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Resource Catalog

- Fact sheets, journal publications, reports, and other resources for parents, community members, patients and healthcare professionals
- Topics included:
  Air Quality, Pesticides, Natural Disasters, BPA, Mold, Lead, Mercury

Acknowledgements

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PEHSU Grand Rounds Webinar Series

Understanding the Role of Environmental Chemicals in Fertility and Reproduction: From Research to Prevention

Carmen Messerlian, PhD
Harvard T.H. Chan School of Public Health

PEHSU Pediatric Environmental Health Specialty Units

Research Acknowledgements

Collaborators

- Dr. Russ Hauser
- Dr. Paige Williams
- Dr. Blair Wylie
- Dr. Antonia Calafat
- Dr. Irene Souter
- Dr. Minguez-Alarcon

Study and Clinical Staff

- Jennifer Ford
- Myra Keller
- Ramace Dadd
- Massachusetts General Hospital Clinical Staff

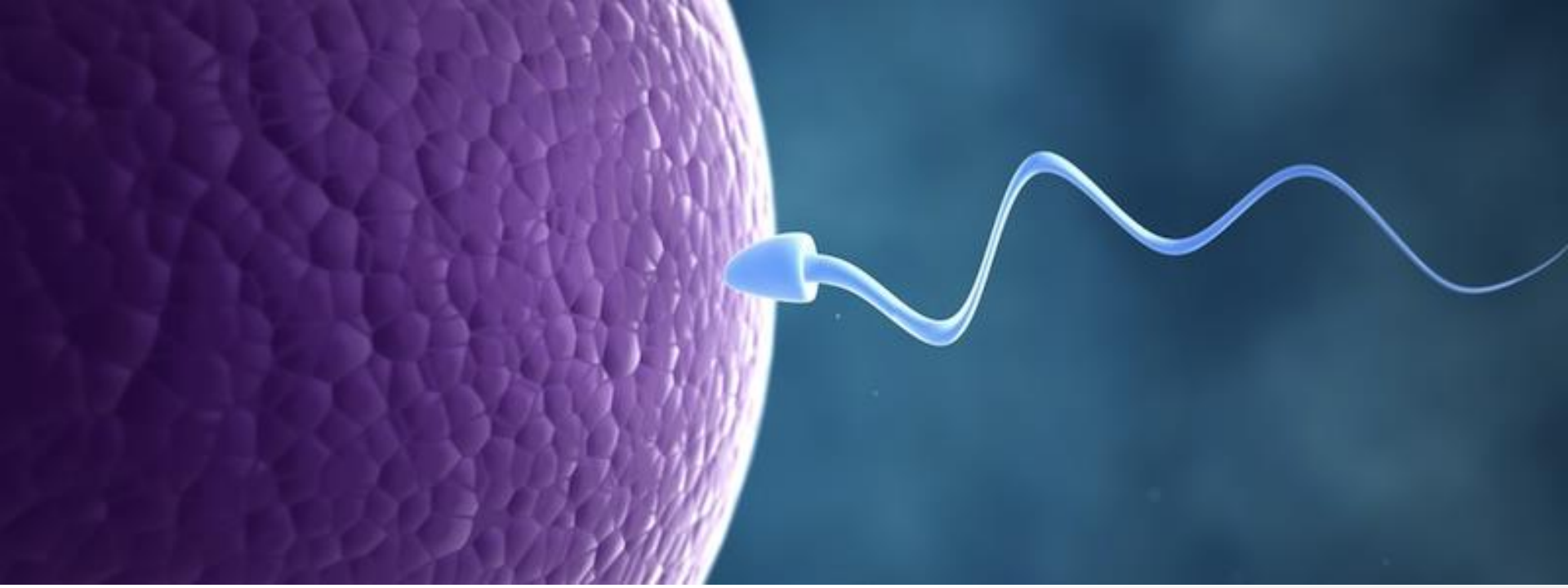
EARTH Study Participants

Funding

- National Institute of Environmental Health Sciences (NIEHS)
- Canadian Institutes of Health Research (CIHR)

Objectives

1. Define endocrine disrupting chemicals (EDCs) and describe sources, routes, and timing of exposure.
2. Understand the toxicological and human literature on phthalates, a large chemical classes with widespread population exposure.
3. Describe how phthalates and phenols may impact reproductive, perinatal, or pediatric health.
4. Understand primary prevention strategies and methods to reduce exposure.



Part I

Why Study Environmental Chemicals and Fertility, Pregnancy, and Child Health Outcomes?

Our chemical world

- We live in an increasingly more complex chemical world

- Global chemical production facts:

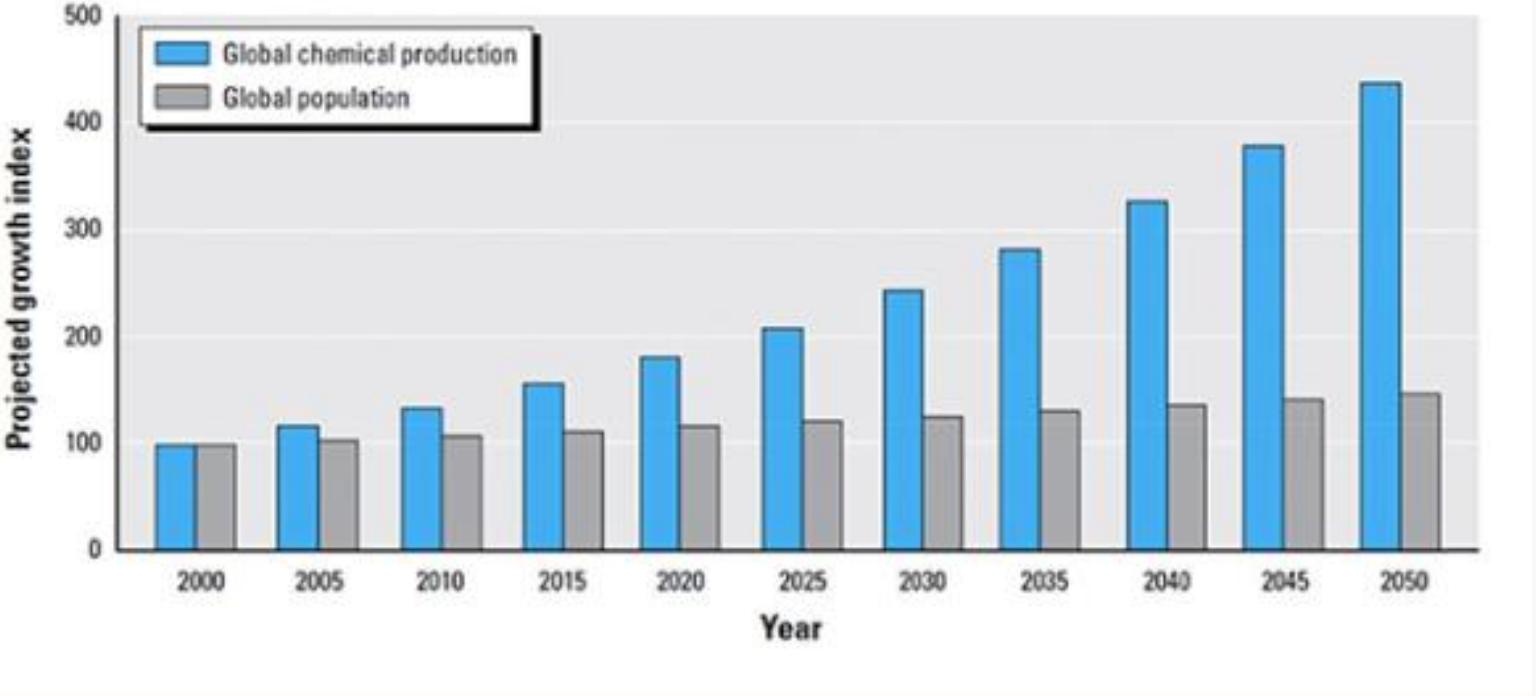
  > 3 trillion USD sales

  >83,000 chemicals in production

  >2,700 high production volume chemicals (>1million kg/year)

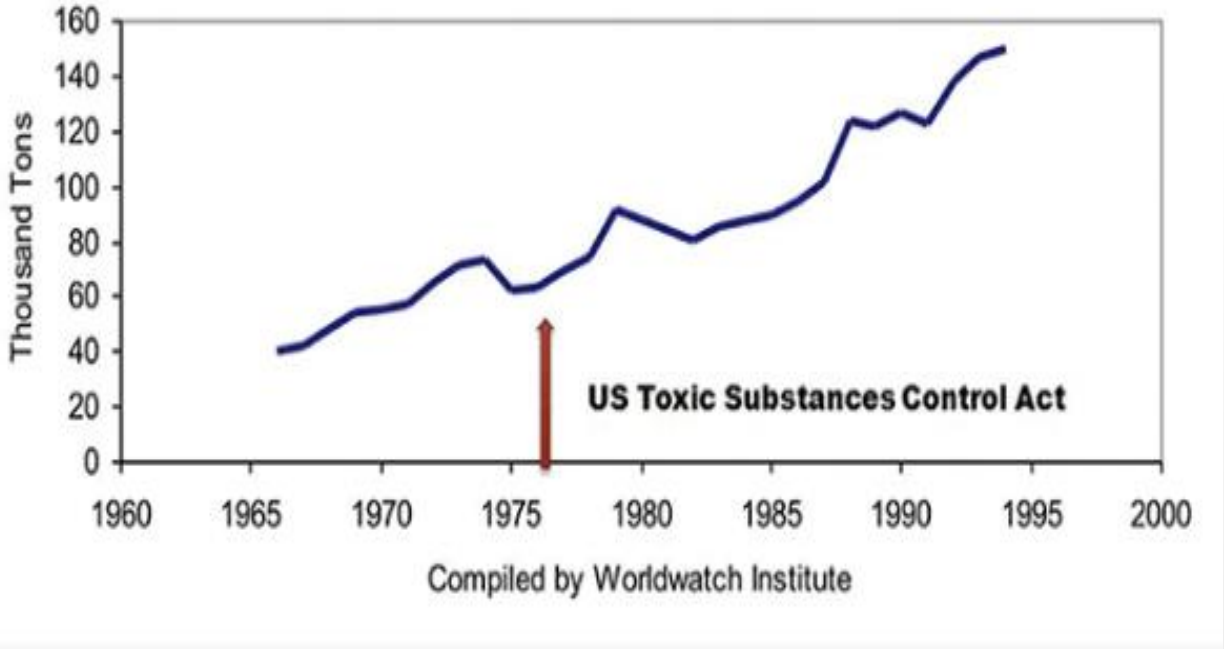
Source: http://www.cefic.org/

Projected growth of worldwide production



Source: The Challenge: Chemicals in Today's Society. Institute of Medicine. 2014. Identifying and Reducing Environmental Health Risks of Chemicals in Our Society: Workshop Summary. Washington, DC: The National Academies Press. doi: 10.17226/18710.

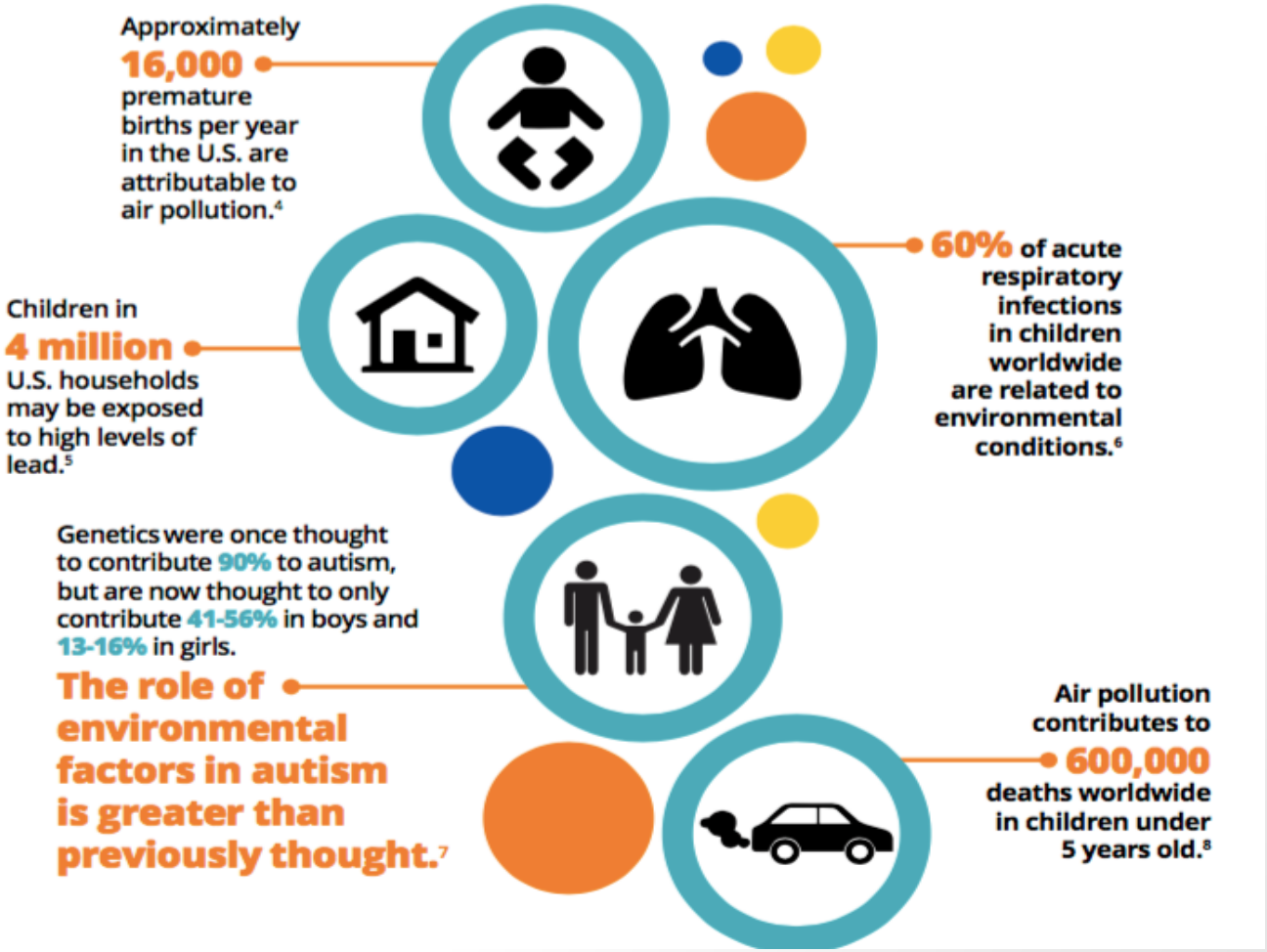
Volume of chemicals in commerce: US synthetic organic chemicals 1966-1994



The vast majority of chemicals in production today have **not** been tested for safety

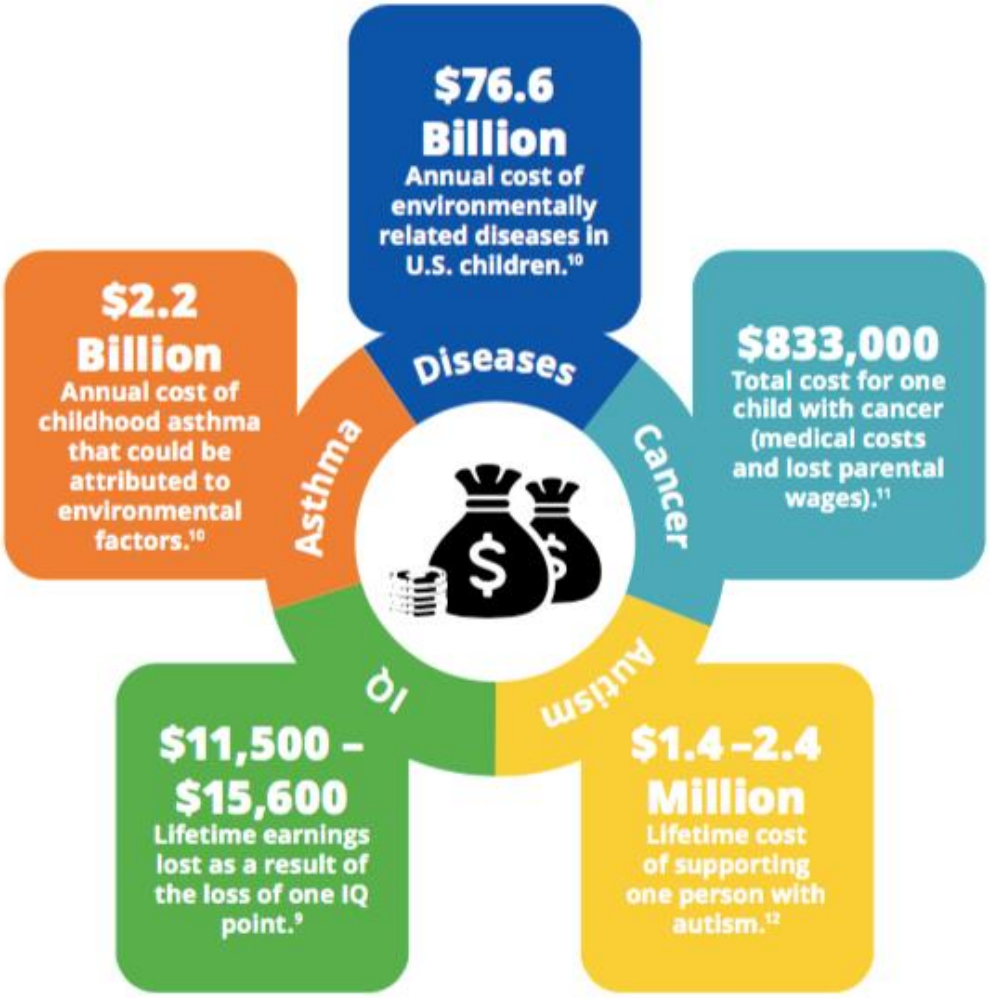
Source: The Challenge: Chemicals in Today's Society. Institute of Medicine. 2014. Identifying and Reducing Environmental Health Risks of Chemicals in Our Society: Workshop Summary. Washington, DC: The National Academies Press. doi: 10.17226/18710.

The environment and children's health



Source: NIEHS/EPA Children's Environmental Health and Disease Prevention Research Centers Impact Report, 2017
https://www.epa.gov/sites/production/files/2017-10/documents/niehs_epa_childrens_centers_impact_report_2017_0.pdf?pdf=chidrens-center-report

Socio-economic burden



Source: NIEHS/EPA Children's Environmental Health and Disease Prevention Research Centers Impact Report, 2017
https://www.epa.gov/sites/production/files/2017-10/documents/niehs_epa_childrens_centers_impact_report_2017_0.pdf?pdf=chidrens-center-report

Environmental chemicals of concern

"Endocrine disrupting chemicals (EDCs) are exogenous chemicals, or mixtures of chemicals, that interfere with any aspect of hormone action."

Zoeller et al., 2012, A Statement of Principles from the Endocrine Society

- Chemicals that can be found in our environment, food, or consumer products that can interfere with hormonal synthesis, metabolism, or action resulting in dysregulation and disruption of hormonal homeostasis
- >800 chemicals identified as known or suspected EDCs
- A small fraction has been tested for safety

Persistent and short-lived EDCs

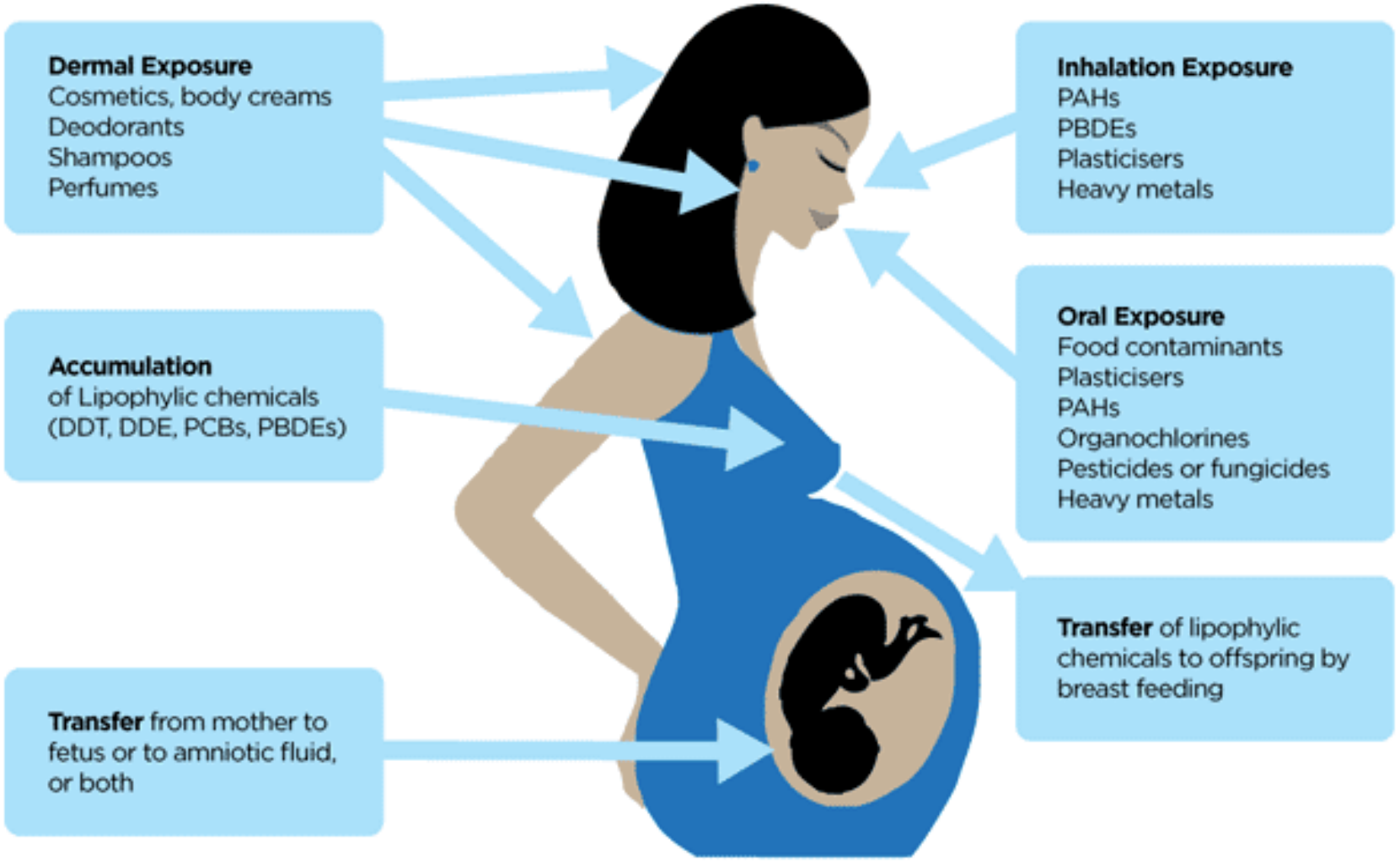
Persistent

- Dioxins
- Polybrominated flame retardants (PBDEs)
- Polychlorinated biphenyls (PCBs)
- Perfluoroalkyl substances (PFASs)
- Organochlorine pesticides (OCPs)

Short-lived

- Phthalates
- Organophosphate flame retardants (OPFRs)
- Phenols
  - Bisphenol A (BPA)
  - Parabens
  - Triclosan

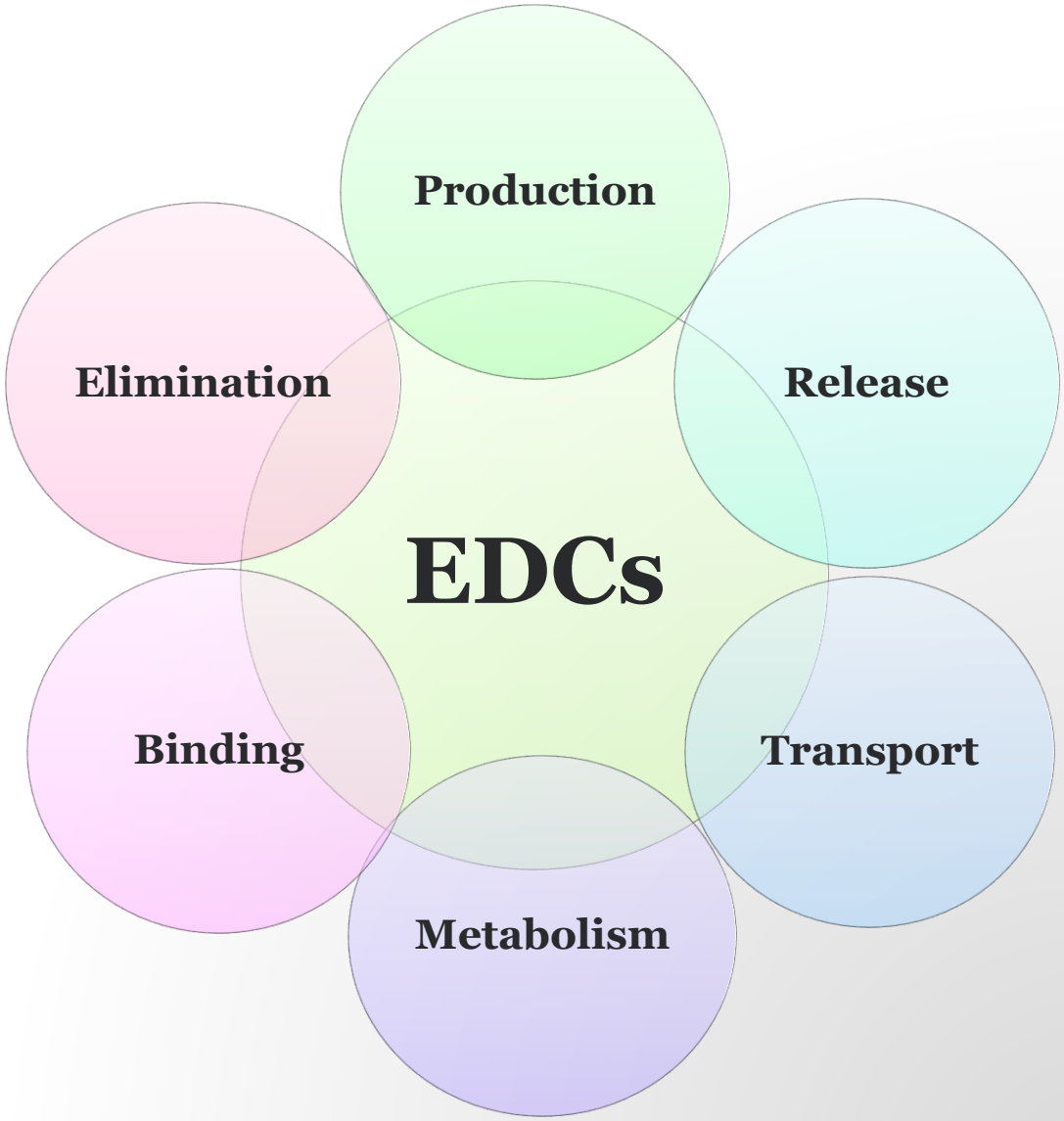
EDC exposure routes



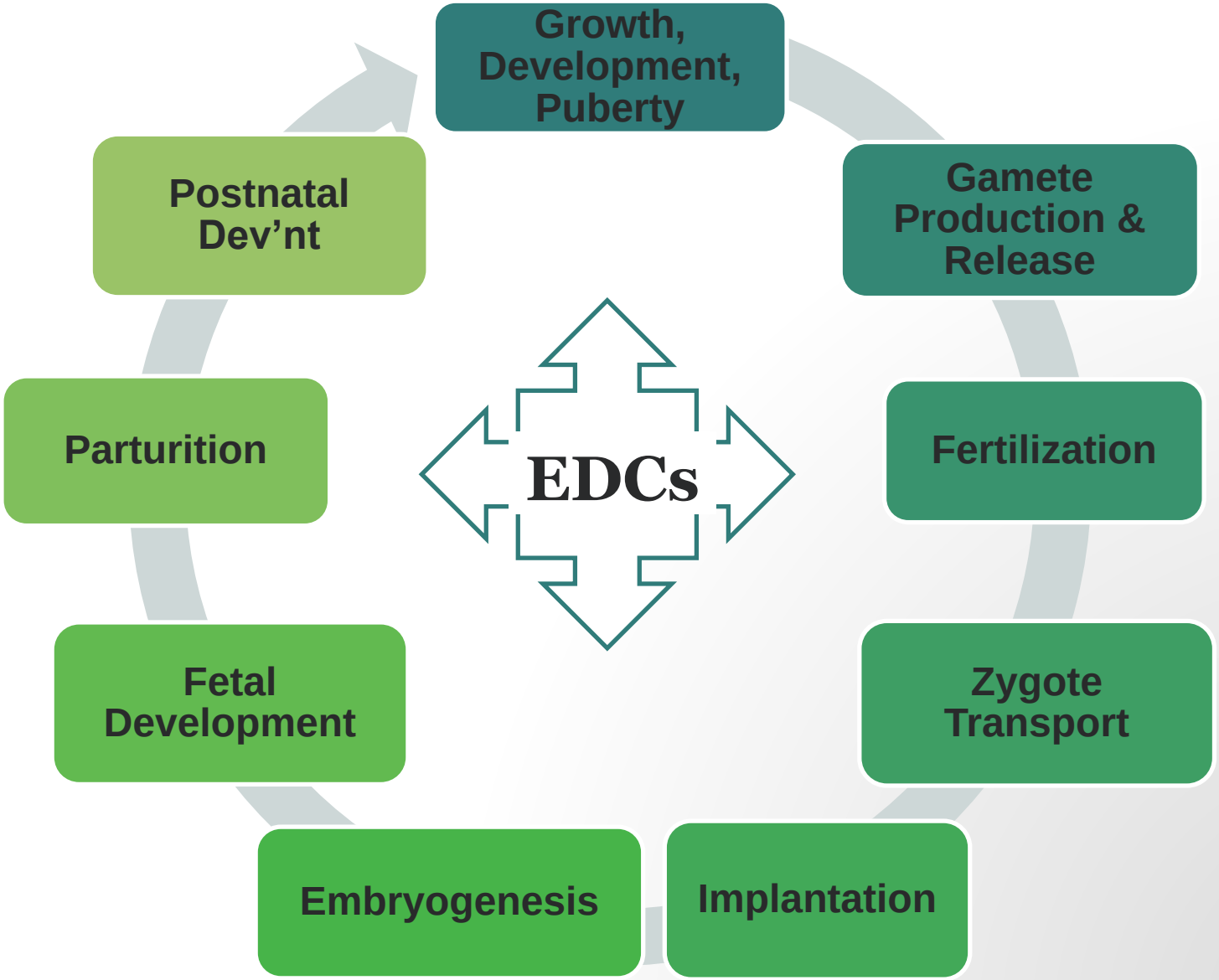
Source: http://welladjusted.co/blog/2011/08/31/toxic-chemicals-in-everyday-products/

EDC activity

- EDCs can have diverse effects in the body
- They have been shown to interfere with production, release, transport, metabolism, binding, and/or elimination of endogenous hormones.



Why should we care about EDCs and reproductive and child health?



Adapted from Casarett & Doull's Essentials of Toxicology, 2015

Why is timing so important?

Timing of exposure is a critical determinant of disease susceptibility

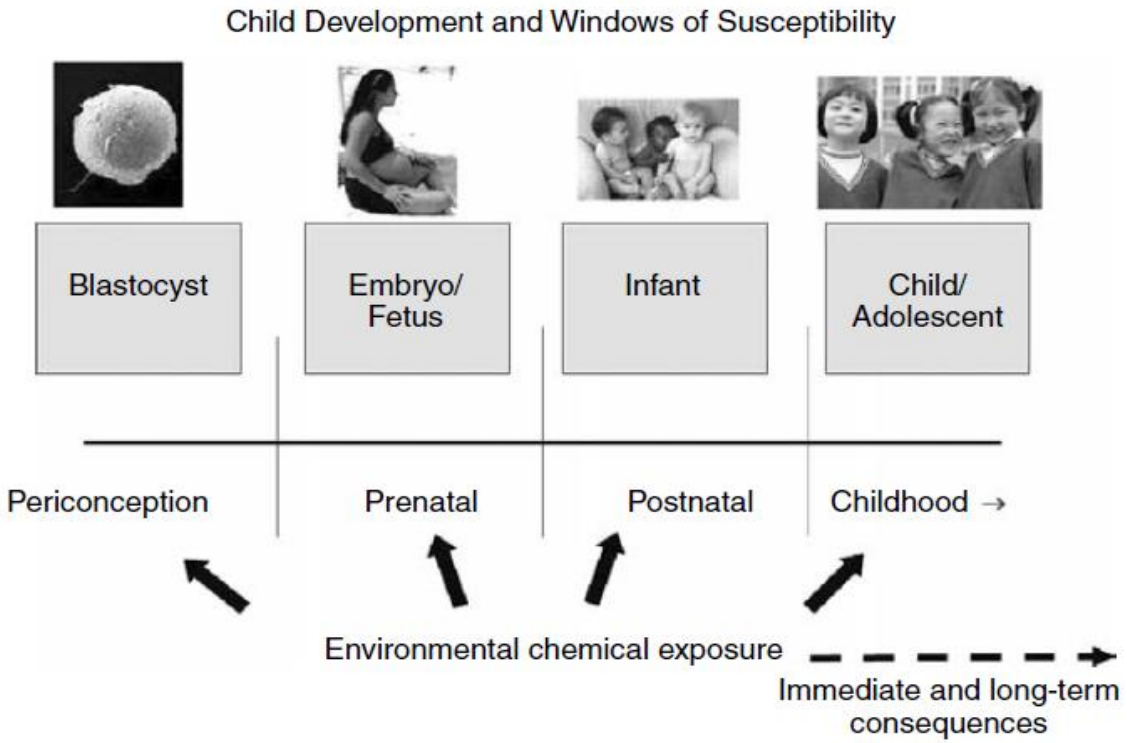


Fig. 1.2. Important developmental time periods during which perturbations, such as from exposure to environmental contaminants, can result in changes that can increase risk of subsequent immediate or long-term adverse health outcomes. (Modified from Louis *et al.* [32].)

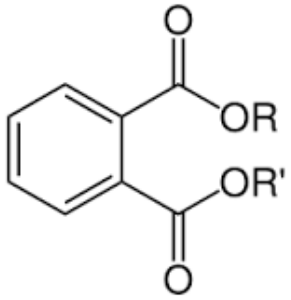
Source: TJ Woodruff, SJ Janssen, LJ Guilllette Jr, L Giudice. (2010). Environmental Impacts on Reproductive Health and Fertility. Cambridge University Press.

Part II

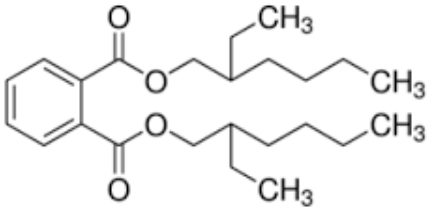
Phthalates, Phenols and Reproductive Health

Phthalates

- Large class of chemicals
- Diverse industrial and consumer applications
- Used since 1920
- Global production: 3 billion kg/year
- 20 + different phthalate compounds on the market (e.g., plasticizers and solvents)
- Short half-life: urine biomarker



Di (2-ethylhexyl) Phthalate (DEHP)



- Used to impart durability and flexibility to plastics - PVC
- Diet is a major source of exposure
- Most of the general population is exposed

What are the reproductive effects in animals?

Reproductive toxicant: male and female animals

- Disrupts ovarian function and inhibits growth of follicles (Hannon et al. 2014)
- "Phthalate Syndrome" - reduced anogenital distance, malformations (Gray and Foster, 2005)

Embryofetotoxic and teratogenic

- Dose, timing and route of exposure

Dams dosed with DEHP in gestation

- Fewer litters
- Fewer live pups per litter
- Lower proportion of pups born alive
- Reduced pup weight (Gray et al. 2006)

What are the reproductive effects in humans?

Prenatal exposure

- Preterm birth: 30-70% increased odds (Ferguson et al. 2014)
- Birth weight: reduced BW in IVF infants (Messerlian et al. 2017)
- Preeclampsia: unclear

Cycle-specific exposure

- IVF outcomes (Hauser et al. 2016)
  - Lower oocyte yield, fewer mature oocytes
  - Reduced clinical pregnancy and live birth rates

Phenols

- A large group of high production volume chemicals
  - Bisphenol A and substitutes: plastics and epoxy resins (bottles, cans)
  - Triclosan: antibacterial properties (personal care and cleaning products)
  - Parabens: preservatives (cosmetics, creams, pharmaceuticals)
  - Benzophenone 3: UV filter (sunscreen, face creams)
- Short half-life: urine biomarker

Part III

Endocrine Disrupting Chemicals and Adverse Fertility, Pregnancy, and Child Health Outcomes

The Environment and Reproductive Health (EARTH) Study

Prospective **preconception** cohort study of couples recruited from the Massachusetts General Hospital Fertility Center

- Women 18 to 45 years
- Men 18 to 55 years
- Eligible to enroll independently or as couple
- Followed: time of entry, through fertility care, pregnancy, and delivery

2004 – present
800 women
500 men
>565 live births

HARVARD T.H. CHAN
SCHOOL OF PUBLIC HEALTH

MGH
1811

Human Reproduction Open, pp. 1–11, 2018
doi: 10.1093/hropen/hoy001

human reproduction open

REVIEW

The Environment and Reproductive Health (EARTH) Study: a prospective preconception cohort

Carmen Messerlian [1], Paige L. Williams[2,3], Jennifer B. Ford[1], Jorge E. Chavarro[2,4], Lidia Mínguez-Alarcón[1], Ramace Dadd[1], Joseph M. Braun[5], Audrey J. Gaskins[4,6], John D. Meeker[7], Tamarra James-Todd[1,2], Yu-Han Chiu[4], Feiby L. Nassan[1,4], Irene Souter[8], John Petrozza[8], Myra Keller[1], Thomas L. Toth[8], Antonia M. Calafat[9], and Russ Hauser[1,2,10,*], for the EARTH Study Team[†]

human reproduction

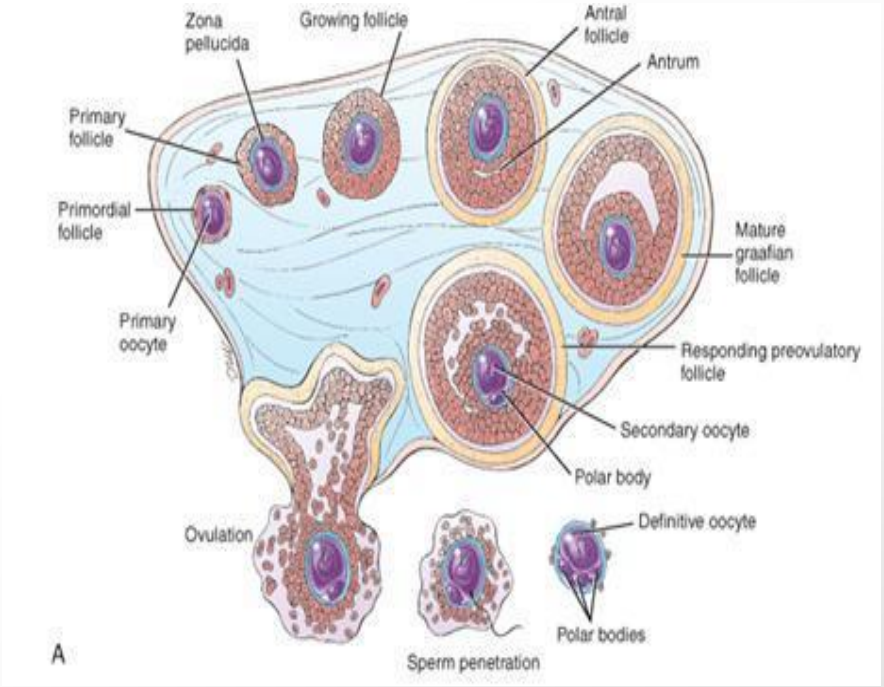
ORIGINAL ARTICLE *Infertility*

Urinary phthalate metabolites and ovarian reserve among women seeking infertility care

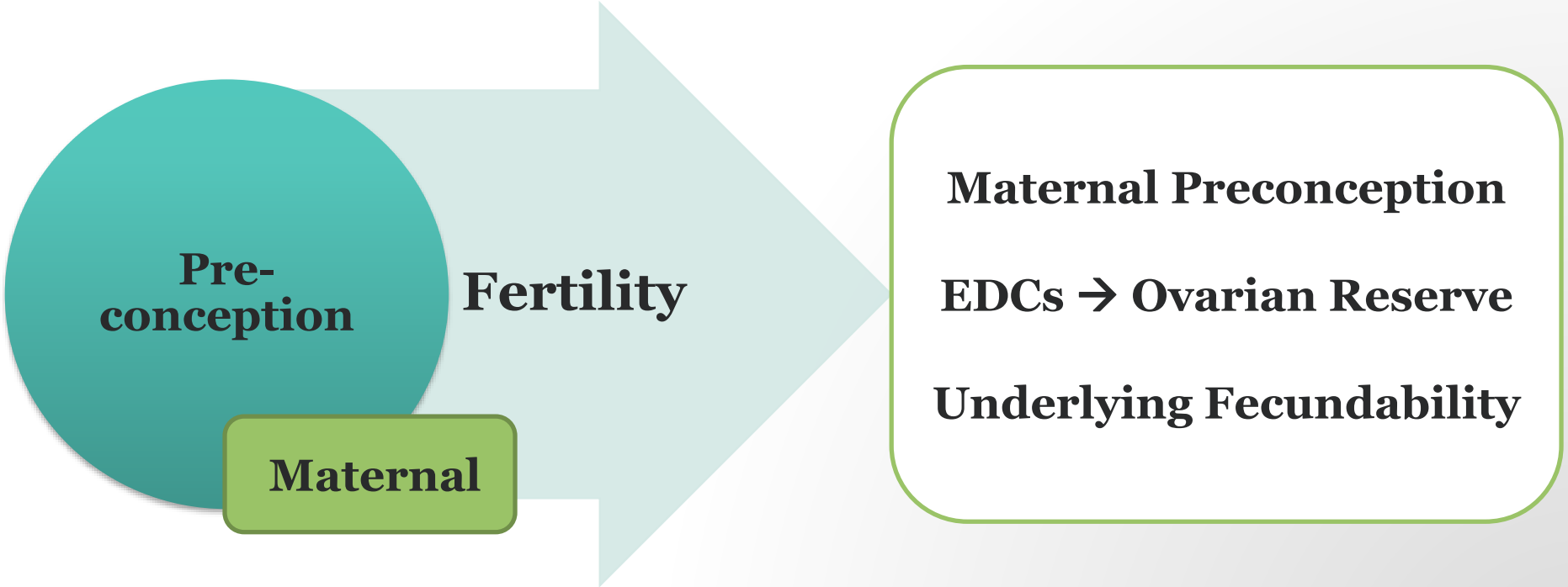
Carmen Messerlian[1,†*], Irene Souter[2,†], Audrey J. Gaskins[3], Paige L. Williams[4,5], Jennifer B. Ford[1], Yu-Han Chiu[3], Antonia M. Calafat[6], and Russ Hauser[1,2,5] for the Earth Study Team

Rationale: Phthalates and ovarian reserve

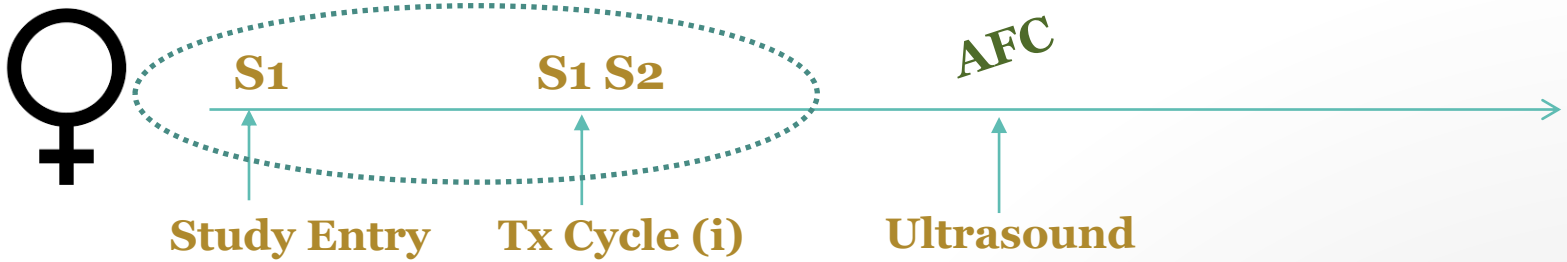
- Ovary: suspected target of DEHP
  - Inhibits antral follicle growth and interferes with estrogen synthesis, metabolism
- Size of the growing antral follicle pool:
  - Indicator of ovulatory potential in both assisted reproduction and natural fertility
- No study on phthalates and the growing antral follicle pool in humans



Objective: To determine whether urinary phthalate metabolite concentrations were associated with antral follicle growth among women seeking fertility care.



Maternal Preconception Window:
average of all urines prior to AFC Scan



11 Phthalate Metabolites and ΣDEHP

Outcome

- Antral Follicle Count (AFC): left + right follicles
- Ultrasound AFC scans on day 3 of unstimulated cycle

Analysis

- Poisson regression: to estimate mean AFC by phthalate quartiles
- Analyses were also stratified by age: <37 and ≥37 years
- Covariates : age, body mass index (BMI), and smoking status

Results

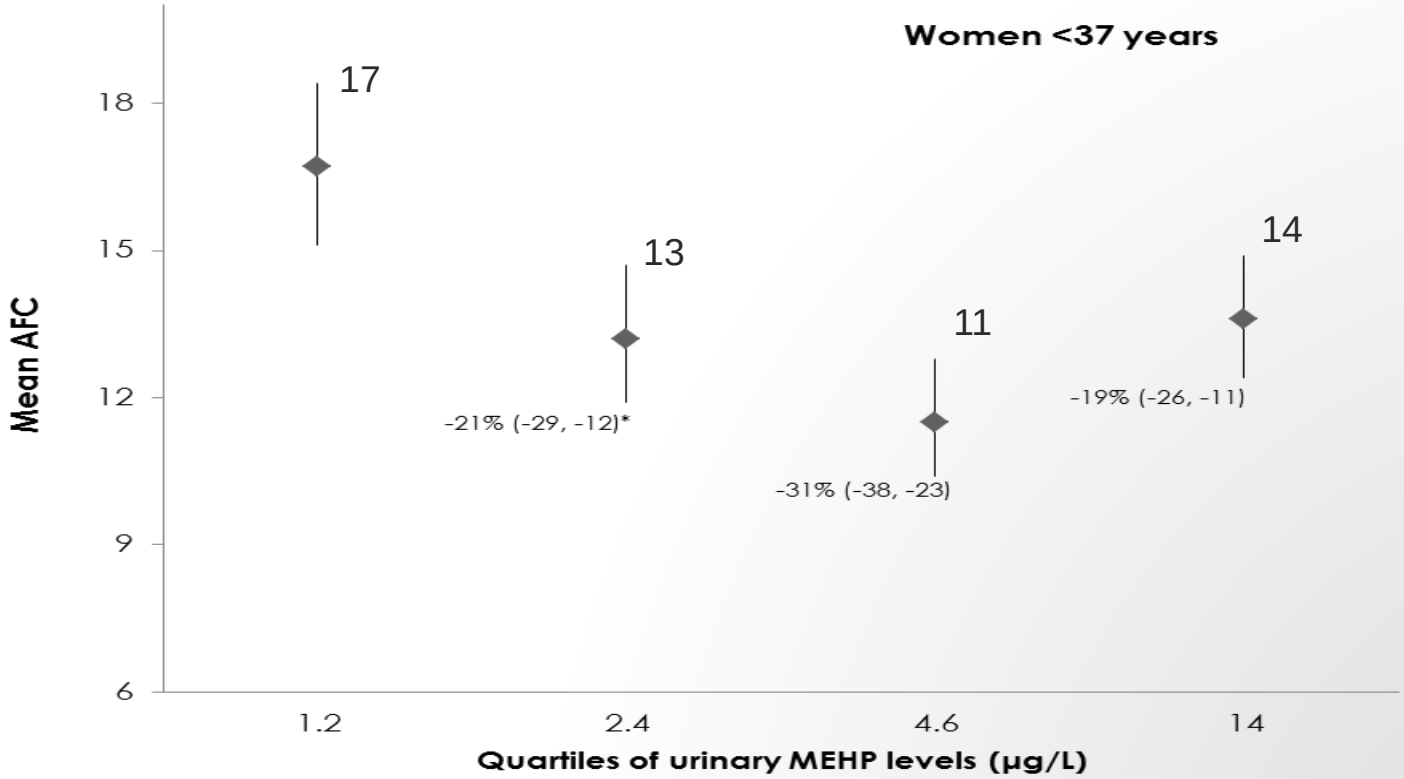
Study Sample

- 215 women
- Excluded
  - PCOS
  - Oophorectomy
  - Difficult to visualize scans

Characteristics

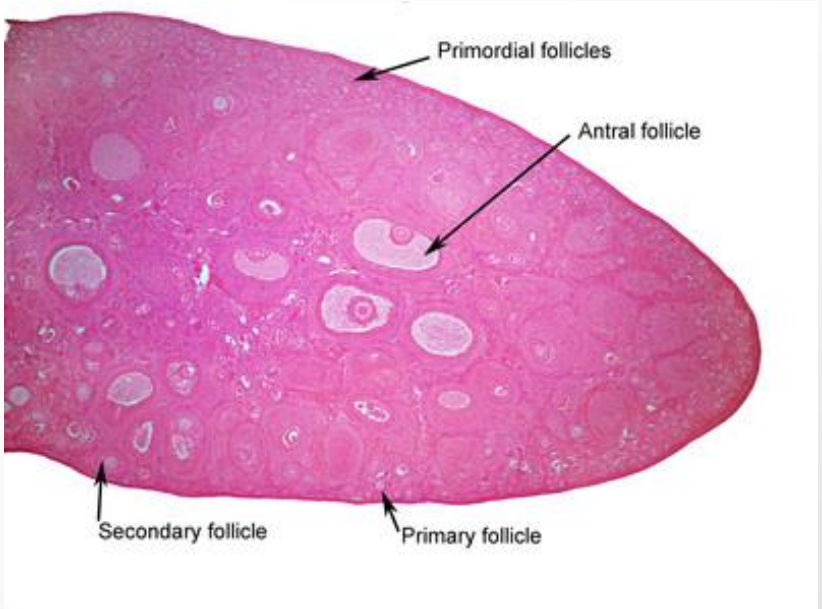
- Average age: 36 years
- Average BMI: 25kg/m^2
- Mostly white, educated, non-smokers
- Causes of Infertility:
  - 42% had a female factor
  - 23% had a male factor
  - 35% had unexplained infertility

CHANGE IN AFC BY QUARTILE OF MEHP



Conclusions

- DEHP metabolites: impact the growing antral follicle pool among women in this cohort
- Strongest findings among women <37 years
- First human study to show reduced ovulatory potential associated with urinary DEHP metabolites
- More studies needed to determine if DEHP diminishes the primordial follicle population or influences follicle recruitment



EPIDEMIOLOGY

Urinary Concentrations of Phthalate Metabolites and Pregnancy Loss Among Women Conceiving with Medically Assisted Reproduction

Messerlian, Carmen; Wylie, Blair J.; Mínguez-Alarcón, Lidia; Williams, Paige L.; Ford, Jennifer B.; Souter, Irene C.; Calafat, Antonia M.; Hauser, Russfor the Earth Study Team

Epidemiology: November 2016 - Volume 27 - Issue 6 - p 879–888
doi: 10.1097/EDE.0000000000000525
Perinatal Epidemiology

Rationale: Phthalates and pregnancy loss

Experimental studies on DEHP

- Embryofetotoxic/teratogenic
- Early and late fetal death
- Fewer litters and decrease in number of pups born alive

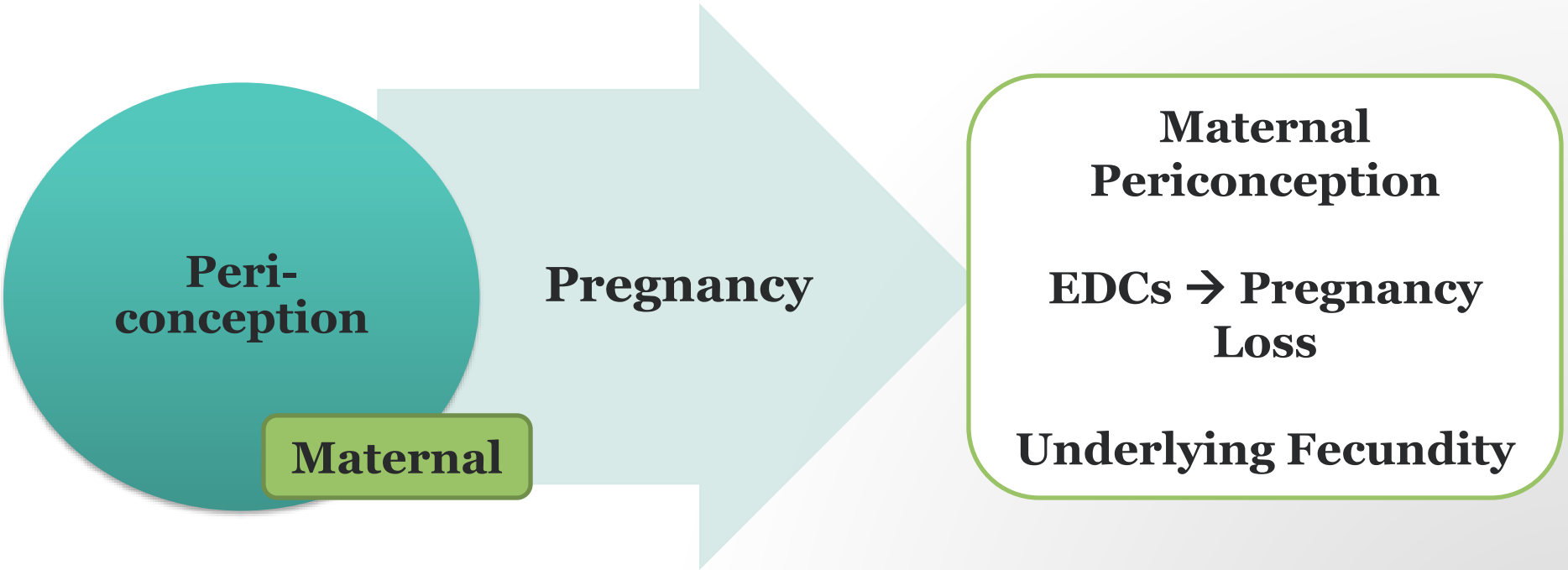
Pregnancy loss: most frequent unintended outcome

- Affects ~31% of all conceptions

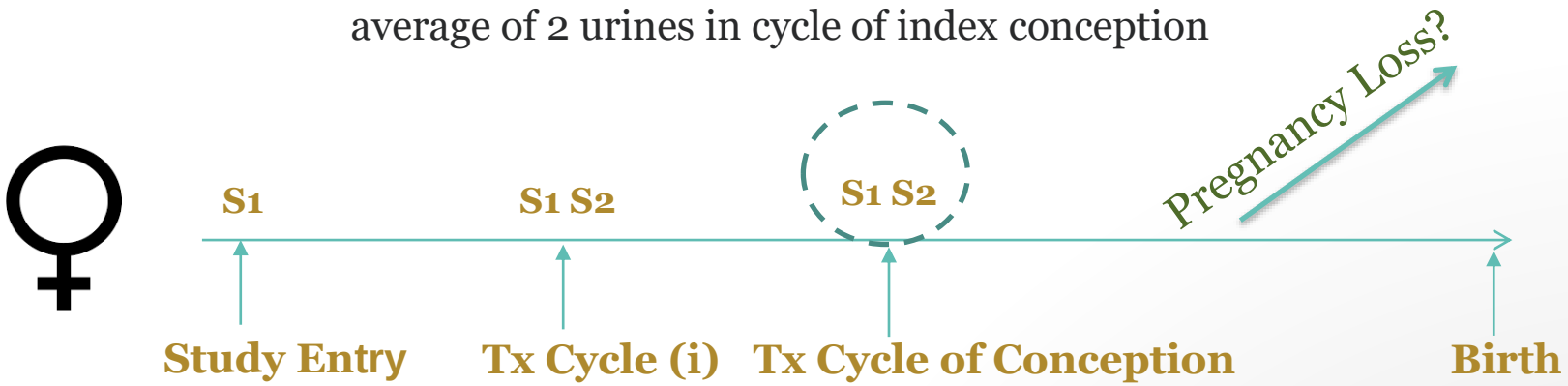
Predictors not well established

- Environmental causes may play a role

Objective: To examine the prospective association of urinary phthalate metabolite concentrations with pregnancy loss among women conceiving with medically assisted reproduction.



Maternal Periconception Window:
average of 2 urines in cycle of index conception



CDC: 11 Phthalate Metabolites and ΣDEHP

Outcomes

- **Biochemical Loss**: demise of a pregnancy confirmed by β-hCG, but not visualized
- **Total Pregnancy Loss**: all loss of <20 weeks gestation

Analysis

- Estimated Risk Ratios (RR) by phthalate quartiles
- Covariates: age, BMI, smoking, infertility diagnosis
- Test for trend: assess dose-response across quartiles

Results

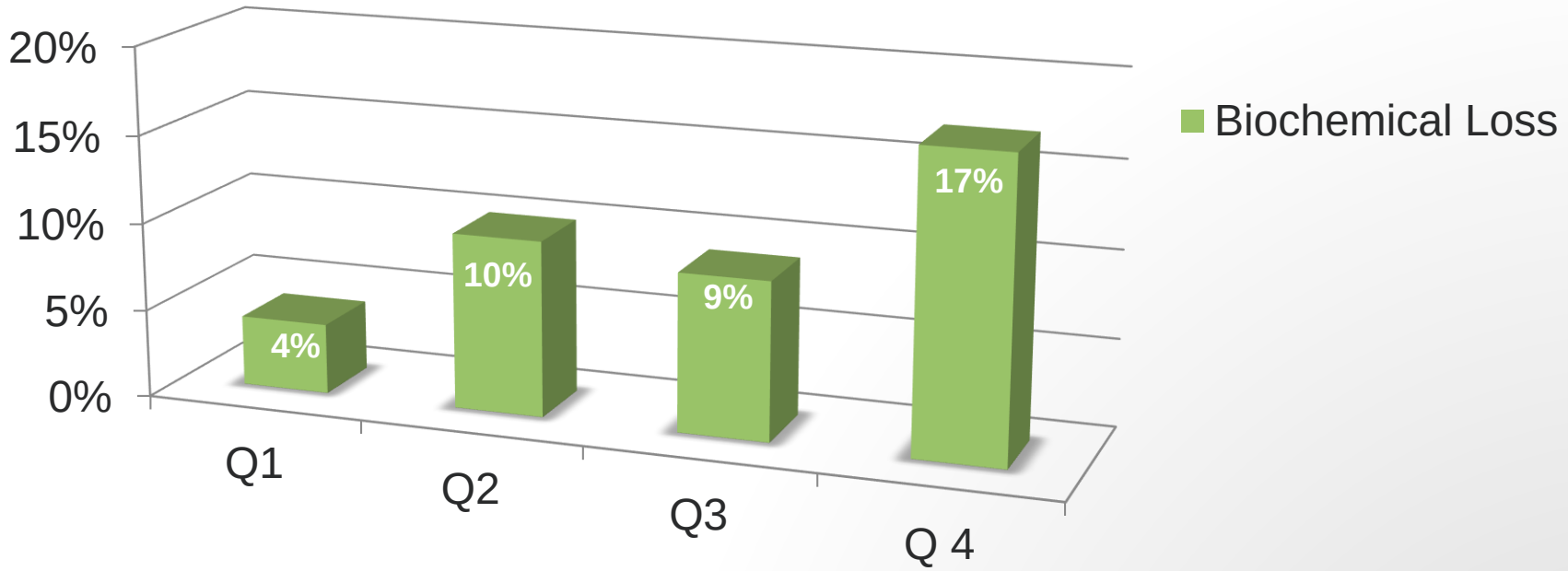
Study Sample

- 256 women
- 303 pregnancies
- 556 urine samples
  - measured during conception cycle of index pregnancy

Characteristics

- Mean age: 34.9 years
- Caucasian: 86%
- College/graduate : 92%
- Nulliparous: 86%
- Female Factor: 34%
- IVF (73%); IUI (27%)
- Biochemical loss: 31/303 (10%)
- All losses: 82/303 (27%)

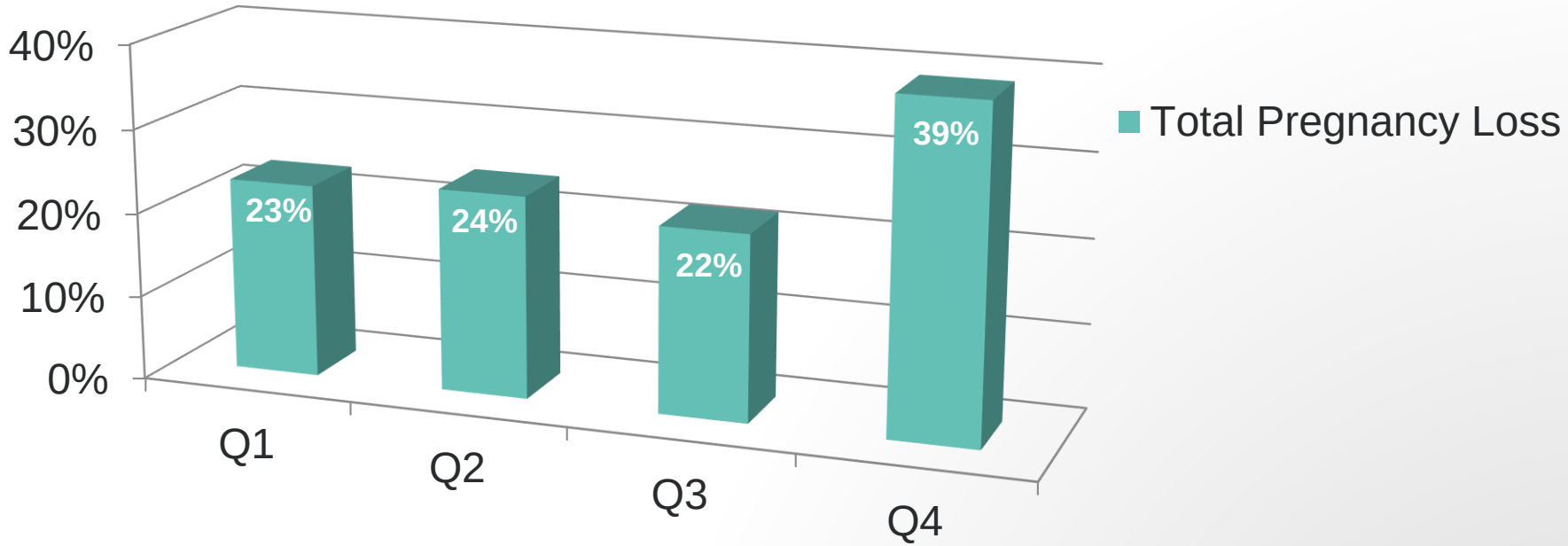
Biochemical Pregnancy Loss by Quartiles of ΣDEHP



RR (95%CI): 2.3 (0.6 - 8.5) | 2.0 (0.6 - 7.2) | 3.4 (1.0 - 11.7) p-trend=0.04

Q2 **Q3** **Q4**

Total Pregnancy Loss (<20 weeks) by Quartiles of ΣDEHP



RR (95%CI): 1.1 (0.6 - 2.0) | 1.0 (0.6 - 1.8) | 1.6 (1.0 - 2.7) p-trend: 0.06

Q2 **Q3** **Q4**

Conclusions

Periconception DEHP exposure

- **Biochemical Loss:** 2-3 fold higher risk
- **Total Pregnancy Loss:** 60% higher risk

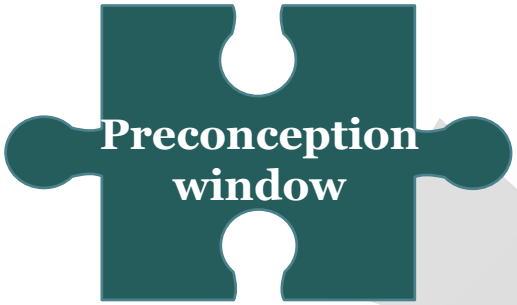
Other non-DEHP phthalates

- Not associated with either outcome

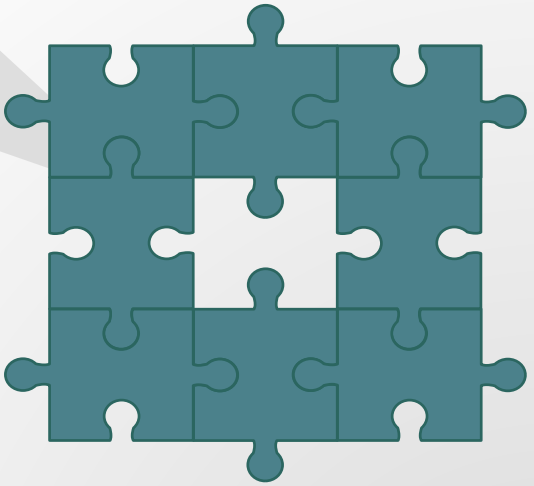
Preliminary evidence

- DEHP may adversely impact early pregnancy outcomes

What about preconception exposure?



Fathers' exposure?



An important and unexplored window of vulnerability

Rationale: Preconception window

Prenatal

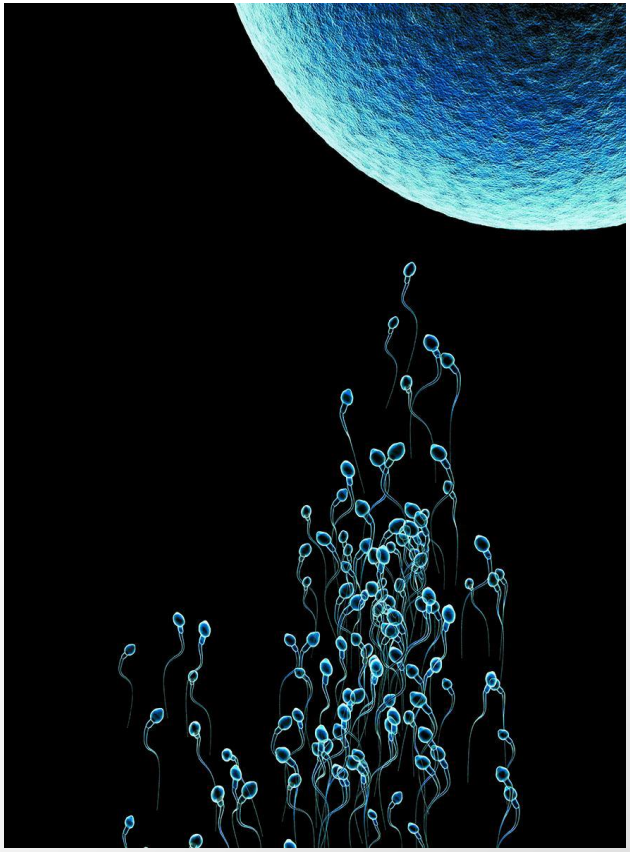
- Most epidemiologic studies on EDCs focus on *in utero* exposure
  - highly relevant critical window of vulnerability
  - large and growing body of evidence

Preconception

- Paternal and maternal exposures prior to pregnancy may impact pregnancy, perinatal, and child health outcomes
- Few studies able to examine the critical preconception window of vulnerability
- Isolating the periconception period may also be important to adverse outcomes

Rationale: Paternal exposure

- Male-mediated developmental toxicity (Olshan and Faustman, 1993)
- Fathers' exposure before conception may impact offspring health via epigenetic alterations transmitted through sperm
  - Sperm carry more than the 23 chromosomes
  - Epigenetic cargo: methylated DNA, non-coding RNAs, protamines, histones critical to fertilization and early embryo programming



Braun, Messerlian, Hauser, *Current Epi Reports* (2017)

Paternal epigenetics and off-spring phenotypes

nature REVIEWS GENETICS

nature.com ▸ journal home ▸ advance online publication ▸ review ▸ full text

NATURE REVIEWS GENETICS | REVIEW

Epigenetic inheritance of acquired traits through sperm RNAs and sperm RNA modifications

Qi Chen, Wei Yan & Enkui Duan

Affiliations | Corresponding authors

Nature Reviews Genetics (2016) | doi:10.1038/nrg.2016.106

Published online 03 October 2016

Cell

Leading Edge

Essay

Daddy Issues: Paternal Effects on Phenotype

Oliver J. Rando[1,*]

[1]Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School, Worcester, MA 01605, USA

*Correspondence: oliver.rando@umassmed.edu

http://dx.doi.org/10.1016/j.cell.2012.10.020

The once popular and then heretical idea that ancestral environment can affect the phenotype of future generations is coming back into vogue due to advances in the field of epigenetic inheritance. How paternal environmental conditions influence the phenotype of progeny is now a tractable question, and researchers are exploring potential mechanisms underlying such effects.

Progress in Biophysics and Molecular Biology 118 (2015) 79–85

Contents lists available at ScienceDirect

Progress in Biophysics and Molecular Biology

journal homepage: www.elsevier.com/locate/pbiomolbio

Review

Epigenetic inheritance and evolution: A paternal perspective on dietary influences

Adelheid Soubry

Epidemiology Research Group, Department of Public Health and Primary Care, Faculty of Medicine, KU Leuven, Kapucijnenvoer 35, Blok D, Box 7001, 3000 Leuven, Belgium

ARTICLE INFO

Article history:
Available online 10 March 2015

ABSTRACT

The earliest indications for paternally induced transgenerational effects from the environment to future generations were based on a small number of long-term epidemiological studies and some empirical observations. Only recently have experimental animal models and a few analyses on human data

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Paternal and maternal urinary phthalate metabolite concentrations and birth weight of singletons conceived by subfertile couples

Carmen Messerlian[a,*], Joseph M. Braun[b], Lidia Mínguez-Alarcón[a], Paige L. Williams[c,d], Jennifer B. Ford[a], Vicente Mustieles[e], Antonia M. Calafat[f], Irene Souter[g], Thomas Toth[g], Russ Hauser[a,d,h], for the Environment and Reproductive Health (EARTH) Study Team

Rationale: EDCs and birth weight

Birth weight

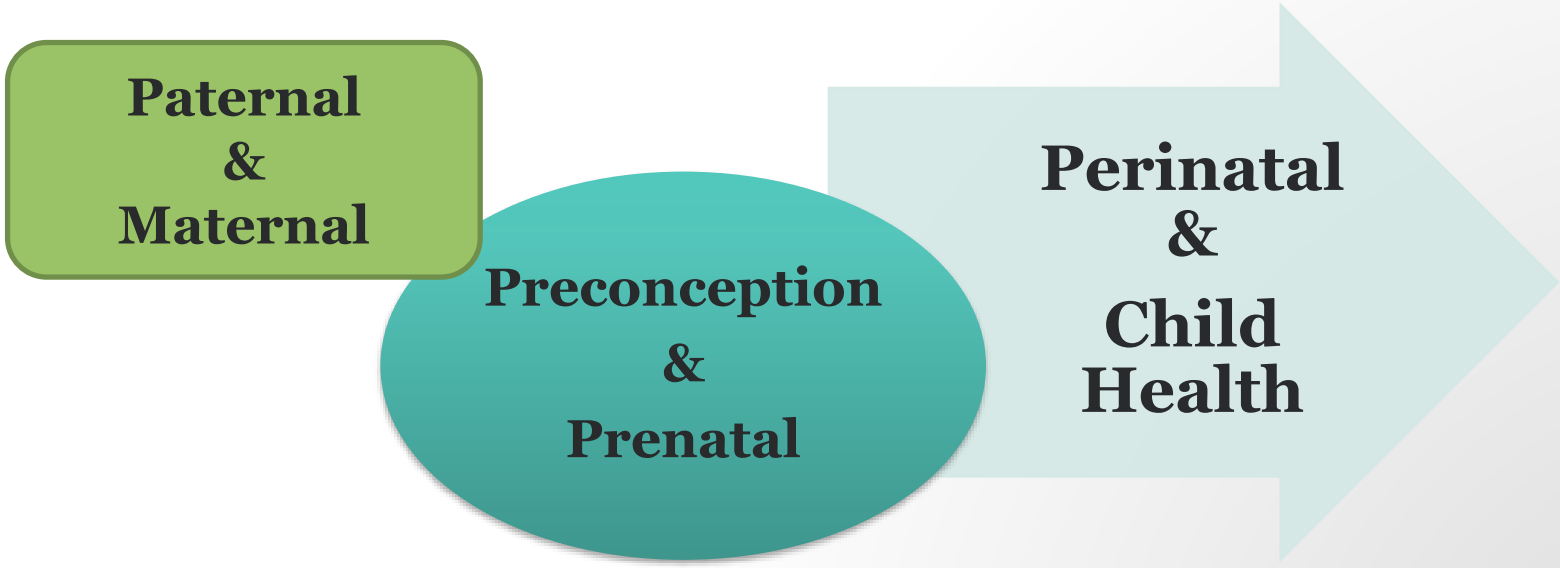
- Predictor of neonatal morbidity and mortality
- ~ 8% of babies are born low birth weight (<2500 g)
- Determinants:
  - gestational age, maternal/paternal anthropometry, maternal nutrition/weight status, and environmental exposures (e.g. tobacco, DES)

Accumulating evidence

- non-persistent chemicals →reduced fetal and infant birth weight

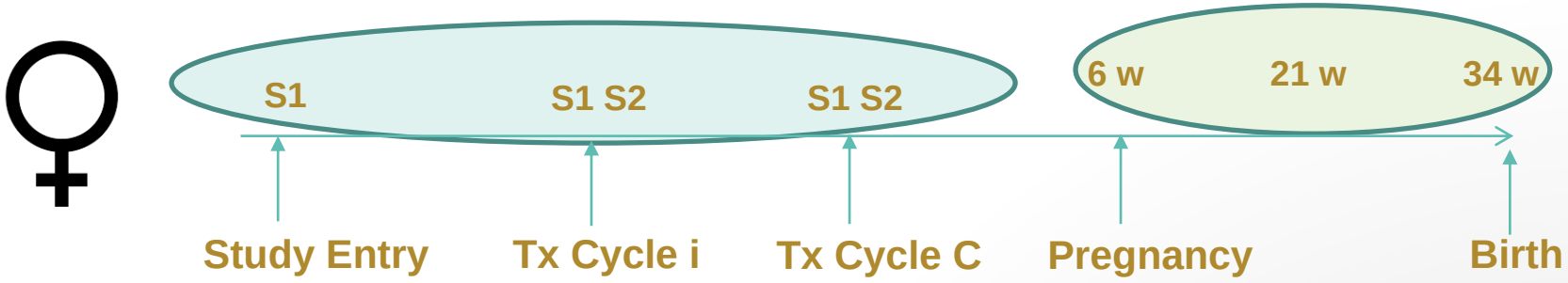
Messerlian et al. 2018

Objective: To examine the association of paternal and maternal preconception and prenatal urinary phthalate metabolite and phenol concentrations with birth weight among singletons conceived by subfertile couples.



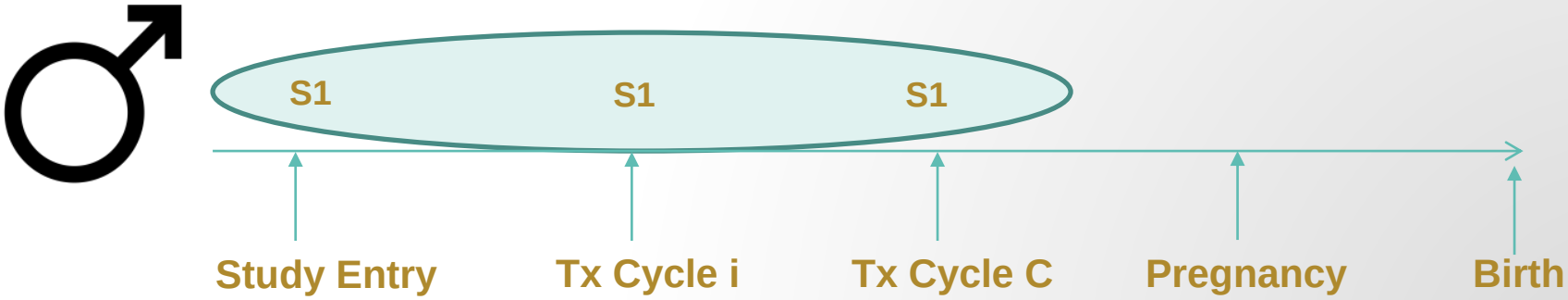
Maternal Preconception Window:
average of all urines before index conception

Maternal Prenatal Window:
average of all pregnancy urines



11 Phthalate Metabolites, ΣDEHP, Σanti-androgenic, phenols

Paternal Preconception Window:
average of all urines before index conception



Methods

Exposures Assessment

- Urinary quantification by the Centers for Disease Control
  - Phthalates:
    - 11 individual metabolites and the sum of DEHP (ΣDEHP)
    - The sum of anti-androgenic phthalates
  - Phenols:
    - Triclosan, Parabens, Benzophenone-3
    - BPA/BPS (under review)

Outcome Assessment

- Birth weight (grams) and head circumference (cm) abstracted from delivery records by study nurses

Methods

Analysis

- Multivariable Linear Regression
  - Estimated difference in birth weight for every log-unit increase in phthalate or phenol concentration
- A priori covariates
  - Maternal and paternal age, BMI and smoking status, maternal education, infertility diagnosis
- Additional adjustment for partner's or prenatal exposure
- Stratified by mode of conception (IVF vs. Non IVF) in phthalate analysis

Results: Parents

Parent Characteristics	Mothers N=364	Fathers N=195
Age at study entry (years)		
Mean ± SD	35.2 ± 3.9	36.0 ± 4.6
Range	27 – 44	26 – 48
BMI (kg/m^2)		
Mean ± SD	23.8 ± 3.8	26.9 ± 3.8
Range	16 – 39	20 – 39
Education (graduate degree), n (%)	197 (58%)	77 (49%)
Never Smoked, n (%)	268 (74%)	137 (70%)
Infertility Diagnosis, n (%)		
Female factor	118 (32%)	42 (40%)
Male factor	91 (25%)	28 (27%)
Unexplained	155 (43%)	36 (33%)

Results: Singleton infants

Infant Characteristics	All Infants N=364	Boys n=192	Girls n=172
Birth Weight			
Mean grams (min-max)	3406 (1310-4790)	3432 (1310-4790)	3376 (2185-4451)
Low Birth Weight			
<2500 g, n (%)	14 (4%)	6 (3%)	8 (5%)
Gestational age at birth			
Mean weeks (min-max)	39.3 (29-42)	39.4 (32-42)	39.3 (29-42)
Preterm birth			
<37 weeks, n (%)	28 (8%)	14 (7%)	14 (8%)

Paternal Preconception Window

Difference in birth weight (g) for every log-unit increase in EDC		
MODELS	**β (95% CI)**	**P-Value**
ΣDEHP		
Covariates + Gestational Age	-90 (-165, -15)	0.02
Benzophenone-3		
Covariates	137 (60, 214)	0.0005

- Paternal ΣDEHP: associated with decreased birth weight in IVF singletons (no sex-specific differences: boys ~ girls)
- Paternal Benzophenone-3: associated with increased birth weight in all infants (boys>girls); however, more apparent among men with high vs normal BMI

Messerlian et al. 2017; Messerlian et al. 2018

Maternal Preconception Window

Difference in birth weight (g) for every log-unit increase in EDC		
MODELS	**β (95% CI)**	**P-Value**
ΣDEHP		
Covariates	-22 (-102, 58)	0.59
BPA		
Covariates	-119 (-212, -27)	0.01
Covariates + Gestational Age	-79 (-153, -5)	0.04
Covariates + Prenatal BPA	-89 (-186, 8)	0.07

- Maternal Preconception ΣDEHP: not associated with birth weight
- **No** association with the 11 individual phthalate metabolites, benzophenone-3, parabens, or triclosan
- BPA associated with an 80 g decrease in birth weight: boys~girls

Messerlian et al. 2017; Mustieles et al., under review

Maternal Prenatal Window

Difference in birth weight (g) for every log-unit increase in EDC		
MODELS	**β (95% CI)**	**P-Value**
ΣDEHP		
Covariates	-122 (-199, -45)	0.002
Covariates + Paternal DEHP	-18 (-137, 100)	0.76
Triclosan		
Covariates	-38 (-76, 0)	0.05
Propylparaben		
Covariates, boys	-67 (-133, -2)	0.05

- Maternal DEHP association no longer present after adjusting for paternal DEHP
- Triclosan associated with decreased birth weight: boys~girls
- Propylparaben associated with decreased birth weight in boys; not in girls

Messerlian et al. 2017; Messerlian et al. 2018

Conclusions

Paternal Preconception

ΣDEHP: decreased birth weight in IVF conceived singletons

Benzophenone-3: increased birth weight – probably BMI related

Paternal exposures may impact offspring health

Maternal Preconception

No notable associations with most EDCs examined

BPA decreased birth weight even after adjusting for GA

Maternal Prenatal

ΣDEHP: not associated w/ adjustment for paternal ΣDEHP

Triclosan and propylparaben: decreased birth weight

Propylparaben: possibly sexually dimorphic

Part IV

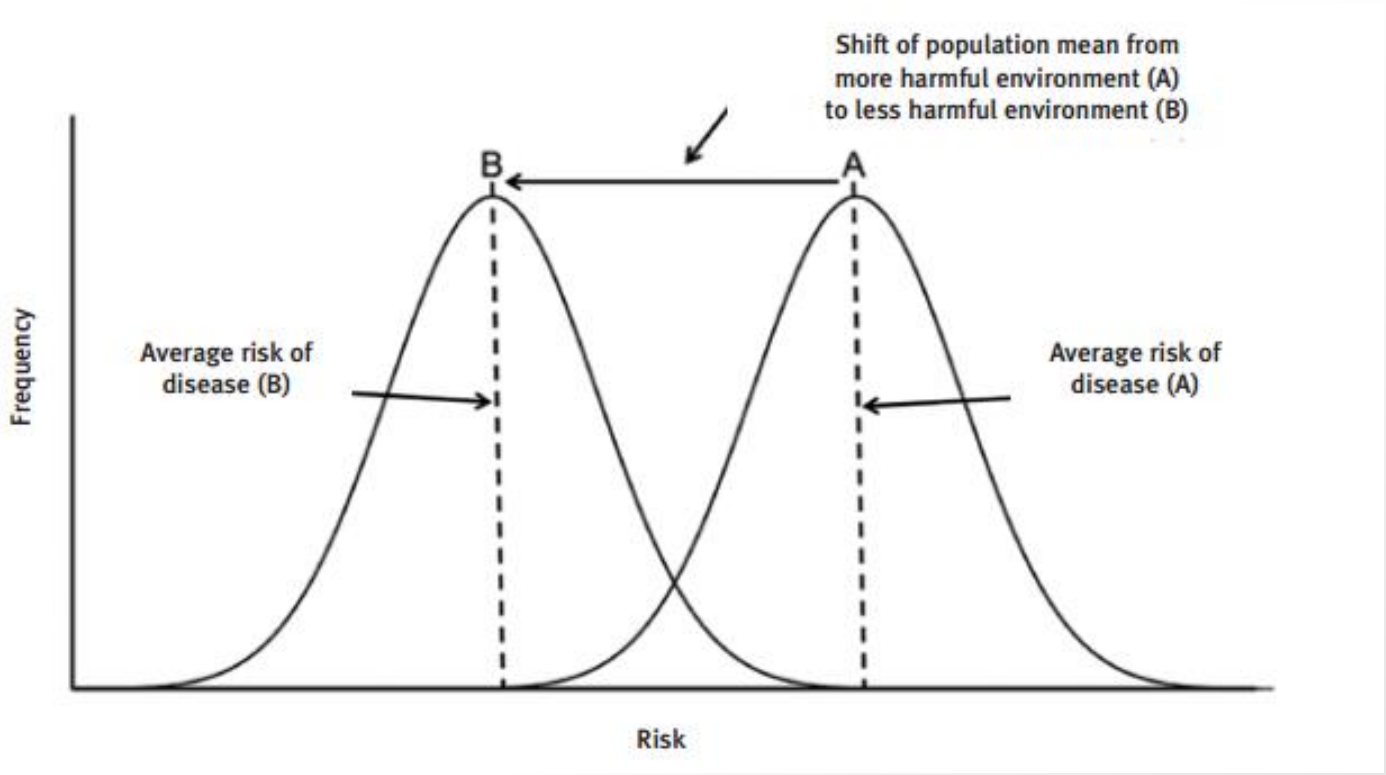
Primary Prevention of EDCs in Reproductive and Pediatric Health

Why does EDC exposure matter?

- Population level exposure → Risk → Population Burden

- Risk may be small, but population level exposure may lead to large burden of disease

Population exposure burden



See: Geoffrey Rose, The Strategy of Preventive Medicine, 1992

Primary prevention strategies

- Reduce exposure across the continuum of exposure- regardless of risk
- All couples and children present should be encouraged to decrease exposure
- We don't know which couple, pregnancy or child will be at risk of adverse outcomes so shifting the distribution of exposure down will benefit those at higher risk as well as those in the middle.

Reducing exposure in areas of choice

Products

- Use non-toxic personal care products
- Use less plastic
- Avoid pesticides and herbicides (e.g., Raid)
- Select flame retardant-free foam products
- Don’t dry clean clothing

Food and Diet

- Avoid canned foods/beverages
- Avoid toxics in your food and water
- Keep mercury out of your diet
- Limit foods high in animal fat
- Avoid storing food/beverages in plastics

Source: https://prhe.ucsf.edu/

Things you can do differently at home

- Clean with non-toxic household cleaners
- Dust and mop often
- Avoid scented products
- Remove your shoes
- Choose safer home improvement products

- Contain harmful chemicals
- Lead, pesticides, flame retardants in dust
- Source of phthalates
- Outdoors can bring in toxic substances into home
- Paints, glues, flooring – VOC

Source: https://prhe.ucsf.edu/

How can we decrease exposure to phthalates?

Food & Beverage

- Common source of exposure to phthalates from processing and packaging materials.
- We can make food and drink choices to reduce exposure.
  - Reduce use of plastic food wrap/bags
  - Replace plastic bottles and food containers with glass or stainless steel
  - Avoid reheating food in plastic containers

Perfumes & Personal Care Products

- Phthalates can be found in some lotions, soaps, make-up, nail-polish.
- Products with "fragrance" listed can contain phthalates.
  - Use "phthalate-free" lotions and soaps
  - Reduce use of products with "fragrance" opting for "fragrance-free" choices
  - Use nail-polish brands that advertise "No Di-Butyl Phthalate" or "No DBP"

Household Goods

- Flooring, blinds, shower curtains, electronics, and other PVC products can be a source of DEHP.
- Scented cleaning products, laundry detergent, synthetic air fresheners can contain phthalates.
  - Use PVC-free products: replace with cotton, bamboo or polyethylene vinyl acetate (PEVA)
  - Use "fragrance-free" cleaning and laundry products

Resources

Casarett & Doull's Essentials of Toxicology, 3rd edition, McGraw-Hill Education, 2015.

Hannon, P. R., et al. (2014). "Daily exposure to Di(2-ethylhexyl) phthalate alters estrous cyclicity and accelerates primordial follicle recruitment potentially via dysregulation of the phosphatidylinositol 3-kinase signaling pathway in adult mice." Biol Reprod **90**(6): 136.

Gray, L. E., Jr., et al. (2006). "Adverse effects of environmental antiandrogens and androgens on reproductive development in mammals." Int J Androl **29**(1): 96-104; discussion 105-108.

Gray LE, Jr, Foster PMD. Significance of experimental studies for assessing adverse effects of endocrine-disrupting chemicals. Pure Appl Chem. 2003;75:2125–2141.

Swan, S. H. (2008). "Environmental phthalate exposure in relation to reproductive outcomes and other health endpoints in humans." Environ Res **108**(2): 177-184.

Lovekamp-Swan, T. and B. J. Davis (2003). "Mechanisms of phthalate ester toxicity in the female reproductive system." Environ Health Perspect **111**(2): 139-145.

Braun, J. M., et al. (2017). "Fathers Matter: Why It's Time to Consider the Impact of Paternal Environmental Exposures on Children's Health." Curr Epidemiol Rep **4**(1): 46-55.

Messerlian, C., Williams, PL., Ford, JB., Chavarro, J., Mínguez-Alarcón, L., Dadd, R., Braun, JM., Gaskins, AJ., Meeker, JD., James-Todd, T., Chiu, Y-H., Nassan, FL., Souter, I., Petrozza, J., Keller, M., Toth, T., Calafat, AM., Hauser, R. (in press). "The Environment and Reproductive Health (EARTH) Study: A Prospective Preconception Cohort." Human Reproduction Open.

Messerlian, C., et al. (2017). "Paternal and maternal preconception urinary phthalate metabolite concentrations and child behavior." Environ Res **158**: 720-728.

Messerlian, C., et al. (2016). "Urinary phthalate metabolites and ovarian reserve among women seeking infertility care." Hum Reprod **31**(1): 75-83.

Messerlian, C., et al. (2016). "Urinary Concentrations of Phthalate Metabolites and Pregnancy Loss Among Women Conceiving with Medically Assisted Reproduction." Epidemiology **27**(6): 879-888.

Ferguson, K. K., et al. (2014). "Environmental phthalate exposure and preterm birth." JAMA Pediatr **168**(1): 61-67.

Rando, O. J. (2012). "Daddy issues: paternal effects on phenotype." Cell **151**(4): 702-708.

Chen, Q., et al. (2016). "Epigenetic inheritance of acquired traits through sperm RNAs and sperm RNA modifications." Nat Rev Genet **17**(12): 733-743.
Soubry, A. (2015). "Epigenetic inheritance and evolution: A paternal perspective on dietary influences." Prog Biophys Mol Biol **118**(1-2): 79-85.

Visuals Acknowledgements and Sources

Slide #7, #43 Img. Source: Free Googe Photos: Img. Source: Free Google Images: https://www.google.com/search?q=microscopic+sperm+and+egg&hl=en&tbm=isch&tbs=rimg:CcVsJP0euOGbIjgVgfIv8zp787Zv1nkKzBzE4dcgeRHF6pyN8RdfrSyoN2qTygsn95iporrxhtUzXoFF5RYZQ94wIioSCRWB8i_1zOnvzETQ6DlyoM4lZKhIJtm_1WeQrMHMQR2oszgwO7cSsqEgnh1yB5EcXqnBHBTV5fDP38DCoSCY3xF1-tLKg3EQkNAgNL-xr6KhIJapPKCyf3mKkRUb4-gw_17Kv0qEgmiuvGG1TNegRExfcZ_1GSxa6yoSCUXlFhlD3jAiEevjwVXz2438&tbo=u&sa=X&ved=0ahUKEwi-0ajZrOfZAhWSxVkKHZ9BCJkQ9C8IGQ&biw=1280&bih=590&dpr=1.5#imgrc=OC2B_6Kjv-6lnM:&spf=1520877099844

Slide #19:

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- Img.2 Source: https://pixabay.com/en/yellow-toys-toddler-play-childhood-2139903/
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Slide #20: Img. Source: Wikimedia, https://commons.wikimedia.org/wiki/File:CBP_Seizes_Hazardous_Toy_Dolls_(10928573653).jpg

Slide #22, #36: Img. Source: https://pixabay.com/en/animal-mouse-experiment-laboratory-1554745/

Slide #36 Img.1 Source: https://pixabay.com/en/animal-mouse-experiment-laboratory-1554745/

Slide#21:

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- Img.2 Source: Free Google Photos: https://www.google.com/search?as_st=y&hl=en&tbs=sur%3Afm&tbm=isch&sa=1&ei=zBmwWvqUD4visAWU9ZWICA&q=plastic+food+packaging&oq=plastic+&gs_l=psy-ab.1.0.0i67k1l3j0j0i67k1l5j0.5867.10830.0.13062.22.19.1.2.2.0.107.1320.16j1.18.0....0...1c.1.64.psy-ab..1.20.1344.0..0i10k1.56.ROX8plS-wXw#imgrc=9UxuBm6W404WUM:
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Slide #2, #23, #36, #42, #44, #48, #59: Shutterstock

THANK YOU!

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