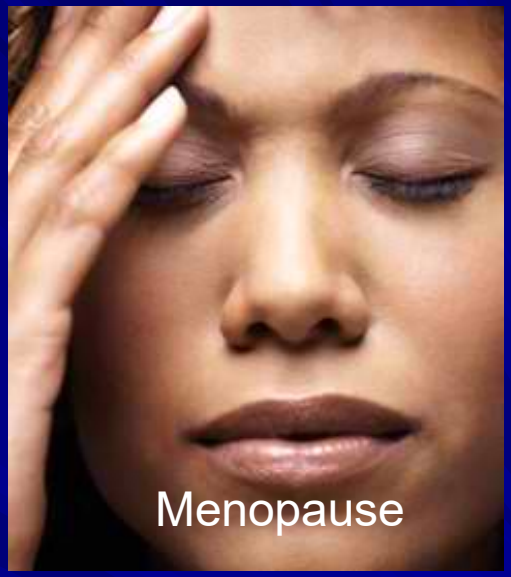




Nilsson E, Larsen G, Manikkam M, Guerrero-Bosagna C, Savenkova MI, Skinner M,et al. PLoS (2012)

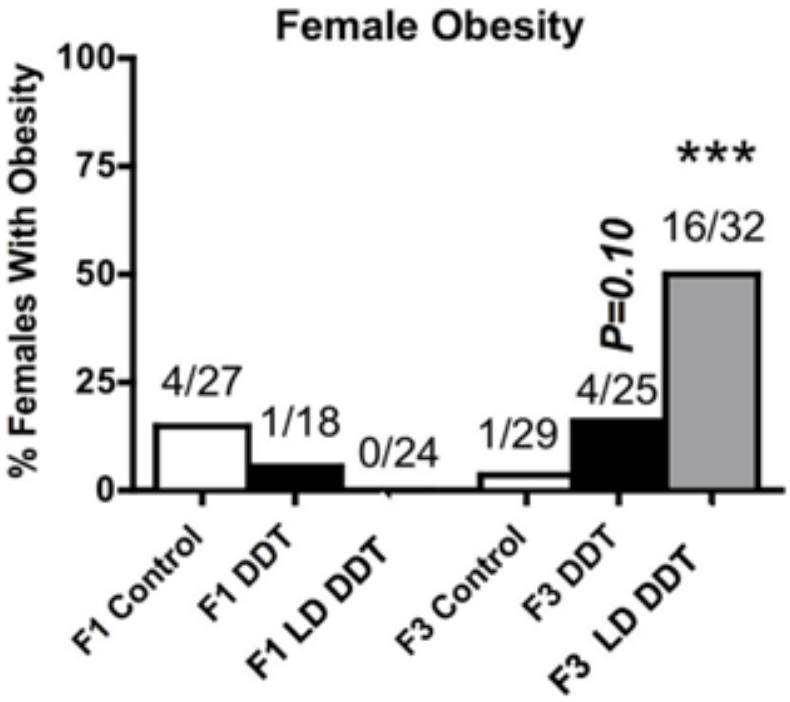
Premature Ovarian Failure POF

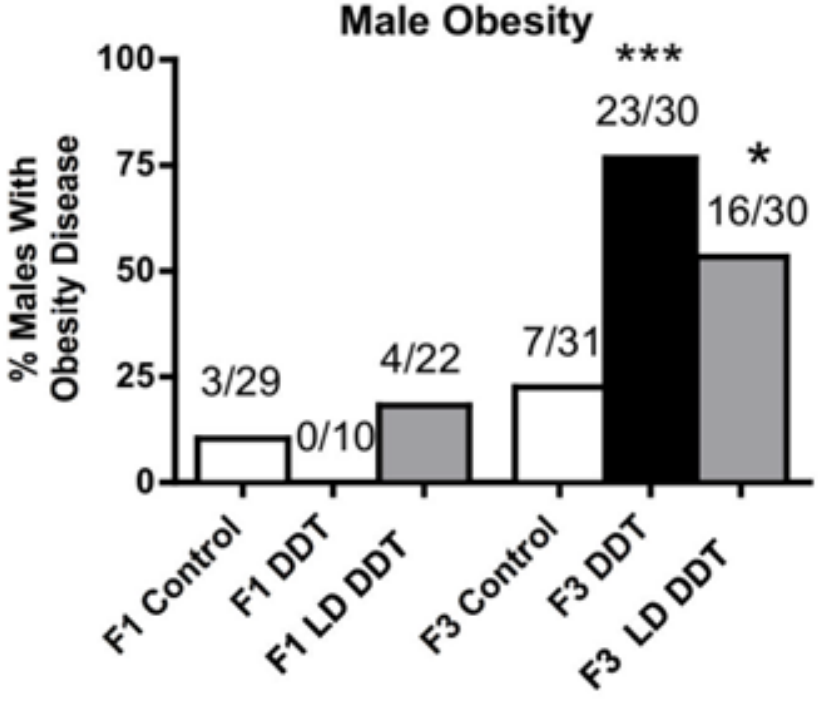




DDT; Transgenerational Obesity

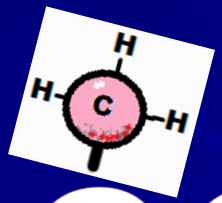
DDT induced transgenerational obesity and associated disease through the female (egg) germline, Thus,female germline can also transmit transgenerational disease.



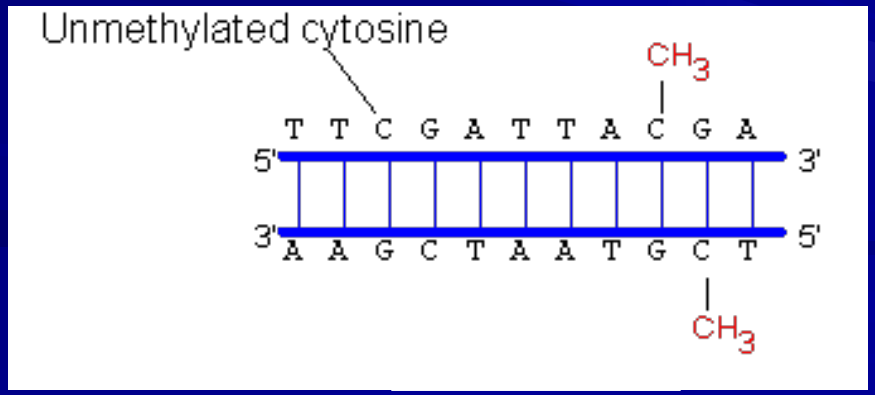


1.Michael K Skinner, Mohan Manikkam, Rebecca Tracey, Carlos Guerrero-Bosagna, Muksitul Haque, Eric E Nilsson. Ancestral dichlorodiphenyltrichloroethane (DDT) exposure promotes epigenetic transgenerational inheritance of obesity. BMC Medicine, 2013; 11 (1): 228 DOI: 10.1186/1741-7015-11-228

DNA Methylation at CpG Site



TTCGATTACGA



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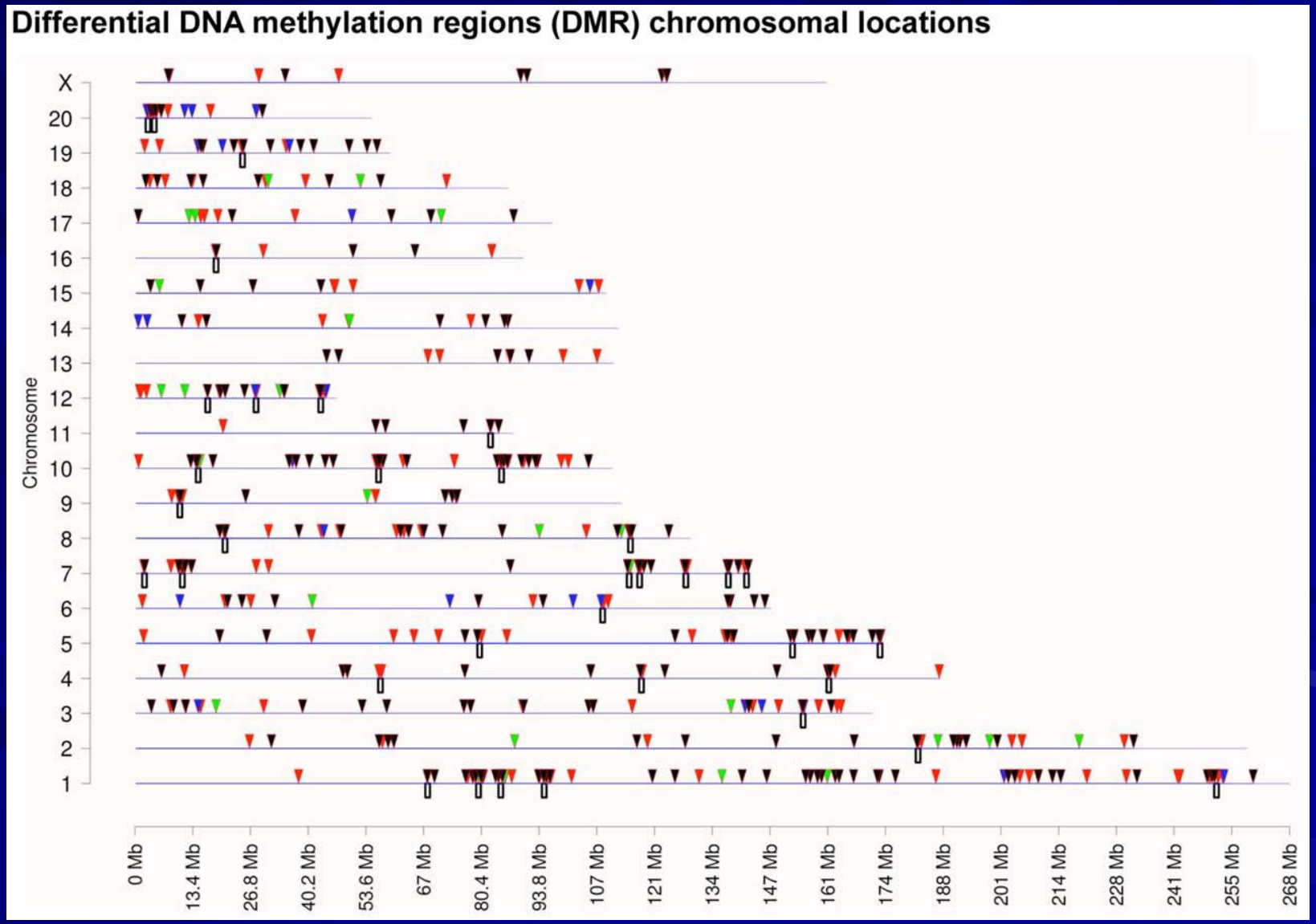
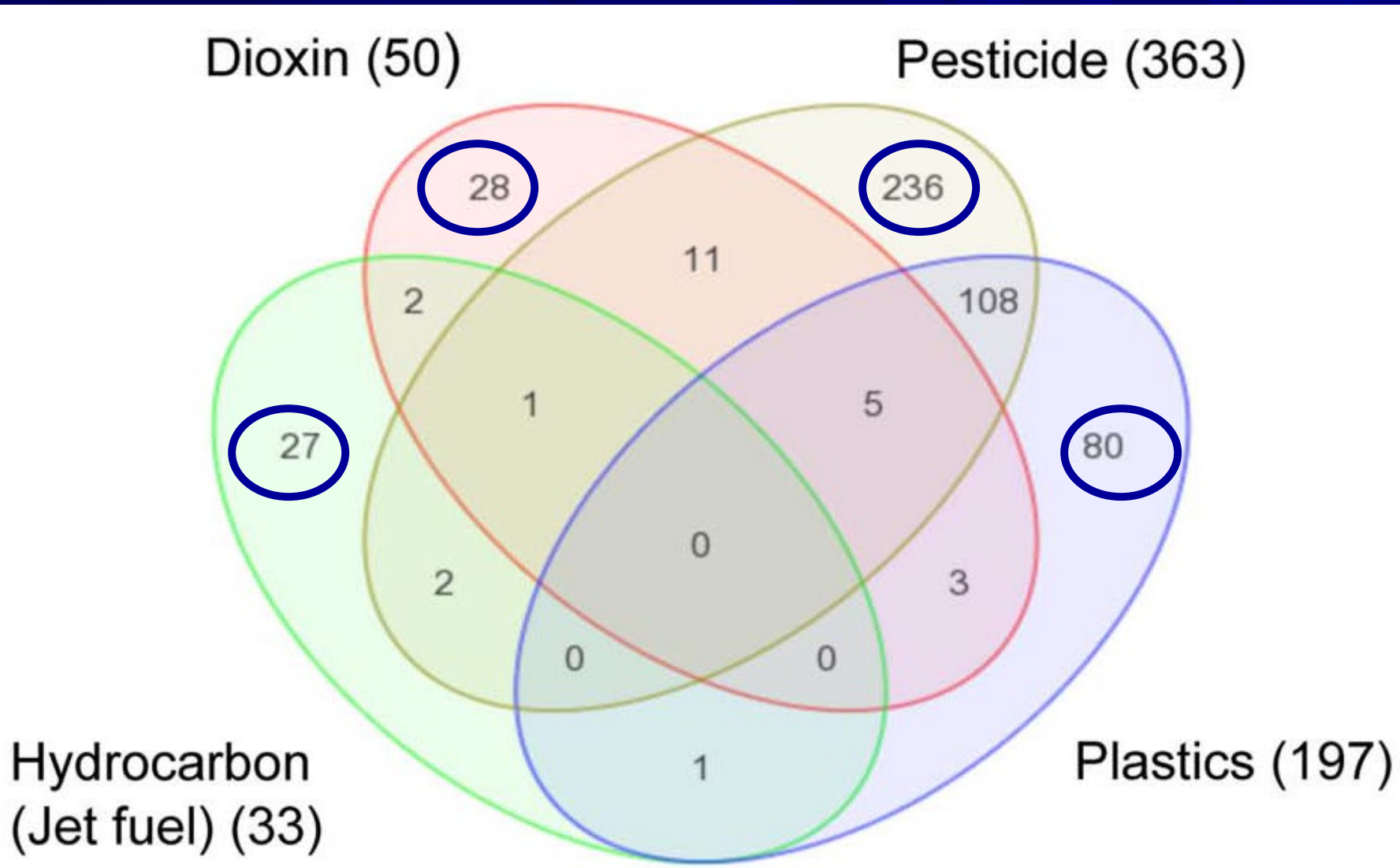


Environmental Chemicals: The New Gene Expression Engineers

Compounds Leave Unique "Imprint" on DNA

Skinner et al. PLoS 2012



Sperm Quality Down!

Temporal trends in sperm count:a systematic review and meta-regression analysis

Hagai Levine, Niels Jørgensen, Anderson Martino-Andrade,
Jaime Mendiola, Dan Weksler-Derri, Irina Mindlis, Rachel Pinotti,
and Shanna H. Swan, Human Reproduction Update, pp. 1–14, 2017

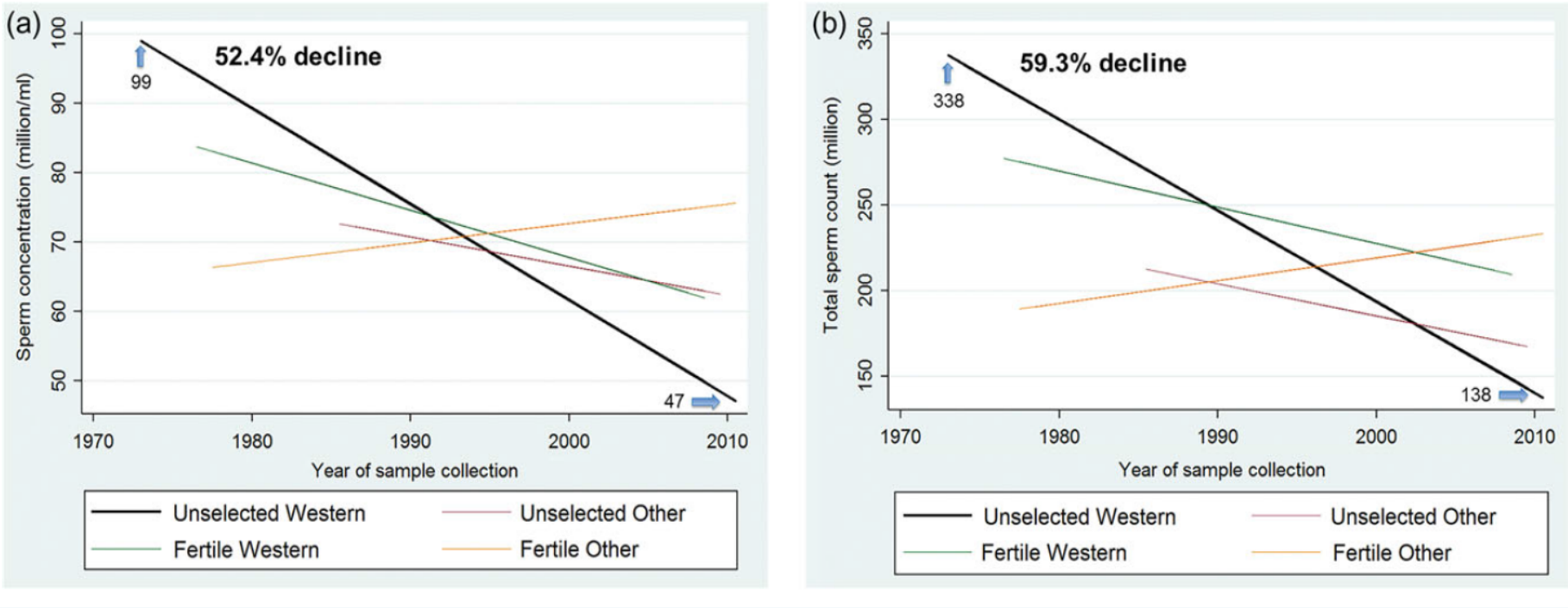
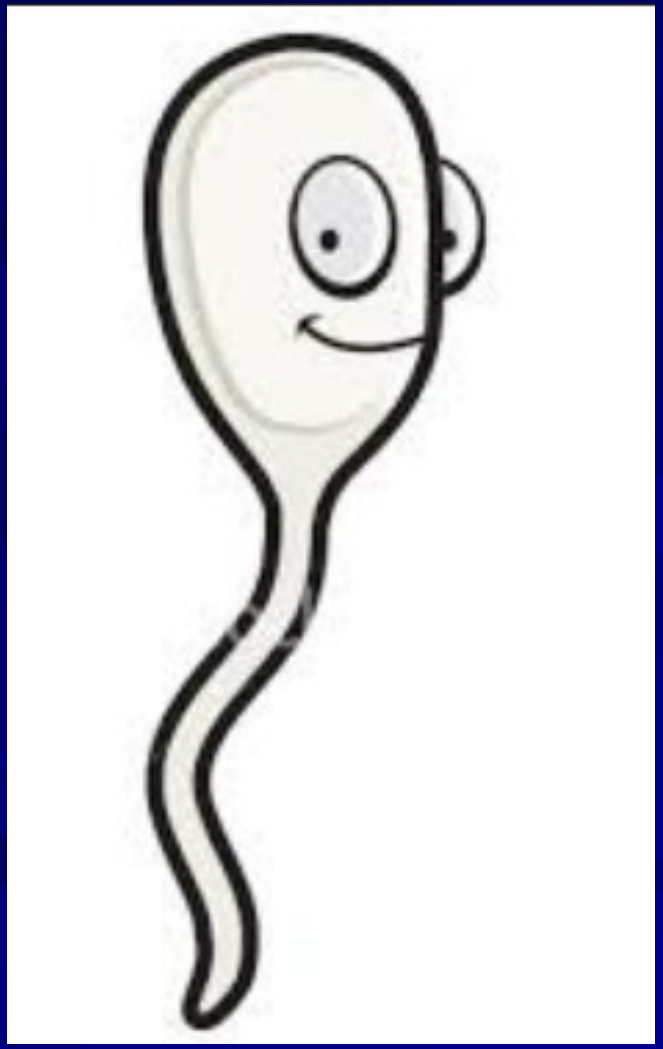
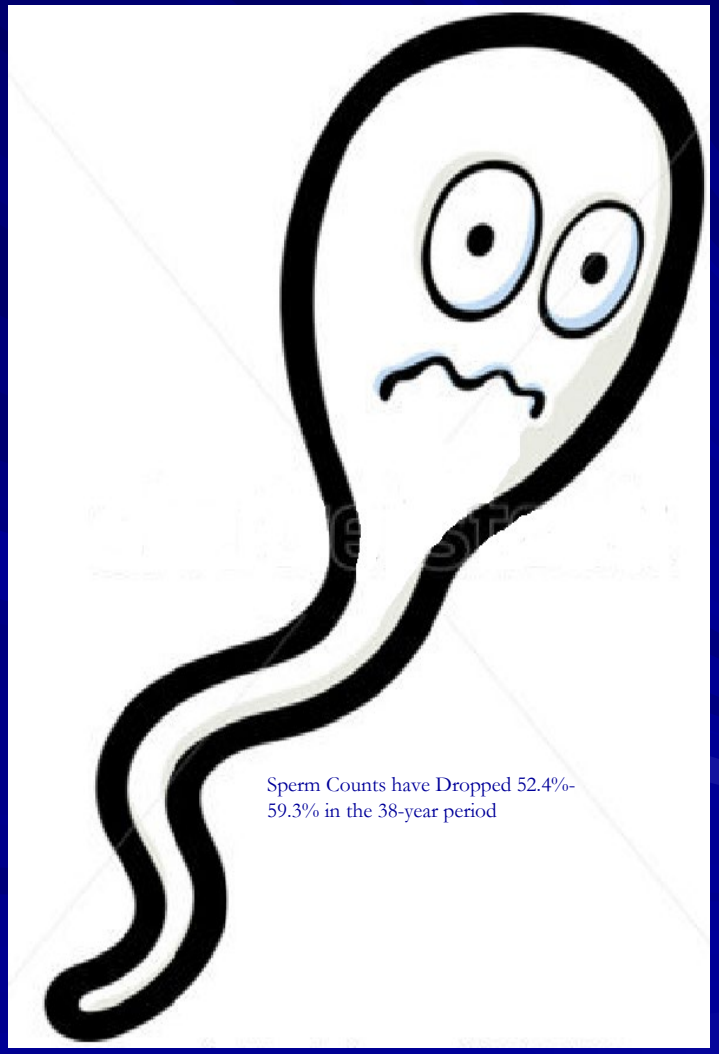


Figure 3 (**a**) Meta-regression model for mean sperm concentration by fertility and geographic groups, adjusted for potential confounders. (**b**) Meta-regression model for mean total sperm count by fertility and geographic groups, adjusted for potential confounders. Meta-regression model weighted by sperm concentration (SC) SE, adjusted for fertility group, time × fertility group interaction, geographic group, time × geographic group interaction, age, abstinence time, semen collection method reported, counting method reported, having more than one sample per men, indicators for study selection of population and exclusion criteria (some vasectomy candidates, some semen donor candidates, exclusion of men with chronic diseases, exclusion by other reasons not related to fertility, selection by occupation not related to fertility), whether year of collection was estimated, whether arithmetic mean of SC was estimated, whether SE of SC was estimated and indicator variable to denote studies with more than one estimate. Total sperm count (TSC) meta-regression models weighted by TSC SE, adjusted for similar covariates and method used to assess

Seriously. This is BAD!





Most men in the US and Europe could be infertile by 2060, according to a new study

US Fertility Rates Declining

- Replacement rate is generally considered to be 2,100 births per 1,000 women.
- TFR has generally been below replacement since 1971. National Center for Health Statistics. Vital statistics of the United States, 2003, volume I, natality. Available from: http://www.cdc.gov/nchs/products/vsus/vsus_1980_2003.htm
- Environmental Chemicals have placed us on a path to extinction.

Early Onset of Puberty & Later Health Problems

- Angina, heart attack,
- Obesity, high cholesterol (metabolic syndrome)
- hypertension
- Diabetes II, cancers
- Hypothyroid
- gynecological/obstetric
- Food allergies,
- Gout,arthritis,
- Anxiety,panic,drepression bipolar,chronic fatigue

Day, F. R. et al. Puberty timing associated with diabetes, cardiovascular disease and also diverse health outcomes in men and women: the UK Biobank study. Sci. Rep. 5,11208; doi: 10.1038/srep11208 (2015).

GYN and Obstetrical

- Premature menopause
- Endometriosis
- Pregnancy induced hypertension
- Hysterectomy
- Low Birth weight child, (preterm)
- Oopherectomy
- Stillbirth
- Uterine Fibroids
- Infertility, PCOS,

Gastrointestinal

- Food allergies
- Gall bladder
- Diverticulitis
- Gastroesophageal Reflux, hiatal hernia
- Irritable bowel
- Coeliac disease
- (Inflammatory bowel,colitis)

Musculoskeletal /other

- Arthritis
- Rheumatoid arthritis
- Osteoarthritis
- Osteoporosis
- Spinal arthritis,spondylitis
- Glaucoma
- Psoriasis
- Asthma, bronchitis,low FEV1

Clinical Implications,Pediatrics

- A child with premature onset or late onset of puberty could be the great grandchild of a farm family with Atrazine exposure.
- An adult male with low sperm quality may be the product of grandparent with atrazine use.
- The epidemic of hyperactive, risk taking males may represent transgenerational epigenetic disease.

Household Pesticide Exposure Hastens Male Puberty
› Pyrethroid pesticides interfere with the body's hormone function
› Boys exposed to pyrethroids had higher levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
© www.medindia.net

Pyrethroids Insecticides Alter Puberty in Boys

(April,2017)

- Pyrethroid pesticides accelerate puberty in boys.
- Zhejiang University in Hangzhou, China (Dr. Jing Liu)
- 463 Chinese boys (9-16 yrs)
- Every 10% increase in 3-PBA led to 4% increase in the levels of luteinizing hormones(LH) and follicle-stimulating hormones (FSH).
- 3-PBA associated with early puberty by 73 to 110%

Neonatology Implications

- We are in the midst of a 1400% increase in newborn addiction to opiates.
- Our mothers are taking antidepressants, ADHD meds, anxiolytics.
- Our babies are the products of in Vitro fertilization (more twins, more epigenetic disease)
- More allergic colitis, more GERD, more preterm birth, smaller babies, shorter pregnancies.
- More maternal Diabetes, hypertension and obesity.

Human Study

- Pregnant Women Enrolled: Projected 80, Actual 144
- Prenatal Urine Samples Collected: Projected 80, Actual 142 / Analyzed 142
- Maternal Blood Samples Collected after Delivery: Projected 80, Actual 86 / Analyzed 78
- Cord Blood Samples Collected at Delivery: Projected 80, Actual 85 / Analyzed 76
- Maternal Buccal Samples Collected after Delivery: Projected 80, Actual 94 / Analyzed 82
- Infant Buccal Samples Collected after Delivery: Projected 80, Actual 94 / Analyzed 83
- Monthly Spot Urines: Projected 240, Actual 263 / Analyzed 263