



Effects of Environmental Chemicals in Pregnancy on Cancer in Two Generations

Case Study: DDT and Breast Cancer

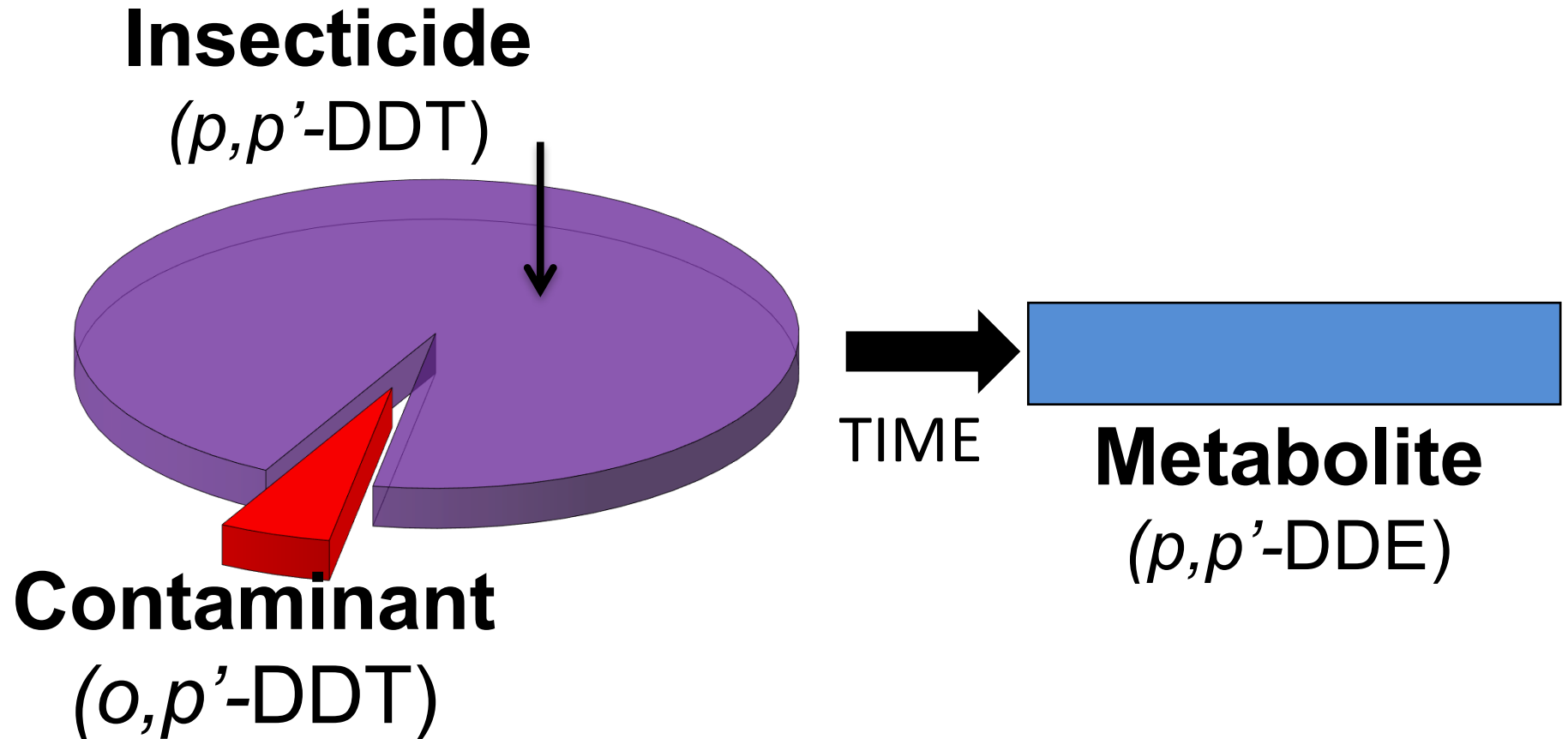
Barbara Cohn, PhD

Child Health and Development Studies
Public Health Institute

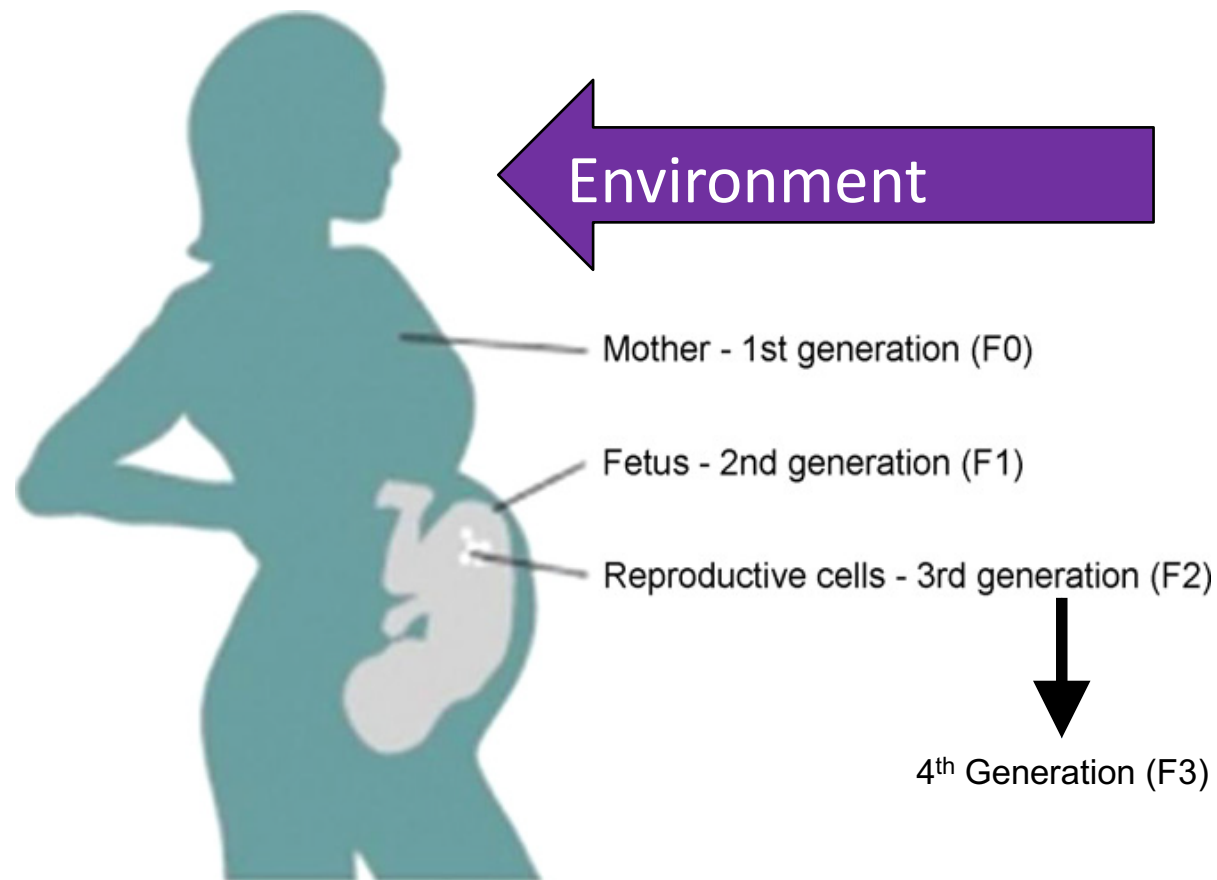
OUTLINE

- Why DDT case study
- Why multi-generational studies
- Child Health and Development Studies
- What we found for mothers and their daughters
- Examples and promise of big data
- Relation to disparities
- Next steps

Alive 1945-2020? You are Exposed to DDT



Exposures to pregnant women impact three generations simultaneously



Adapted from Perera F, Herbstman J, Reproductive Toxicology PMID: 21256208

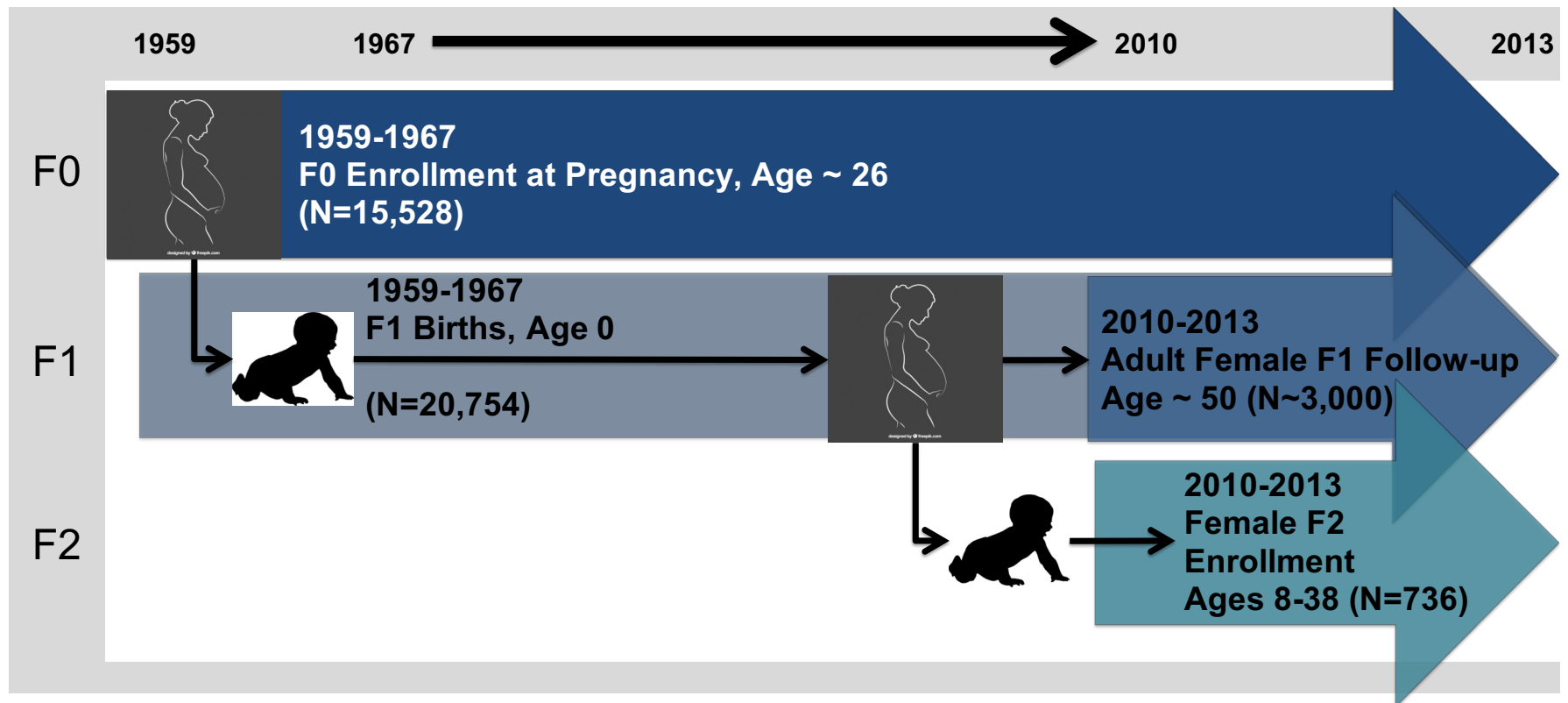
- Initiated in 1959
- Enrolled ~ 20,000 pregnancies by 1967
- Partnership with Kaiser Foundation Health Plan, Oakland, California



Recruitment success

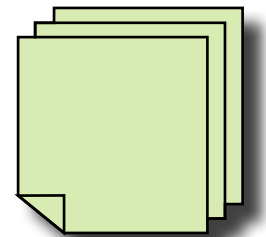
- >98% of eligible families participated in the CHDS between 1959 and 1967.
- CHDS collected information on over 20,000 pregnancies, from 15,000 women

Child Health and Development Studies (CHDS): population-based multi-generational cohort



Interviews provide prospective risk factors

- Socio-economic (F0, F1, F2)
- Demographics (F0, F1, F2)
- Behavior (F0, F1, F2)
- Pregnancy history (F0, F1, F2)
- Attitudes and stressors (F0, F1)



Medical records for accurate health data

- Medical conditions 6 months *before* and during pregnancy, and labor and delivery (F0)
- Prenatal weight and blood pressure, hemoglobin, albumin and urinary glucose (F0)
- Growth and development (F1)
- Cancer (F0, F1)



Blood samples enable assays for biomarkers and environmental exposures

- Over 65,000 serum samples (F0+F1+F2)
- Drawn at each trimester, post-partum (F0)



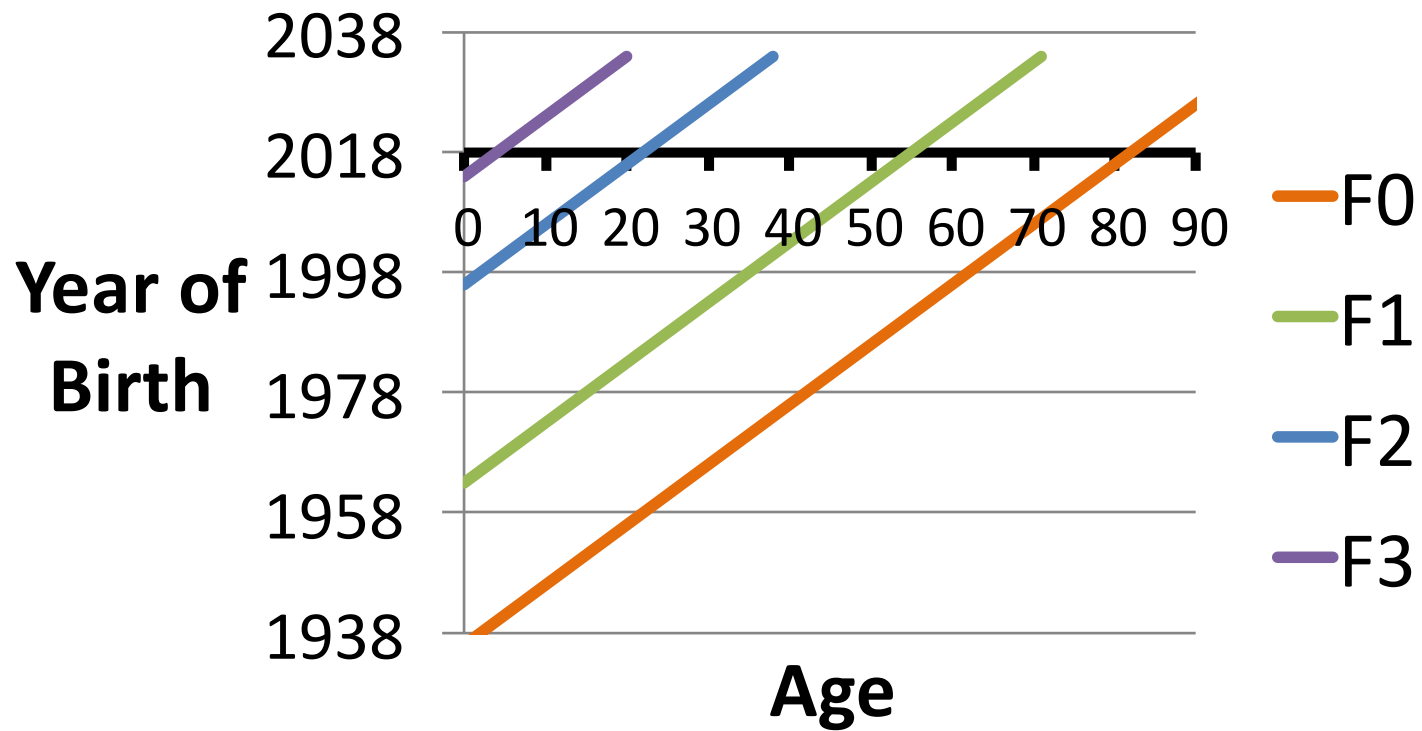
Examination studies provide further life-course perspective on F1 and F2

- Exams at ages 5, 9-11, 15-17, 30, 44, 50 (F1)
- Exam at age 20 (F2)
- Biospecimens at age 30, 50 (F1)
- Biospecimens at age 20 (F2)

Residence, Cancer and Deaths Tracked

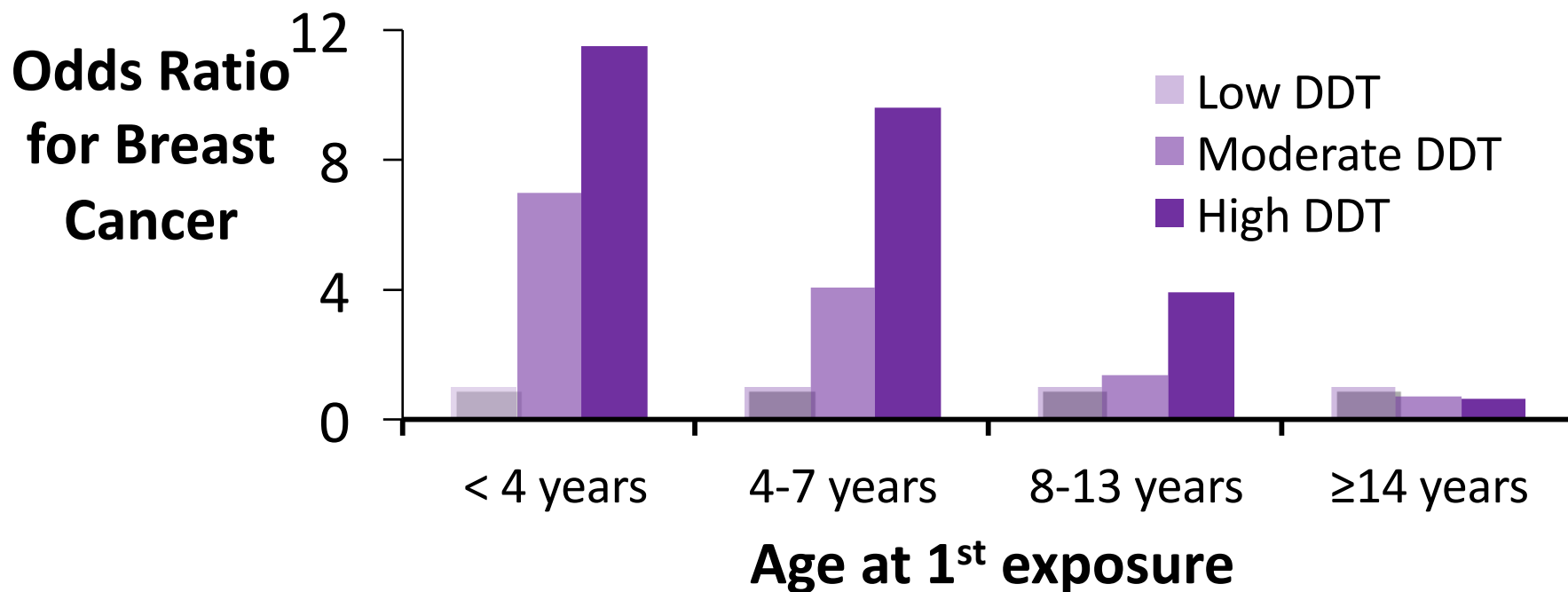
- Residence history
- Link to the California Cancer Registry
- Link to the California and National Death files

Birth Year and Ages of CHDS Generations

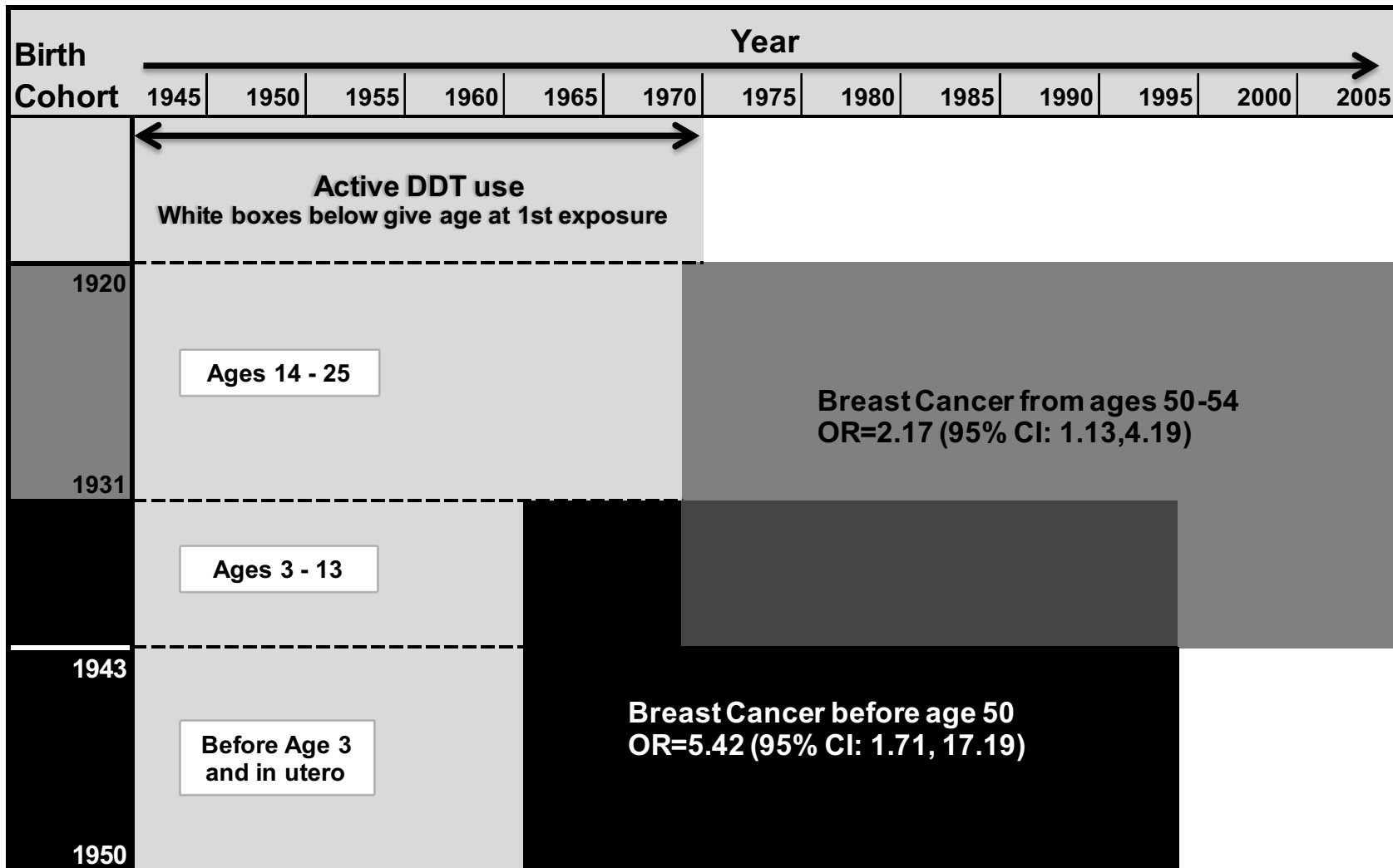


Exposure & Outcome Windows Count: DDT and Mother's (F0) Breast Cancer

MOTHERS (F0): pregnancy *p,p'*-DDT associated with breast cancer before age 50 for women exposed before puberty



Cohn, et. al., EHP, 2007 Oct;115(10):1406-14.



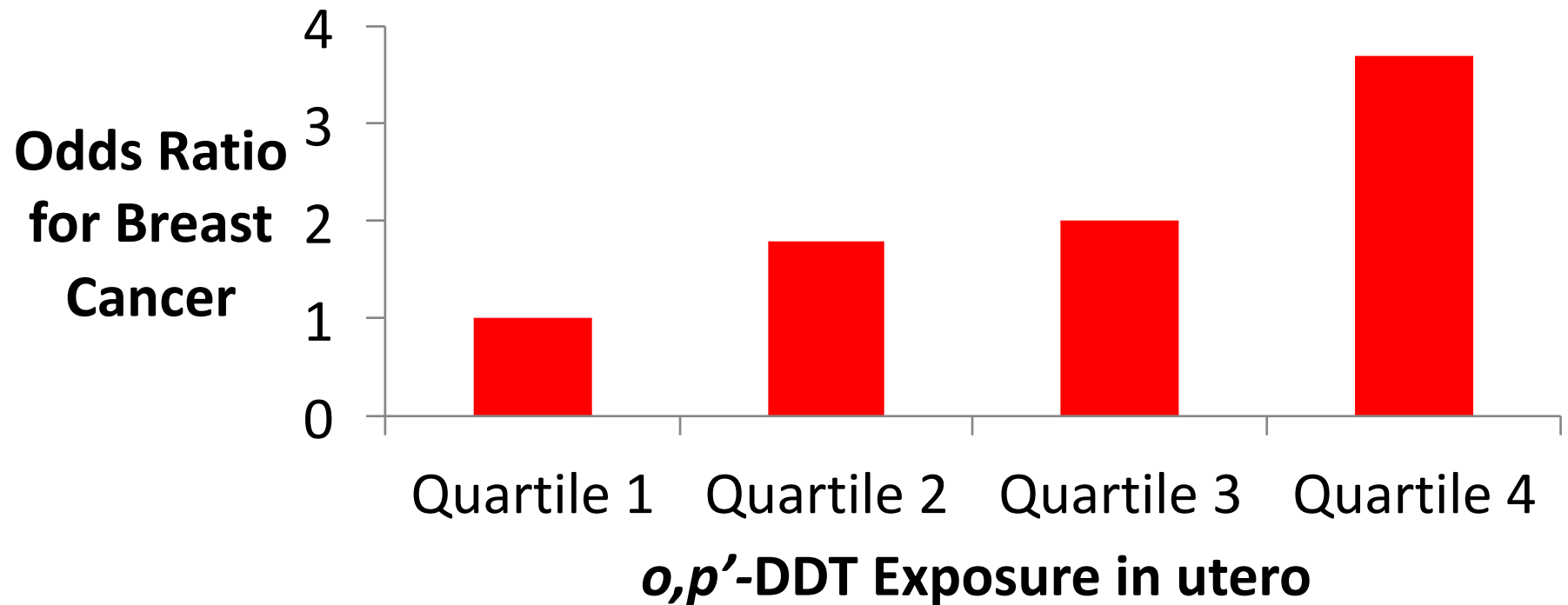
F0: Shifting Outcome Windows for Breast Cancer

Cohn, B.A., Cirillo, P.M. and Terry, M.B., 2019. DDT and Breast Cancer: Prospective Study of Induction Time and Susceptibility Windows. *JNCI: Journal of the National Cancer Institute*.

<https://doi.org/10.1093/jnci/djy198>

DDT and Daughter's (F1) Breast Cancer

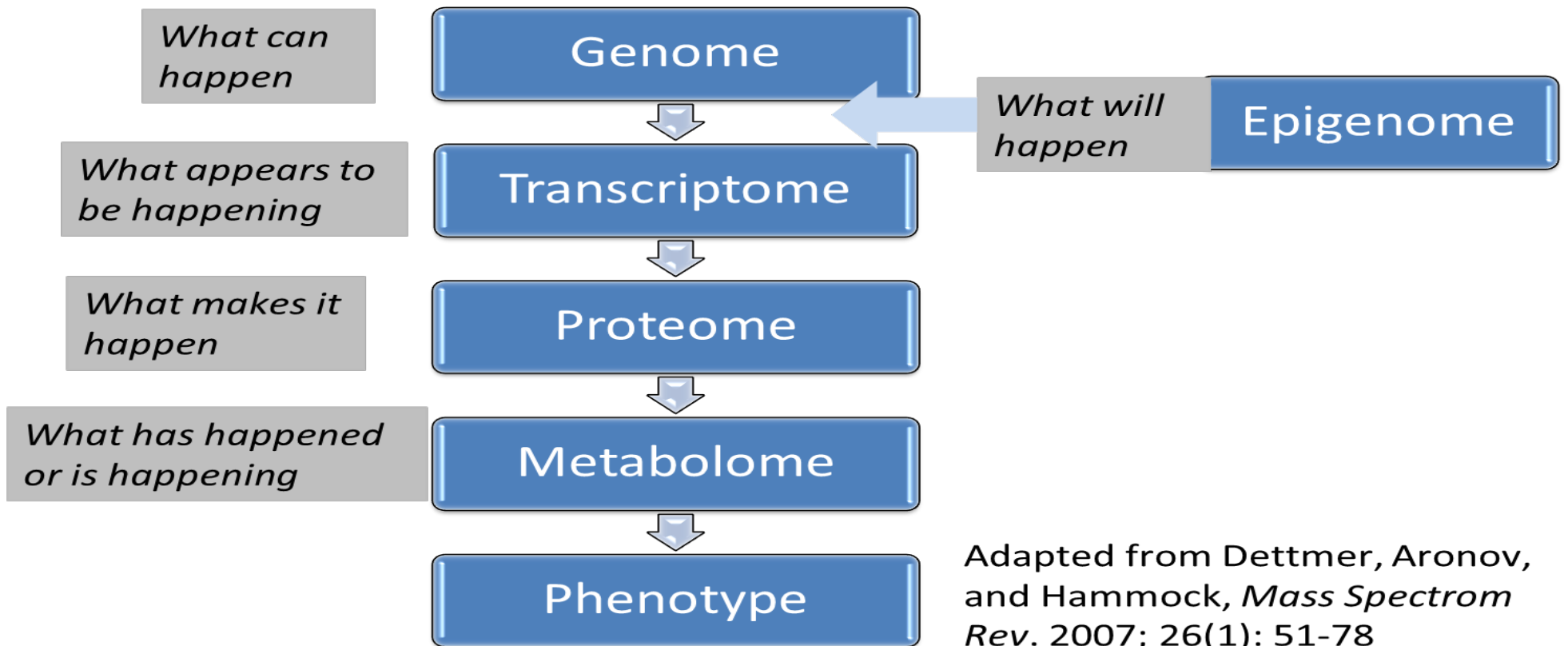
F1: *in utero* o,p'-DDT increases risk of breast cancer



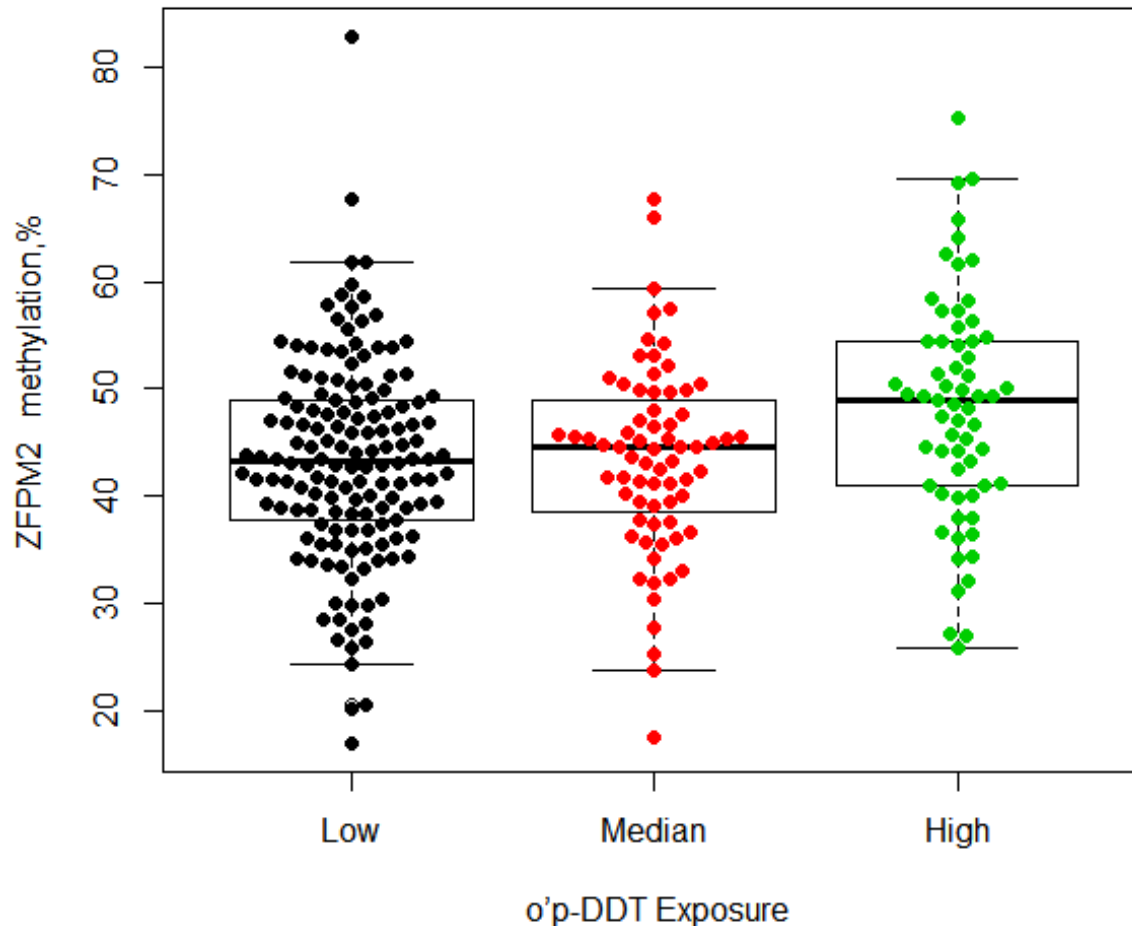
Cohn, La Merrill, Krigbaum, Yeh, Park, Zimmermann, Cirillo; JCEM 2015 [10.1210/jc.2015-1841](https://doi.org/10.1210/jc.2015-1841)

Translation: 'Omics Linked to Epidemiologic Findings

Multiple biological systems are potential targets and mediators of exposure effects



ZFPM2 Methylation



DDT Associations with DMRs for F1 Breast Cancer Related Gene

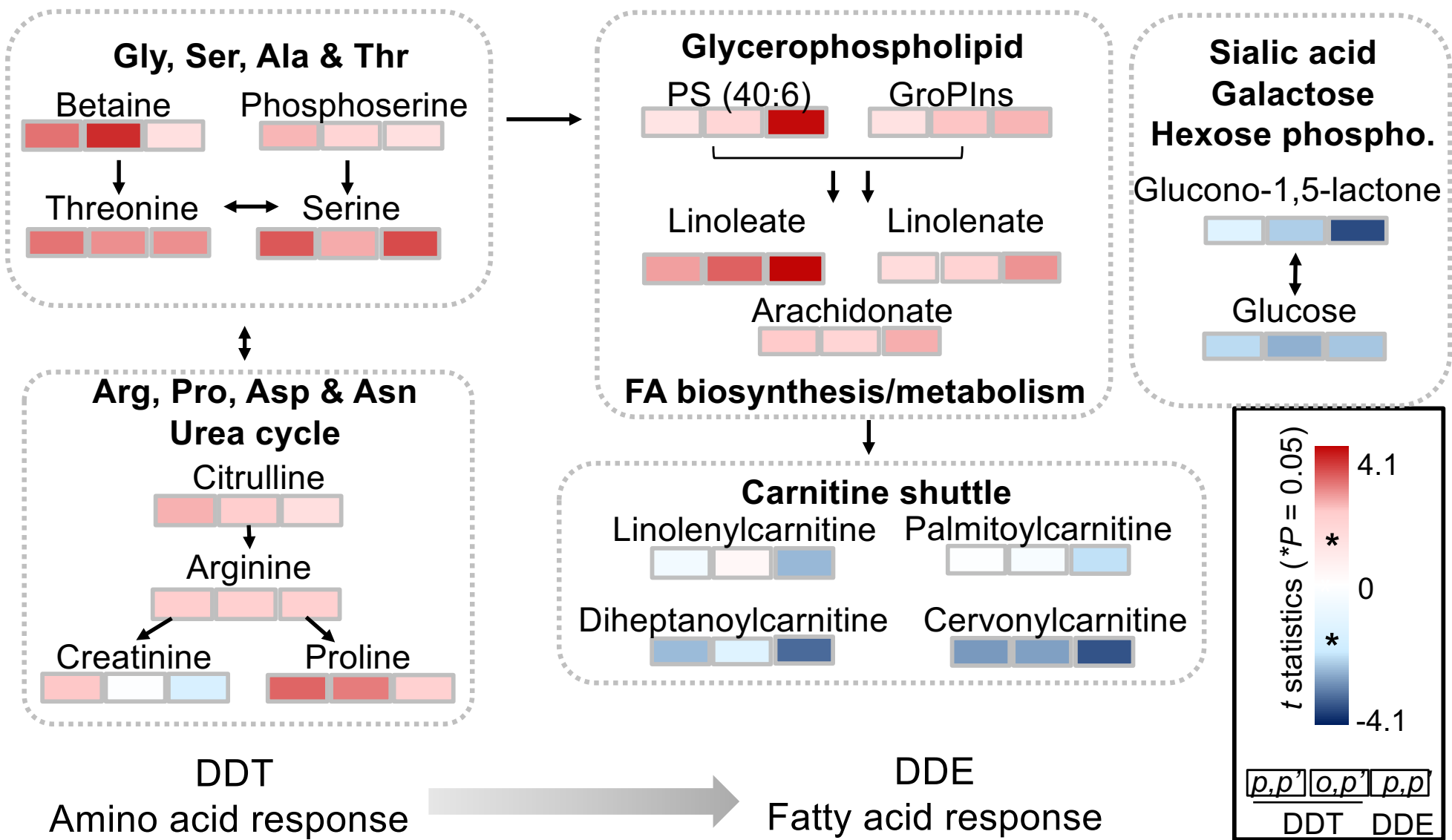
In utero DDT is associated with differentially methylated regions (DMRs) for three breast cancer-related genes, *CCDC85A*, *CYP1A1*, and *ZFPM2*, shown here

Wu HC, Cohn BA, Cirillo PM, Santella RM, Terry MB. *Reprod Toxicol.* 2019. Epub 2019/03/02. doi: 10.1016/j.reprotox.2019.02.010. PubMed PMID: 30822522.

Metabolome Wide Association Study of serum DDT and DDE in Pregnancy and Early Postpartum

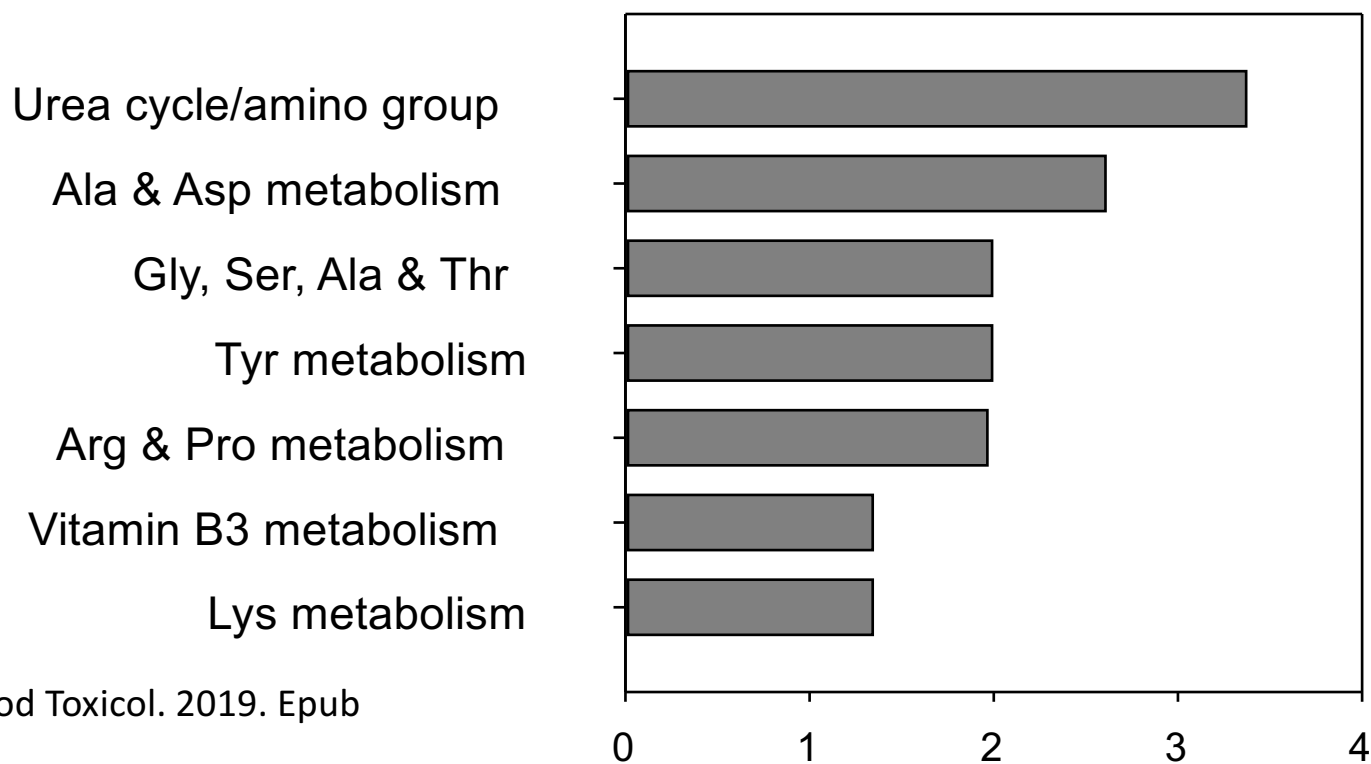
Hu, X., Li, S., Cirillo, P., Krigbaum, N., Tran, V., Ishikawa, T., La Merrill, M.A., Jones, D.P. and Cohn, B., 2019. *Reproductive Toxicology*.

<https://doi.org/10.1016/j.reprotox.2019.05.059>



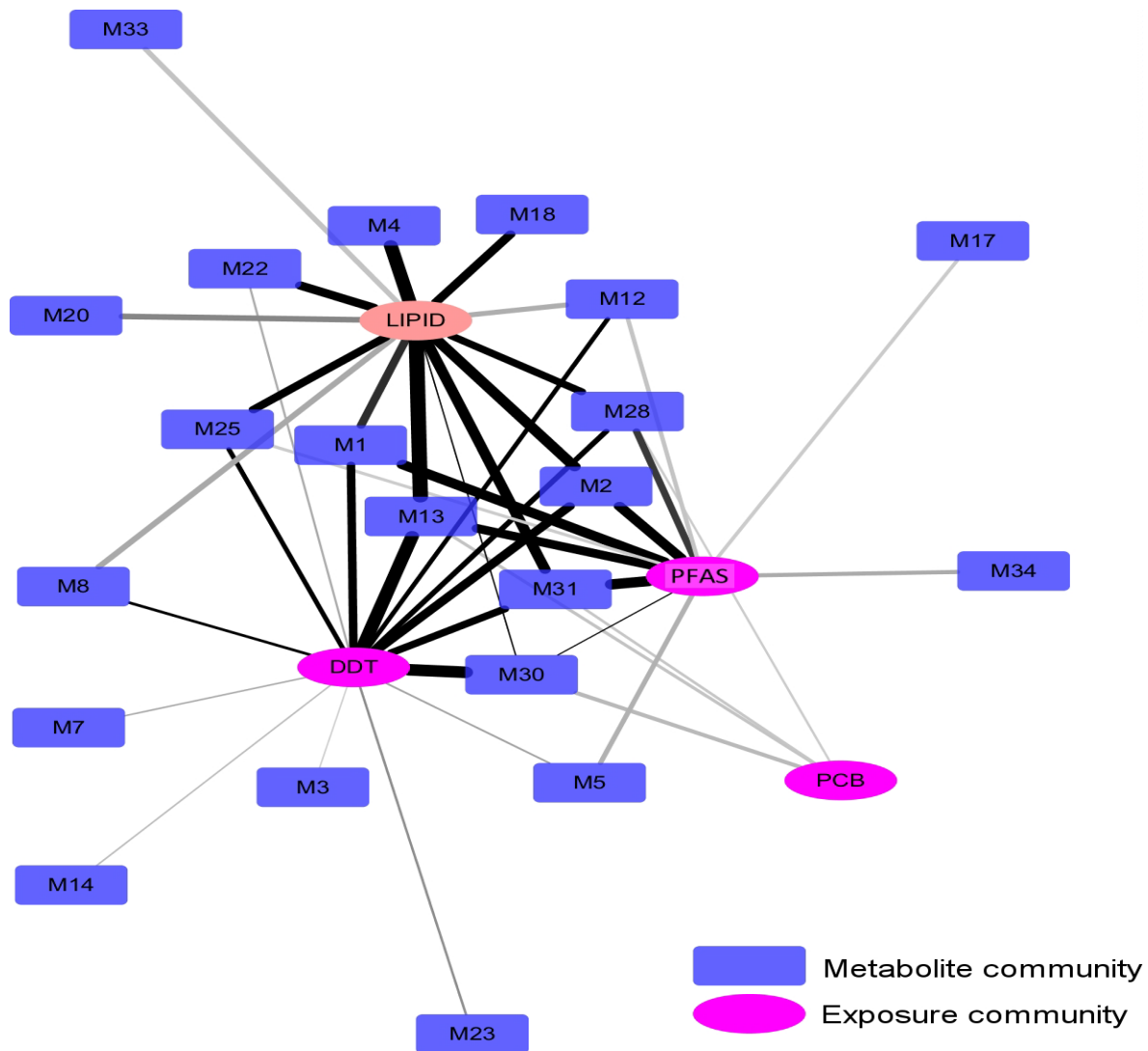
Transdisciplinary Team Science: Developmental Toxicology

The metabolic association of *p,p'*-DDT recapitulated in mouse model



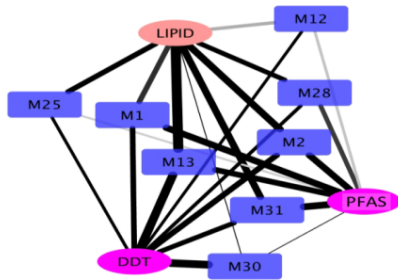
Hu X Et al., *Reprod Toxicol.* 2019. Epub
2019/03/02. doi:
10.1016/j.reprotox.2019.05.059

Transdisciplinary Team Science:
Bioinformatics for Biomarker
Discovery

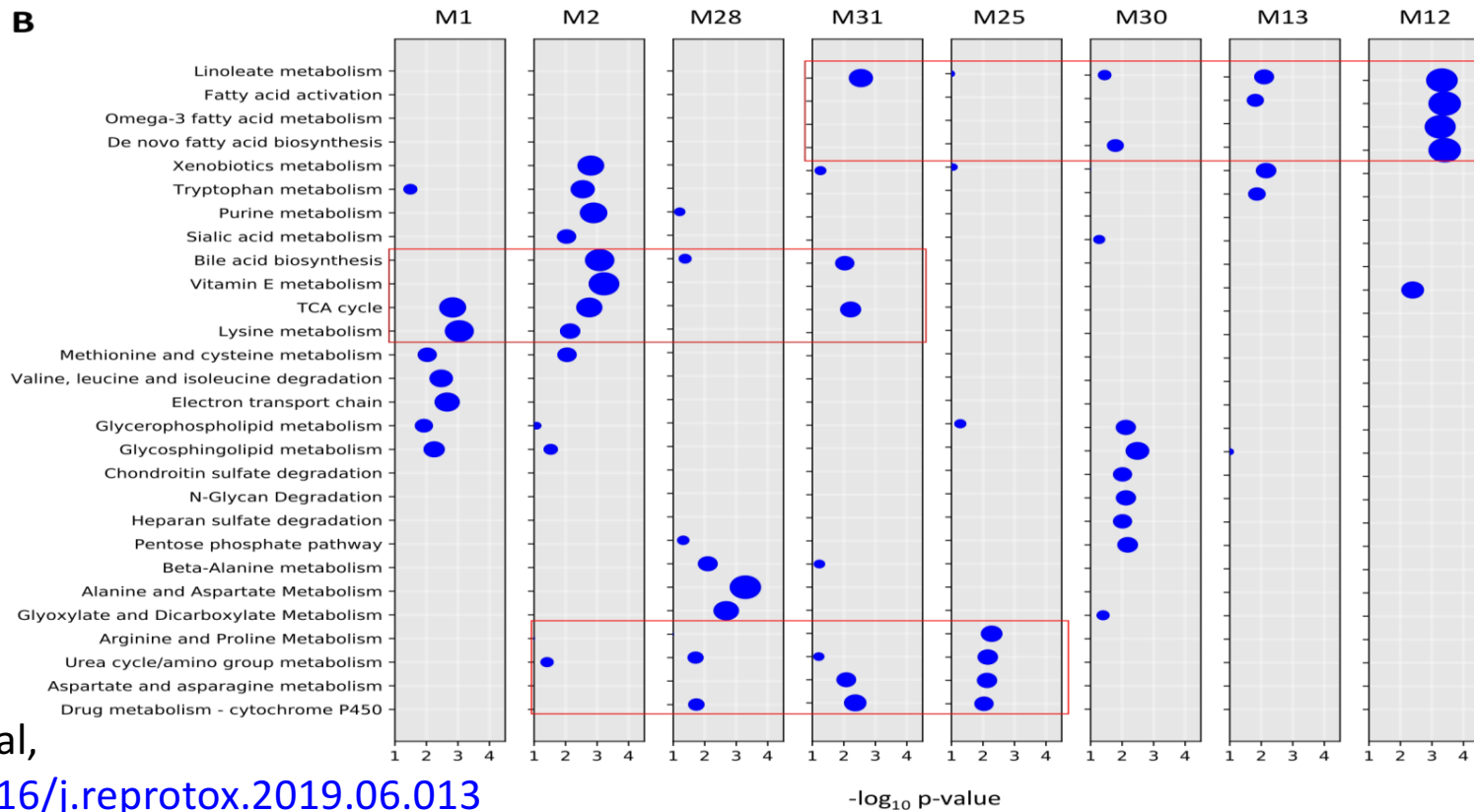


Understanding mixed environmental exposures using metabolomics via a hierarchical community network model in CHDS in the 1960's

Shuzhao Li Et al,
doi.org/10.1016/j.reprotox.2019.06.013

A

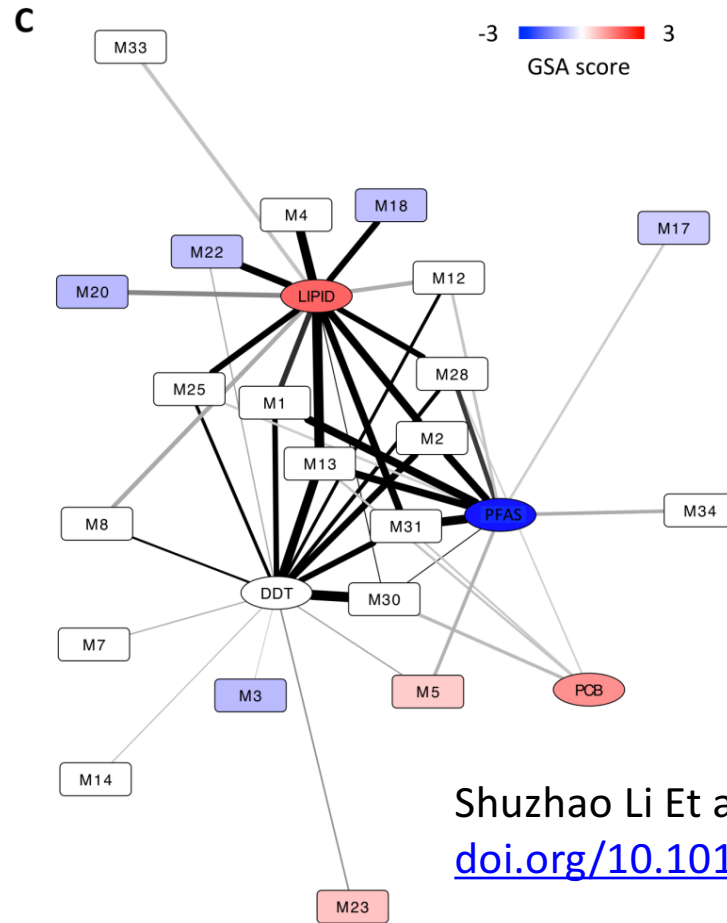
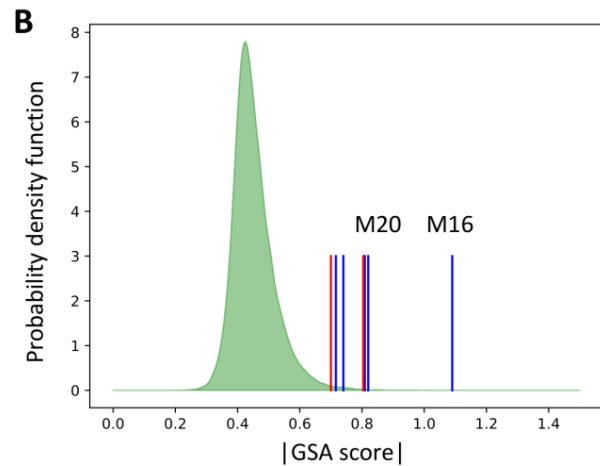
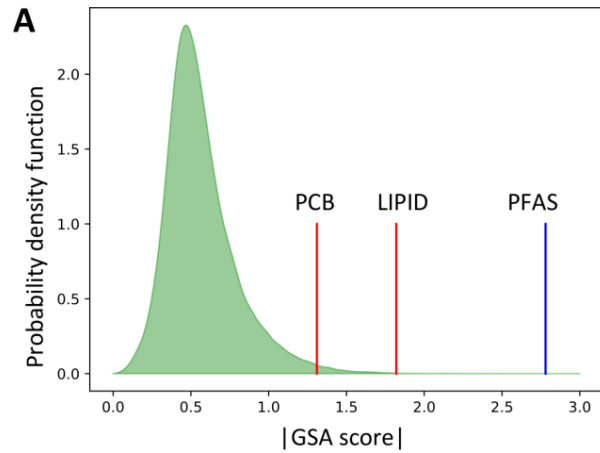
A small number of metabolic phenotypes may account for the response to a large class of environmental chemicals.

B

Shuzhao Li Et al,

doi.org/10.1016/j.reprotox.2019.06.013

F0 Metabolome and F1 breast cancer (Preliminary analysis N= 50 cases)



The significant communities ($p < 0.05$) associated with F1 breast cancer. **Red** higher in cases; **blue** lower in cases.

Shuzhao Li Et al,
doi.org/10.1016/j.reprotox.2019.06.013

DISPARITIES

- A number of legacy chemicals like DDT have been linked to many adverse health outcomes.
- Many were banned in the 1970s and the significant reduction in serum levels we find by comparing the mothers to their daughters in CHDS affirms that policy changes can lead to protection.
- Despite these reductions, African Americans in the CHDS had excess serum levels for more of the 24 measured environmental chemicals in both mothers and the daughter's generation.
- This continued disparity suggests that African Americans have sustained a disproportionate body burden that may contribute to poorer health outcomes in African Americans.

Summary

- DDTs predict breast cancer in mothers depending on age at exposure and age at outcome
- *In utero* DDTs predict breast cancer in daughters and correlate to epigenetic changes in their breast cancer-related genes
- Environmental chemicals may share common metabolism pathways leading to prevention opportunities
- Disparities in environmental exposures occurred in the 1960s and continue in the next generation.
- Environmental exposures may play a role in health disparities.

**Special Issue *Reproductive Toxicology*
“Womb to Breast Cancer”**

Barbara A. Cohn and Mary Beth Terry
Guest Editors

DUE by March 2020
OPEN ACCESS

What about Grandchildren?

- Now completing work on DDT during grandmother pregnancy and risk in their granddaughters. **Stay tuned!**

Future of CHDS

- CHDS is the only opportunity for 3 and 4 generation cancer research on environmental chemicals.
- Seeking funds to secure the cohort for the future of science: to store biospecimens, communicate with CHDS members and enroll great-grandchildren.
- Please contact me if you have ideas or can help.

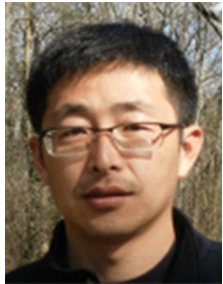
We Thank Funders

California Breast Cancer Research Program several critical awards most notably our Three Generations of Breast Cancer Study (15ZB-0186)

National Institutes of Health (Multiple Institutes over 60 years but mainly NICHD)

State of California which created and supports the California Cancer Registry, The Vital Status and Department of Motor Vehicle Files –without which this cancer birth cohort could not exist.

It takes a village... really more like a state and nation



Shuzhao Li



Dean Jones



CHDS Researchers



CHDS Participant Advisory Council



Piera
Cirillo



Michele
La Merrill



Mary Beth
Terry



June-Soo
Park



Myrto
Petreas

Metabolome Wide Association Study of serum DDT and DDE in Pregnancy and Early Postpartum

Hu, X., Li, S., Cirillo, P., Krigbaum, N., Tran, V., Ishikawa, T., La Merrill, M.A., Jones, D.P. and Cohn, B., 2019. *Reproductive Toxicology*.

<https://doi.org/10.1016/j.reprotox.2019.05.059>

