Using the key characteristics of endocrine disruptors to organize mechanistic support of the developmental basis of endocrine disruption

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What are Endocrine Disrupting Chemicals?

Endocrine Disrupting Chemicals (EDCs) are defined by the Endocrine Society as:

"an exogenous [non-natural] chemical, or mixture of chemicals, that interferes with any aspect of hormone action."

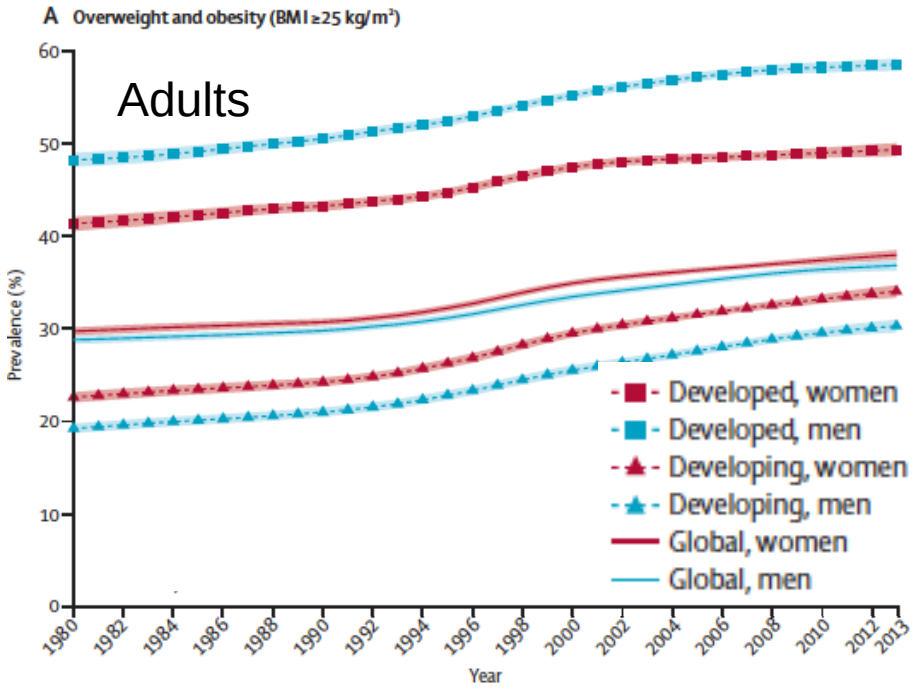
Endocrinology, September 2012, 153(9):4097–4110

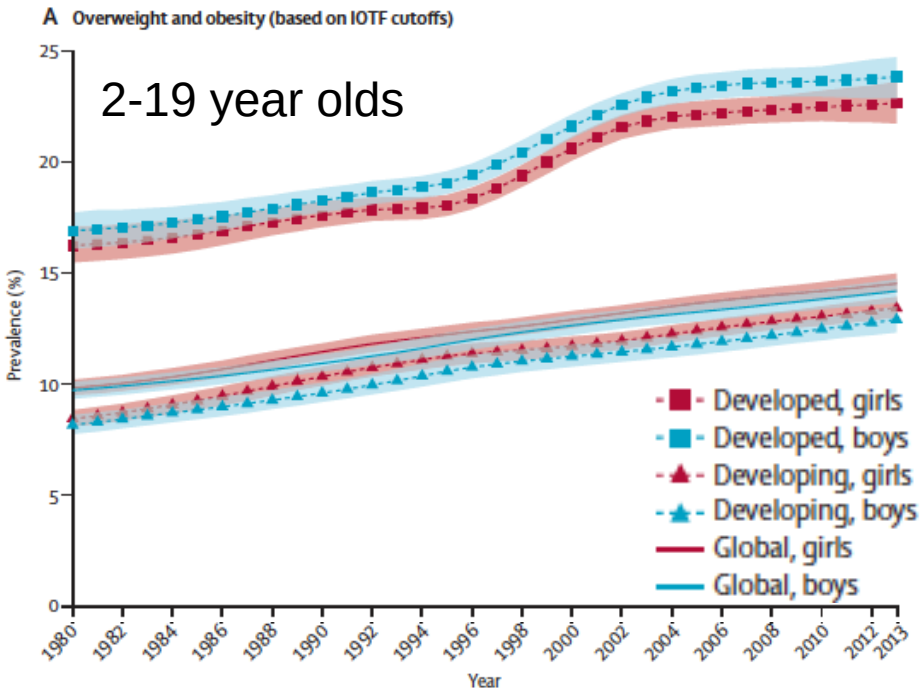
POSITION STATEMENT

Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from The Endocrine Society

R. Thomas Zoeller, T. R. Brown, L. L. Doan, A. C. Gore, N. E. Skakkebaek, A. M. Soto, T. J. Woodruff, and F. S. Vom Saal

Overweight and obesity are on the rise worldwide

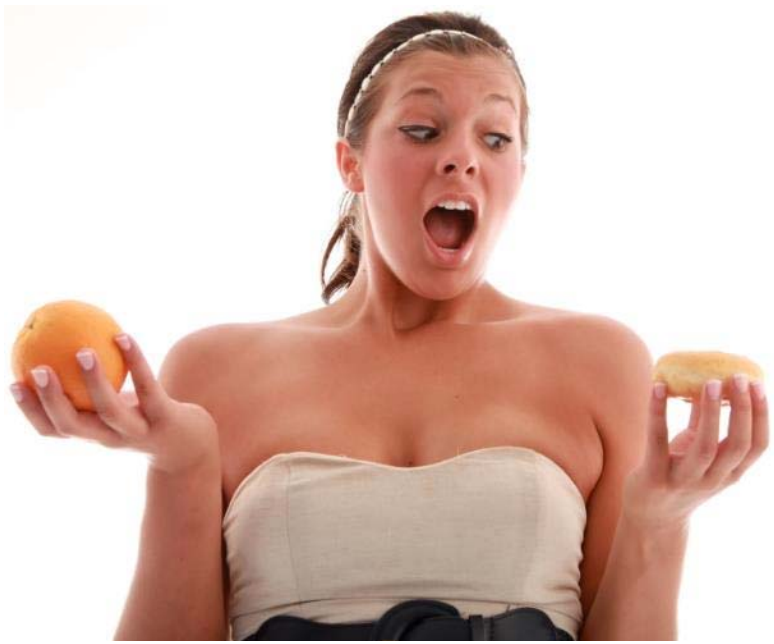




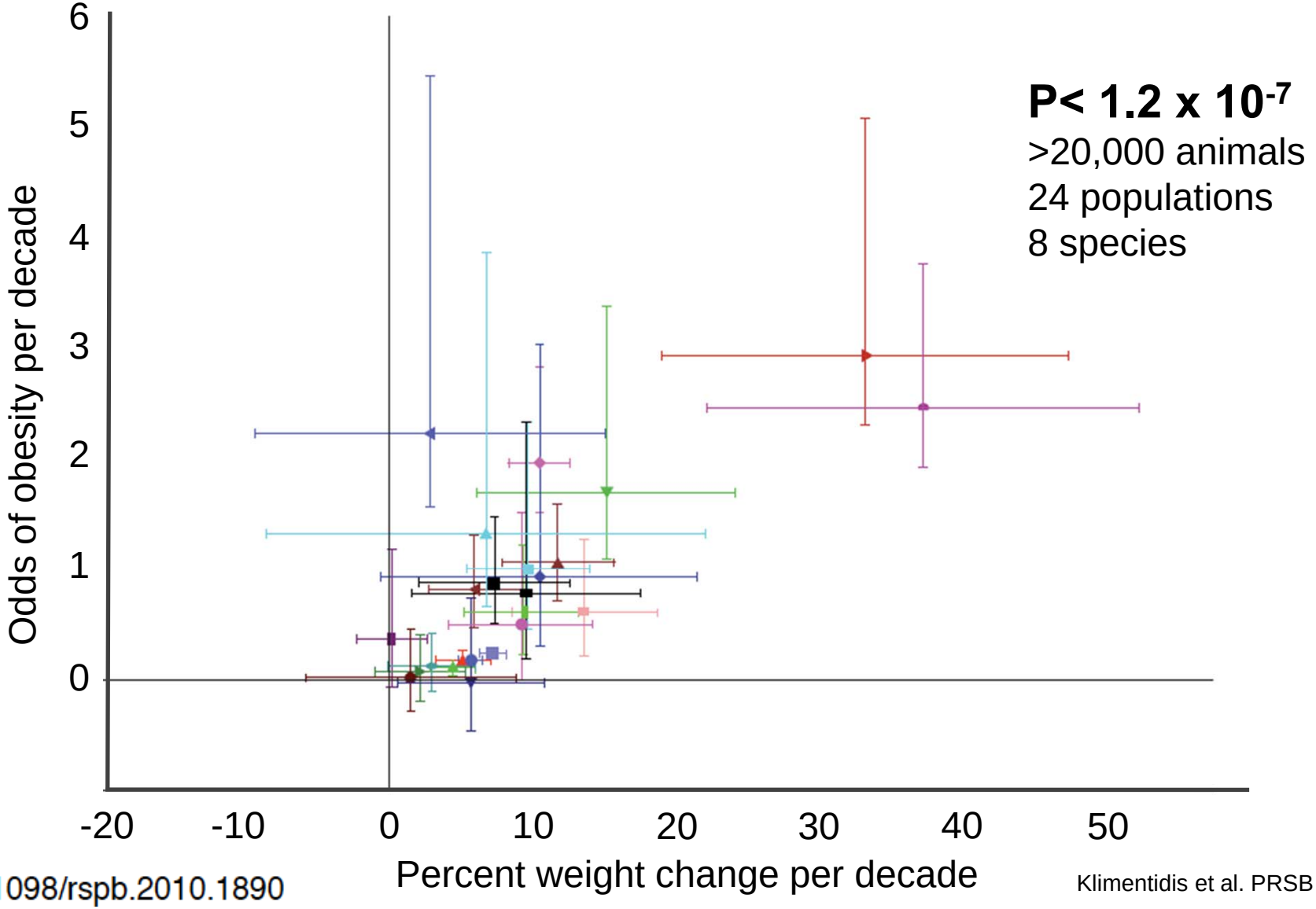
Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014 384: 766-81.

WHY IS THE PREVALENCE INCREASING?

It is changing faster than a
lone genetic cause would predict



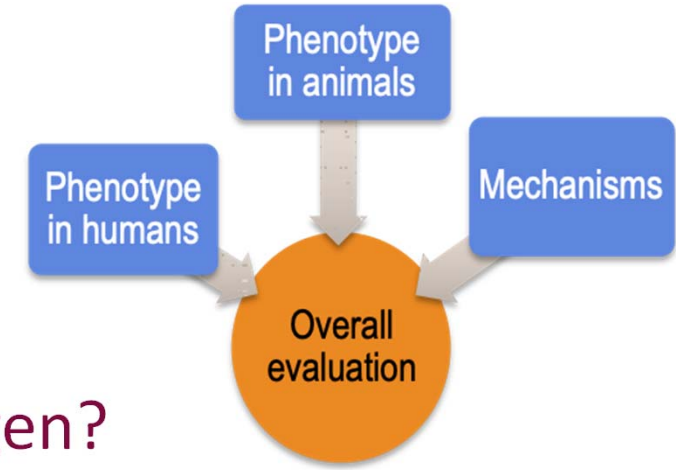
Average body weight & obesity have been rising in animals over time



doi: 10.1098/rspb.2010.1890

Klimentidis et al. PRSB 2010

Let us learn history lessons



- Who decides if a chemical is a carcinogen?
  - **Many groups** (GHS, EU, USEPA, USNTP, CalEPA Prop 65) decide from Monographs of the **International Agency for Research on Cancer IARC**, part of the World Health Organization
- How does IARC identify carcinogens?

  ⬇ Epidemiology, rodent assays

  ⬆ Mechanistic, *in vitro* assays
- Key Characteristics of Carcinogens
  - A framework for organizing data related to the intrinsic properties of carcinogens
  - Incomplete 'mechanistic pathway' ≠ decision-making inaction
  - Help identify data gaps

Environmental Health Perspectives • VOLUME 124 | NUMBER 6 | June 2016

Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis

Martyn T. Smith,[1] Kathryn Z. Guyton,[2] Catherine F. Gibbons,[3] Jason M. Fritz,[3] Christopher J. Portier,[4] Ivan Rusyn,[5] David M. DeMarini,[3] Jane C. Caldwell,[3] Robert J. Kavlock,[3] Paul F. Lambert,[6] Stephen S. Hecht,[7] John R. Bucher,[8] Bernard W. Stewart,[9] Robert A. Baan,[2] Vincent J. Cogliano,[3] and Kurt Straif[2]*

Expert Meeting on Advancing the Key Characteristics Framework to Reproductive Toxicants and EDCs

- March 7-8th, 2018 in Berkeley CA
- Sponsored by: CalEPA
- Zoeller and La Merrill invited to lead the evaluation of whether developing KCs of EDCs was feasible

https://doi.org/10.1038/s41574-019-0273-8

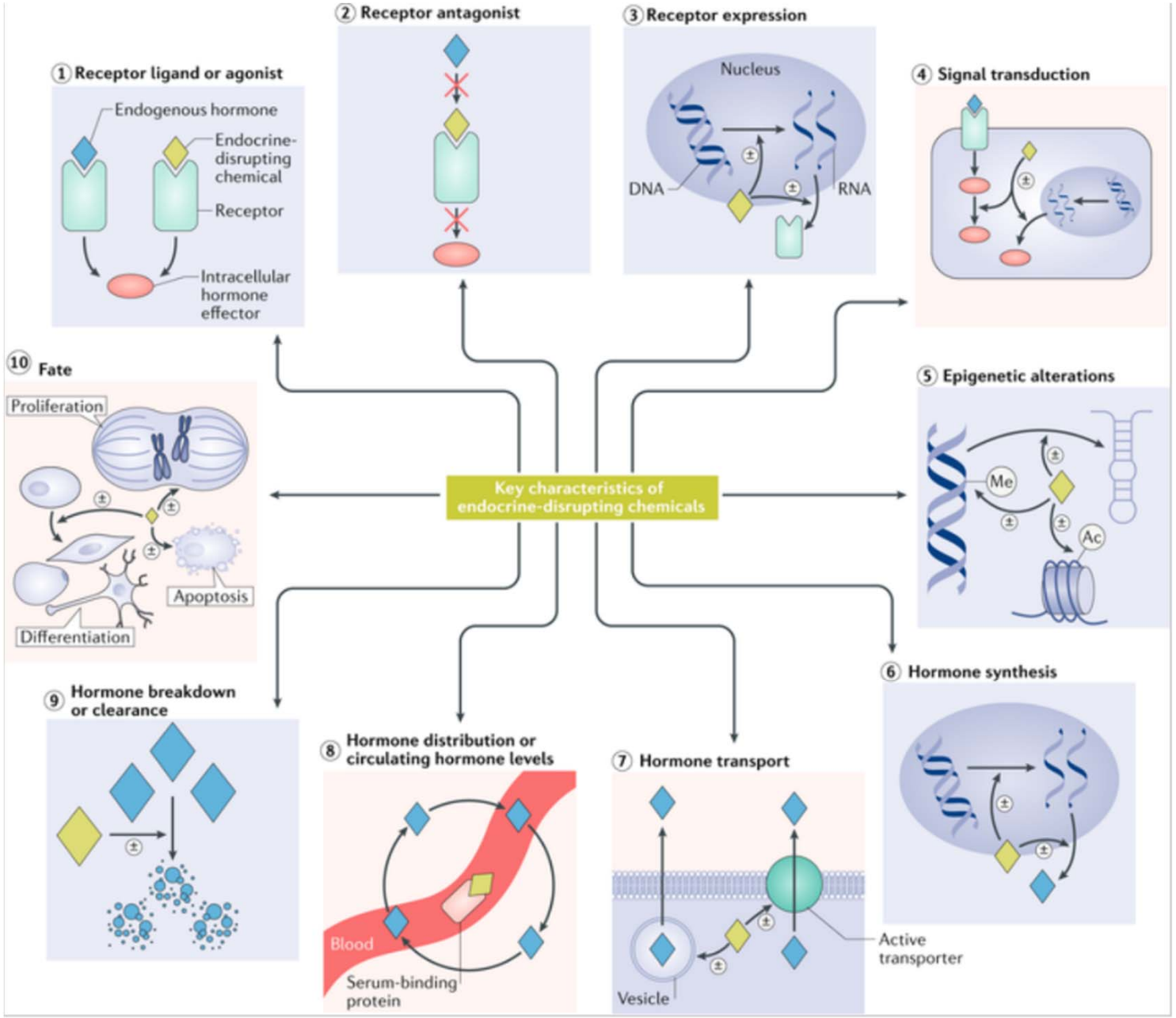
CONSENSUS STATEMENT

NATURE REVIEWS | ENDOCRINOLOGY
OPEN

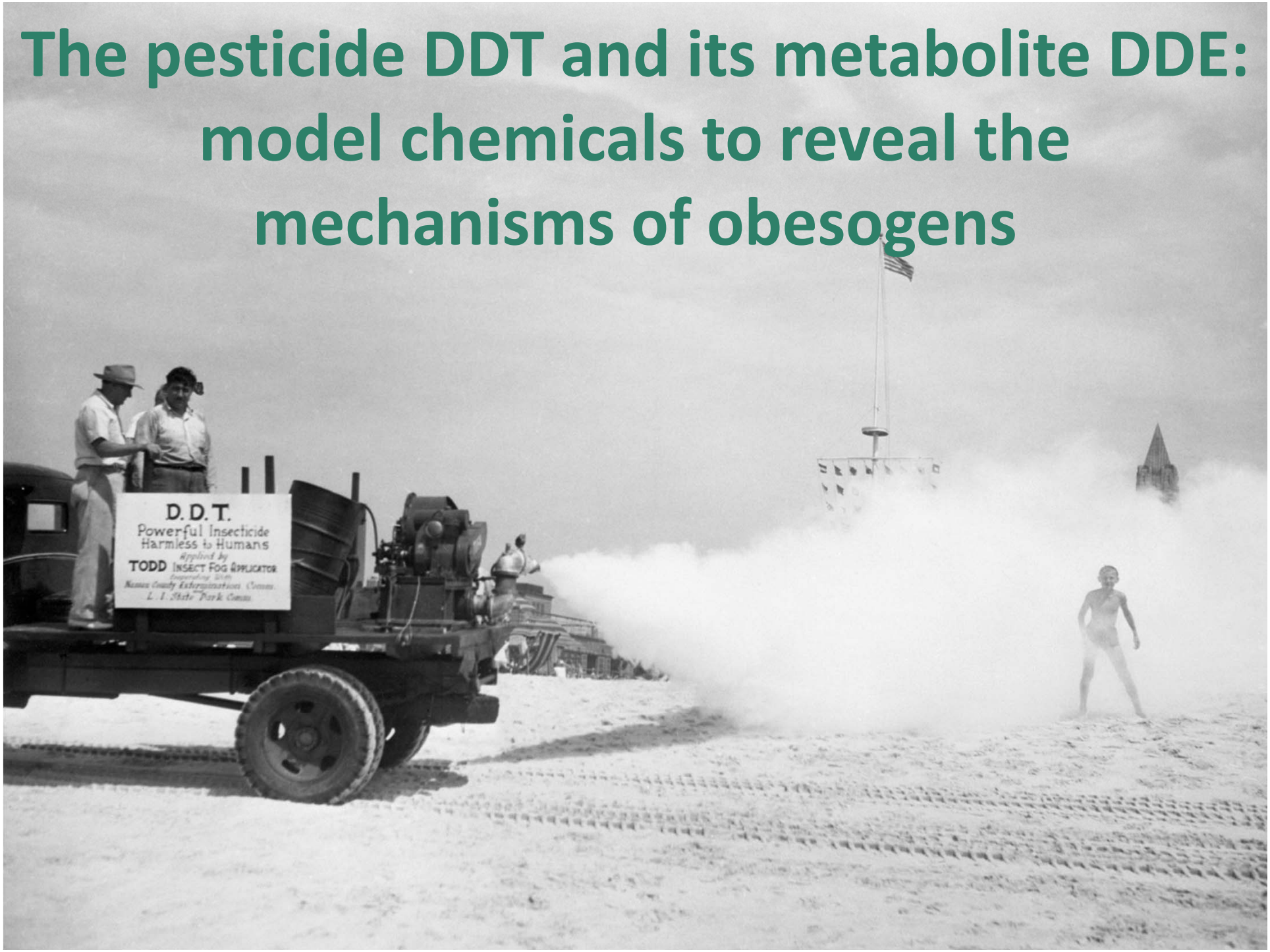
Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification

Michele A. La Merrill[1], Laura N. Vandenberg[2], Martyn T. Smith[3], William Goodson[4], Patience Browne[5], Heather B. Patisaul[6], Kathryn Z. Guyton[7], Andreas Kortenkamp[8], Vincent J. Cogliano[9], Tracey J. Woodruff[10], Linda Rieswijk[3,11], Hideko Sone[12], Kenneth S. Korach[13], Andrea C. Gore[14], Lauren Zeise[15] and R. Thomas Zoeller[16]

Universal EDC Characteristics Are



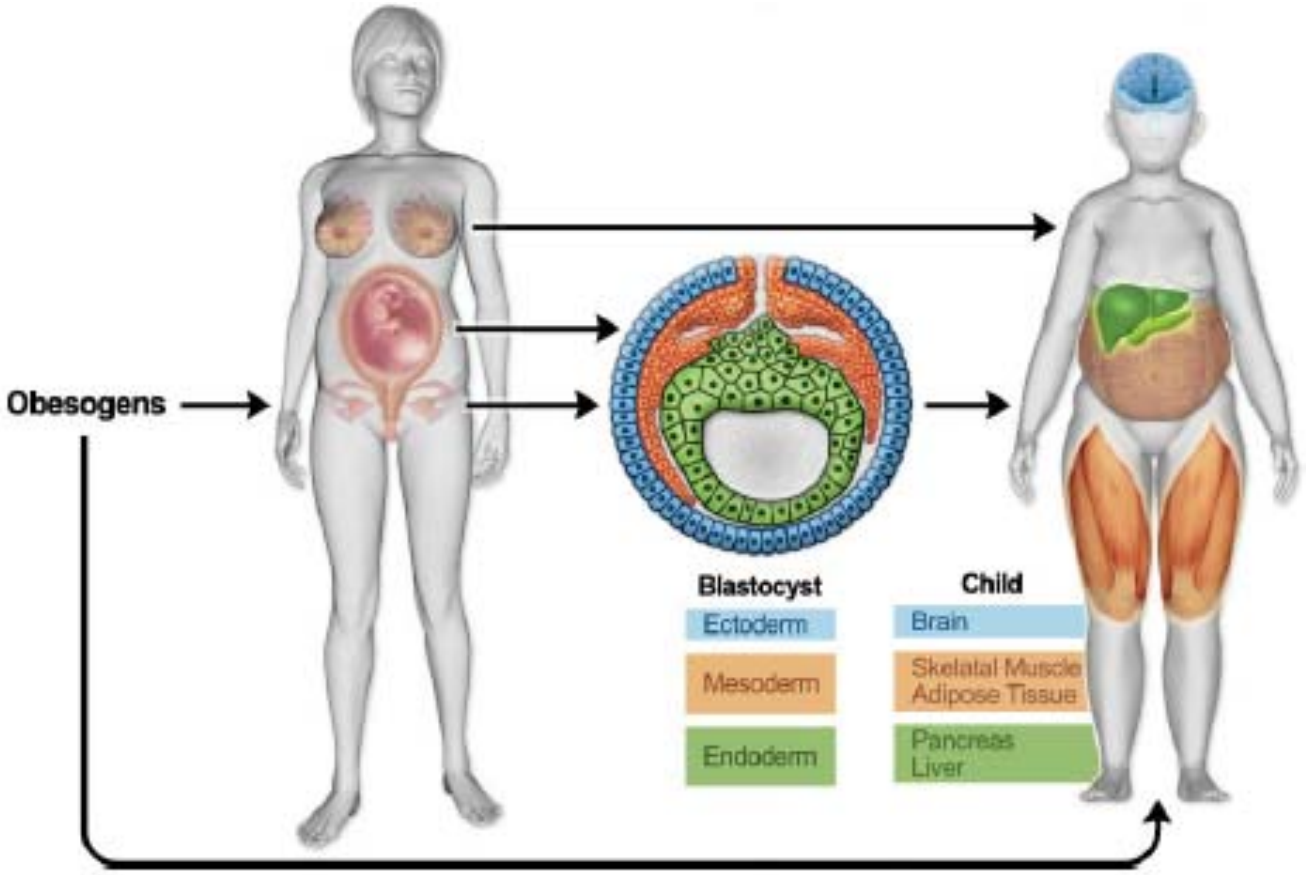
The pesticide DDT and its metabolite DDE: model chemicals to reveal the mechanisms of obesogens



What does “yesterday’s chemical” have to do with today’s diseases?

Developmental Origins of Adult Disease

Chronic adult disease: let's consider developmental orgins

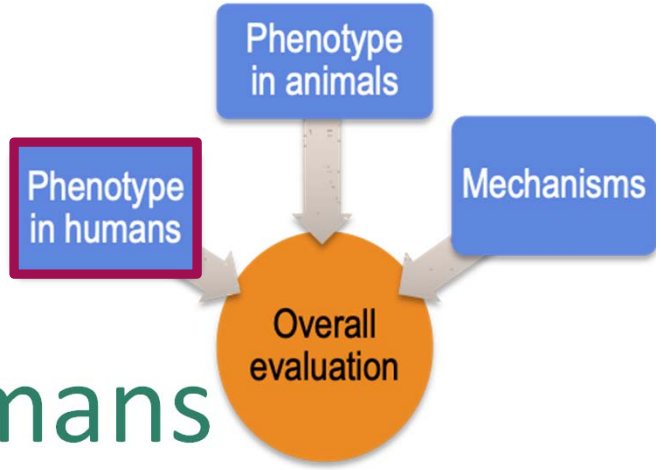


Childhood Obesity and Environmental Chemicals

Michele La Merrill, PhD, MPH,[1] and Linda S. Birnbaum, PhD, DABT[2]

MOUNT SINAI JOURNAL OF MEDICINE 78:22–48, 2011

KCs in Data integration: DDT/E phenotype in humans



- More than 100 epidemiology studies
  - Numerous are longitudinal
  - Numerous assess exposure prenatally
  - Associations between DDT and DDE and adverse outcomes such as
    - obesity,
    - diabetes mellitus,
    - infertility,
    - and cancers

Meta-analyses & systematic reviews of DDE exposure support association with obesity

obesity reviews doi: 10.1111/j.1467-789X.2011.00871.x

Etiology and Pathophysiology

Endocrine-disrupting chemicals and obesity development in humans: A review

J. L. Tang-Péronard[1,2], H. R. Andersen[2], T. K. Jensen[2] and B. L. Heitmann[1,3]

obesity reviews doi: 10.1111/obr.12463

Etiology and Pathophysiology

Do environmental pollutants increase obesity risk in humans?

Y. Wang,[1,2] K. Hollis-Hansen,[1,2] X. Ren,[1] Y. Qiu[1,3] and W. Qu[4,5]

Environmental Health Perspectives

Association between Exposure to *p,p′*-DDT and Its Metabolite *p,p′*-DDE with Obesity: Integrated Systematic Review and Meta-Analysis

German Cano-Sancho,[1] Andrew G. Salmon,[2] and Michele A. La Merrill[1]

[1]Department of Environmental Toxicology, University of California, Davis, Davis, California, USA
[2]Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, California, USA

Published 18 September 2017.

Conclusions: We classified *p,p′*-DDT and *p,p′*-DDE as "presumed" to be obesogenic for humans, based on a moderate level of primary human evidence, a moderate level of primary *in vivo* evidence, and a moderate level of supporting evidence from *in vivo* and *in vitro* studies. https://doi.org/10.1289/EHP527

Child Health and Development Studies: prospective birth cohort

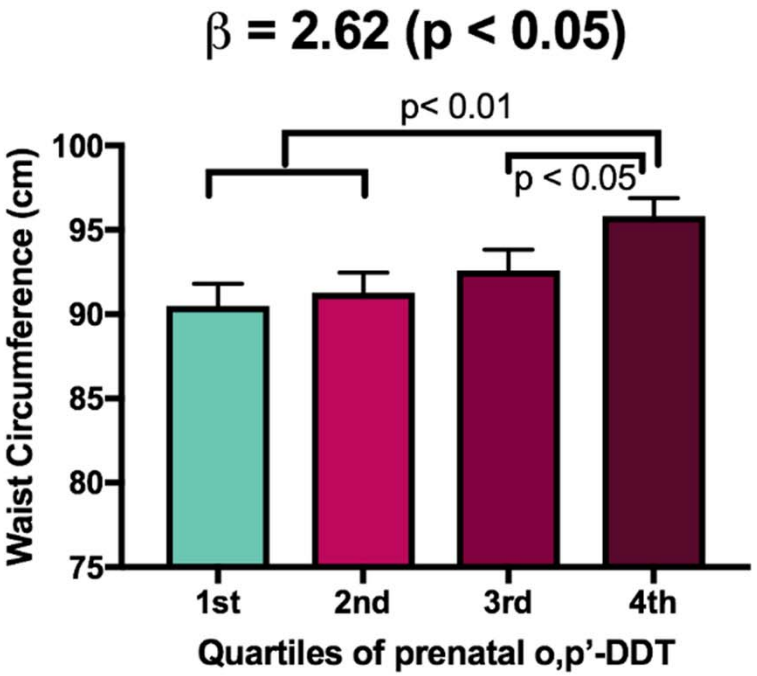
chds
Child Health and Development Studies

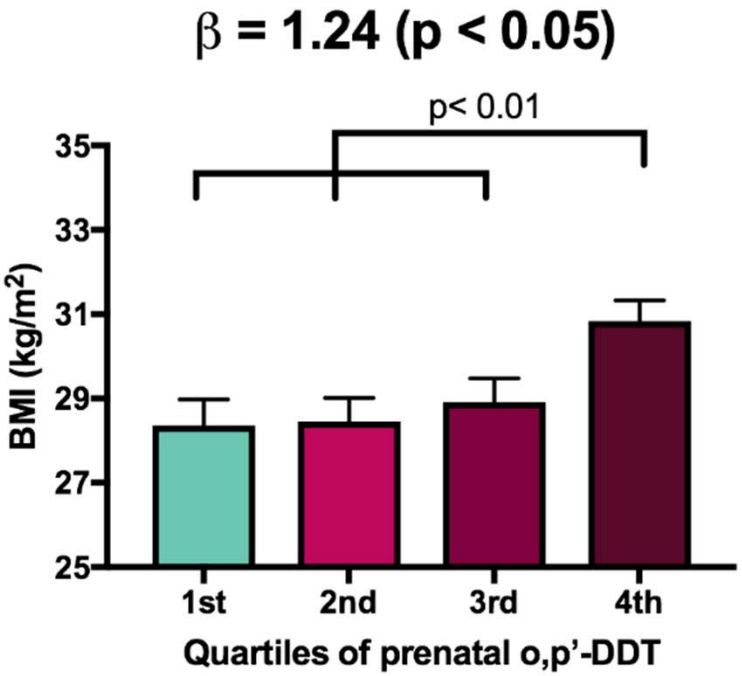
~15,000 pregnant women in the Kaiser Permanente Health Plan joined the CHDS in 1960s.

> 500 maternal serum samples from 1960 subjected to GC/MS for analysis of a mixture of 20 POPs.

> 50 year health follow-up in >500 adult daughters.

Prenatal DDT exposure positively associated with adiposity of women in their fifties





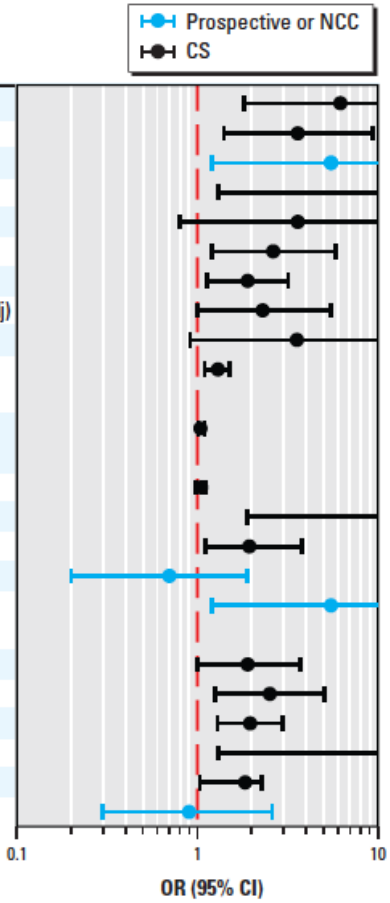
Only association in a mixture of 2 dozen POPs

chds
Child Health and Development Studies

La Merrill et al.
Intl J of Obesity 2020

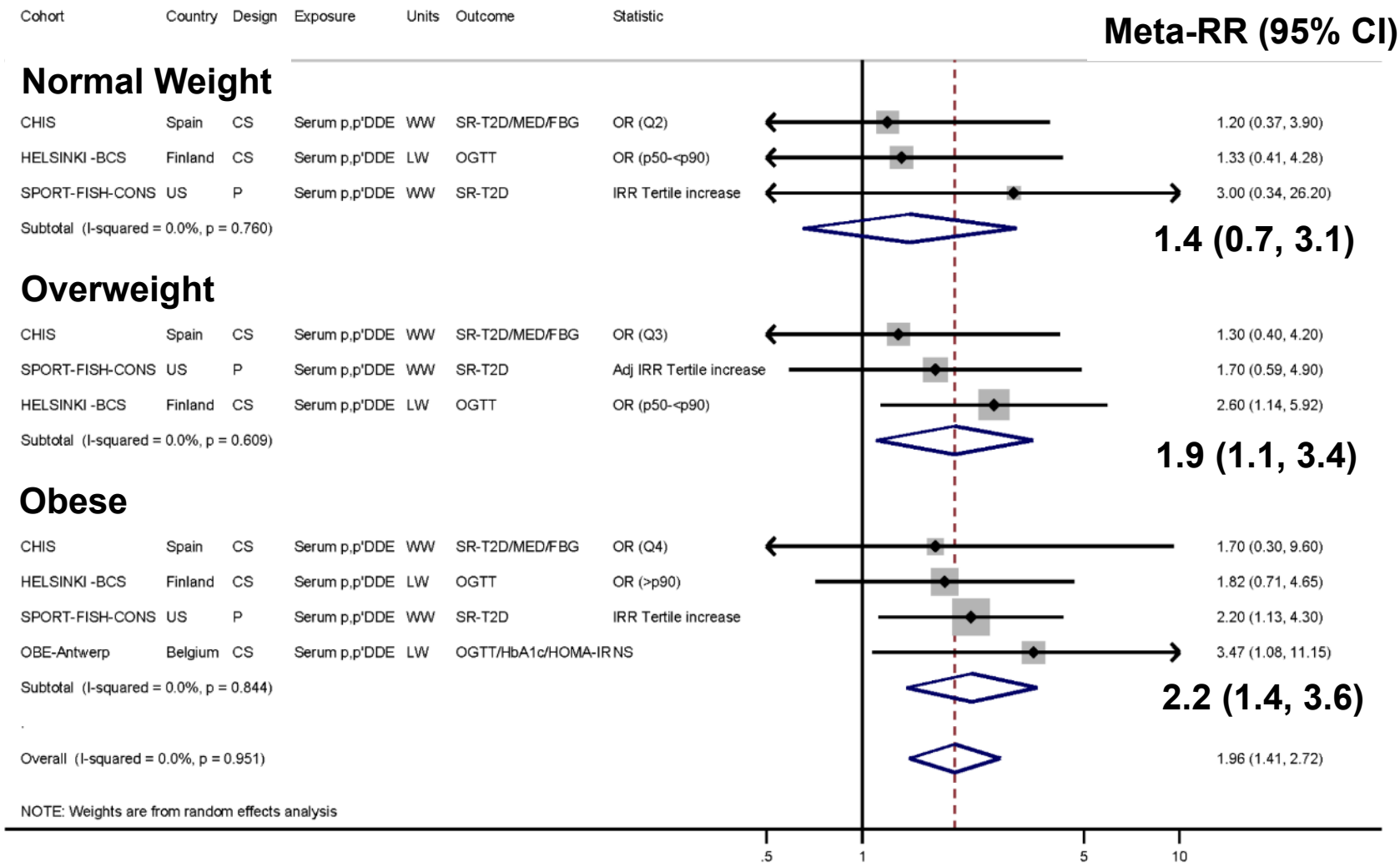
DDT and DDE are associated with diabetes in humans

Reference	Chemical	Study description (*n*)	Outcome assessment	Adj OR (95% CI)[a]	Exposure contrast[b]
Codru et al. 2007	DDE	USA (Akwesasne), Mohawks; CS, ♂♀ (352)	FBG, medication	6.2 (1.8, 21.9)	T3 vs. T1 (ng/g lipid adj)
Turyk et al. 2009b	DDE	USA (Great Lakes), fish eaters; CS; ♂♀ (503)	Self-report	3.6 (1.4, 9.4)	Q4 vs. Q1 (ng/g lipid adj)
Turyk et al. 2009a	DDE	USA (Great Lakes), fish eaters; prospective; ♂♀ (471)	Self-report	5.5 (1.2, 25.1) IRR	T2 vs. T1 (ng/g ww)
Son et al. 2010	*o,p′*-DDT	South Korea (Uljin); CS, ≥ 40 years, ♂♀ (80)	FBG, medication	12.3 (1.3, 113.2)	T3 vs. T1 (ng/g lipid std)
Son et al. 2010	*p,p′*-DDD	South Korea (Uljin); CS, ≥ 40 years, ♂♀ (80)	FBG, medication	3.6 (0.8, 16.3)	T3 vs. T1 (ng/g lipid std)
Cox et al. 2007	*p,p′*-DDE	USA, HHANES 1982–1984; CS, ≥ 20 years, ♂♀ (1,303)	Self-report	2.63 (1.2, 5.8)	> 75th vs. <25th %ile (ng/g ww)
Everett et al. 2010	*p,p′*-DDE	USA, NHANES 1999–2004; CS, ≥ 20 years, ♂♀ (3,049)	Self-report, HbA1c	1.9 (1.13, 3.18)	≥ 168.6 vs. <168 (ng/g lipid adj)
Lee et al. 2006	*p,p′*-DDE	USA, NHANES 1999–2002; CS, ≥ 20 years, ♂♀ (2,106)	FBG, self-report	2.3 (1, 5.5)	75th to < 90th %tile vs. ND (ng/g lipid adj)
Philibert et al. 2009	*p,p′*-DDE	Canada (northern Ontario); First Nation, ♂♀ (101)	Self-report	3.56 (0.91, 13.08)	> 75th vs. ≤ 75th %ile (ng/g lipid std)
Rignell-Hydbom et al. 2007	*p,p′*-DDE	Sweden (east/west coast), fishermen's wives; CS, ♀ (543)	Self-report	1.3 (1.1, 1.5)	Per 100-ng/g lipid increase, adj
Rylander et al. 2005	*p,p′*-DDE	Sweden (national registry), fishermen's wives; CS, ♀ (184)	Self-report	1.05 (1.01, 1.10)	Per 100-ng/g lipid increase, adj
Rylander et al. 2005	*p,p′*-DDE	Sweden (national registry), fishermen; CS ♂ (196)	Self-report	1.05 (0.98, 1.11)	Per 100-ng/g lipid increase, adj
Son et al. 2010	*p,p′*-DDE	South Korea (Uljin); CS, ≥ 40 years, ♂♀ (80)	FBG, medication	12.7 (1.9, 83.7)	T3 vs. T1 (ng/g lipid std)
Ukropec et al. 2010	*p,p′*-DDE	Slovakia (eastern, polluted); CS, ≥ 21 years, ♂♀ (2,047)	FBG, 2 hr glucose	1.94 (1.11, 3.78)	QU5 vs. QU1 (ng/g lipid adj)
Lee et al. 2010	*p,p′*-DDE	USA (multisite), CARDIA; NCC, ≥ 18 years, ♂♀ (180)	FBG, medication	0.7 (0.2, 1.9)	Q4 vs. Q1 (ng/g lipid adj)
Rignell-Hydbom et al. 2009	*p,p′*-DDE	Sweden (Lund) WHILA; NCC, ♀ (742)	OGTT	5.5 (1.2, 25)	> 4.60 vs. ≤ 4.60 ng/mL (not lipid adj)
Cox et al. 2007	*p,p′*-DDT	USA, HHANES 1982–1984; CS, ≥ 20 years, ♂♀ (1,303)	Self-report	1.9 (1, 3.7)	≥ 2.0 vs. < 2.0 (ng/g ww)
Everett et al. 2007	*p,p′*-DDT	USA, NHANES 1999–2002;CS, ≥ 20 years, ♂♀ (1,830)	Self-report, HbA1c	2.52 (1.26, 5.02)	20.8–26.6 vs. ≤ 20.7 (ng/g lipid adj)
Everett et al. 2010	*p,p′*-DDT	USA, NHANES 1999–2004; CS, ≥ 20 years, ♂♀ (3,049)	Self-report, HbA1c	1.96 (1.29, 2.98)	≥ 20.7 vs. < 20.7 (ng/g lipid adj)
Son et al. 2010	*p,p′*-DDT	South Korea (Uljin); CS, ≥ 40 years, ♂♀ (80)	FBG, medication	10.6 (1.3, 84.9)	T3 vs. T1 (ng/g lipid std)
Ukropec et al. 2010	*p,p′*-DDT	Slovakia (eastern, polluted); CS, ≥ 21 years, ♂♀ (2,047)	FBG, 2 hr glucose	1.84 (1.03, 2.27)	QU3 vs. QU1 (ng/g lipid adj)
Lee et al. 2010	*p,p′*-DDT	USA (multisite), CARDIA; NCC, ≥ 18 years, ♂♀ (180)	FBG, medication	0.9 (0.3, 2.6)	Q4 vs. Q1 (ng/g lipid adj)

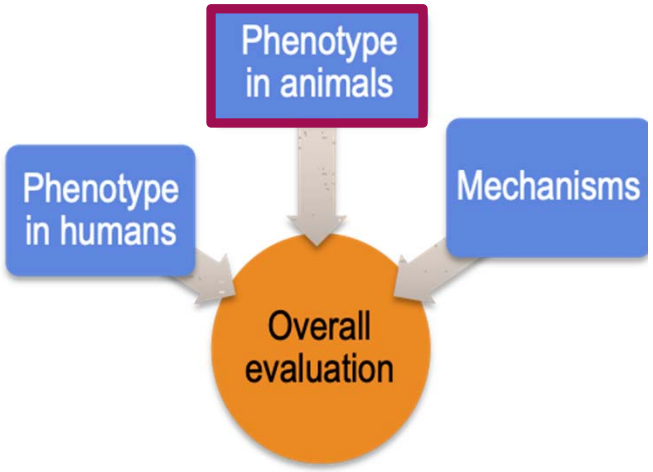


Taylor et al. 2013

Human studies indicate obesity increases risk of association between DDE and diabetes

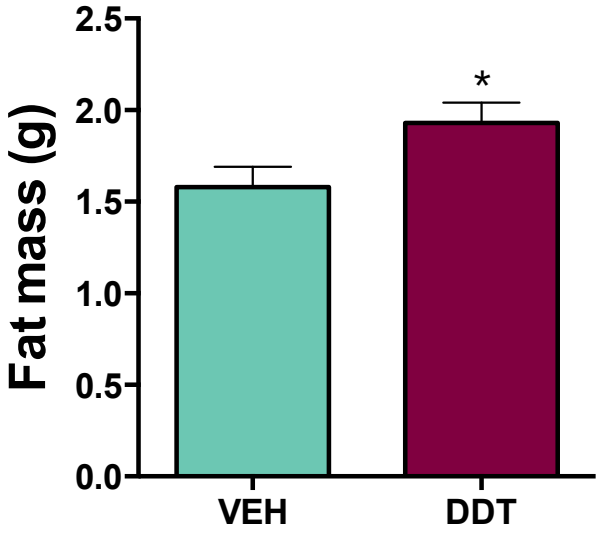


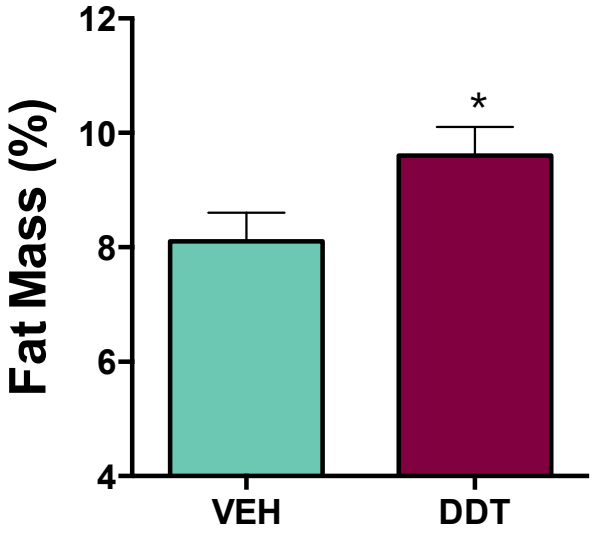
KCs in Data integration: DDT/E phenotype in animals

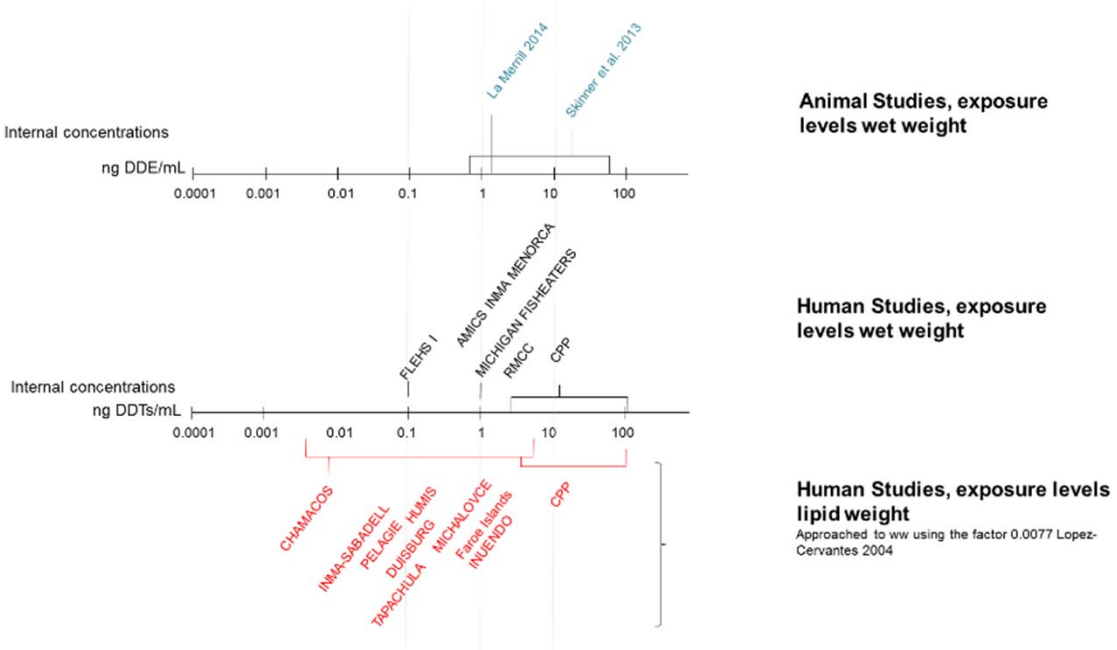


- Two rodent species
  - Developmental exposure to DDT and DDE
    - Leads to increased body and fat mass in subsequent generations
- Three rodent species
  - Exposure to DDT and/or DDE
  - Causes disruption of energy expenditure

Perinatal DDT increase adiposity in adult mice

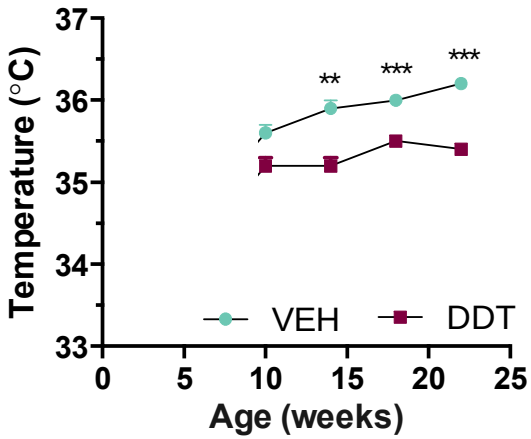


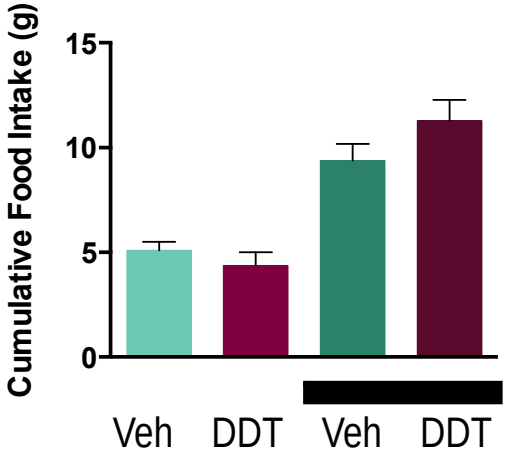


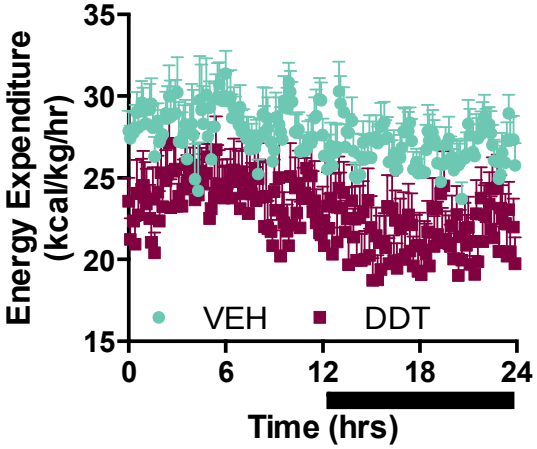


La Merrill et al. PLOS ONE 2014
Cano-Sancho et al. EHP 2017

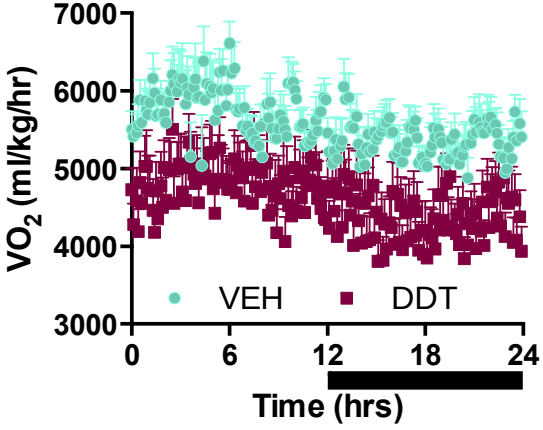
Perinatal DDT decreases Energy Expenditure (EE) and metabolism in adult mice



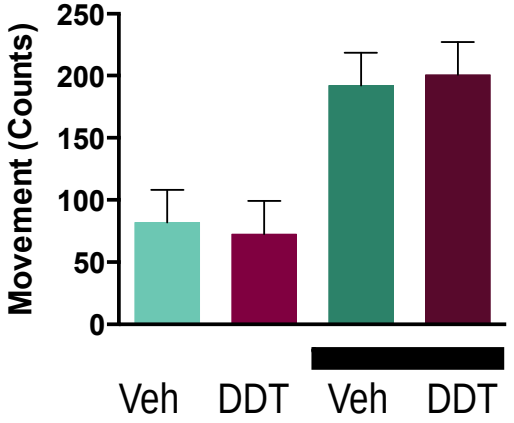




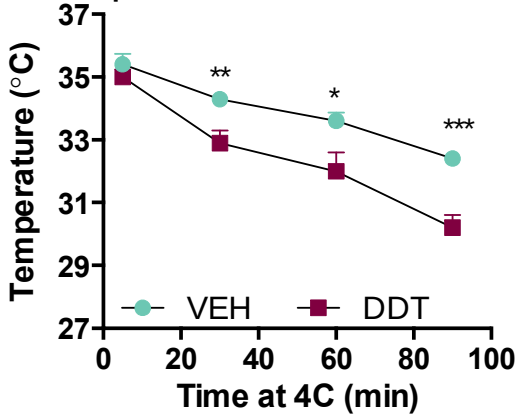
Resting metabolic rate ≅ 70% EE



Activity ≅ 20% EE



Adaptive thermo ≅ 10% EE

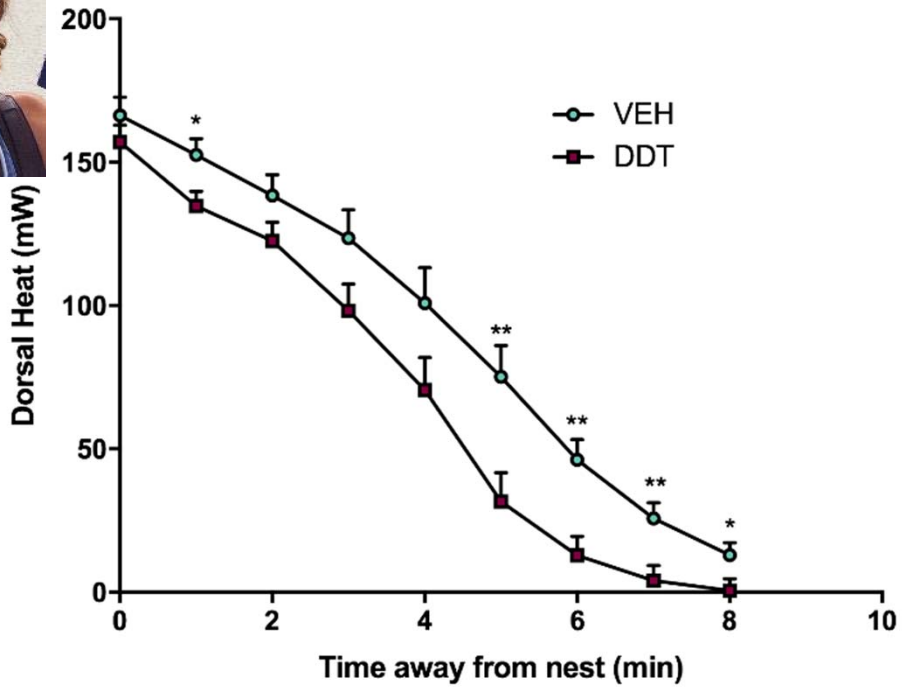


La Merrill et al PLOS ONE 2014

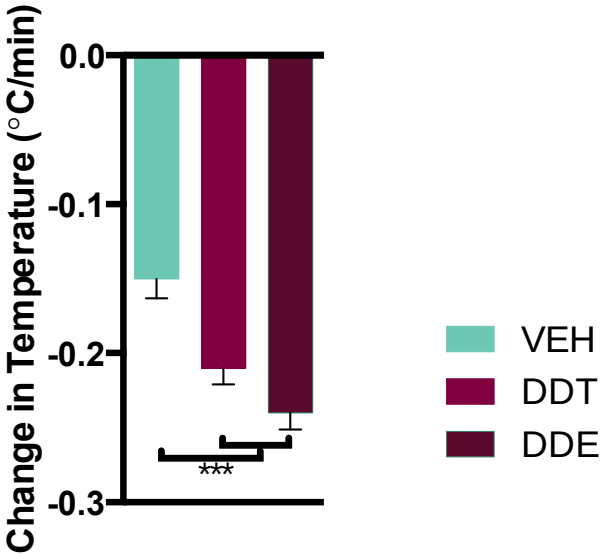
Is reduced adaptive thermogenesis in adult mice initiated in early life?

Perinatal DDT & DDE
impair response to cold in neonatal mice

Postnatal day 5



Postnatal day 12

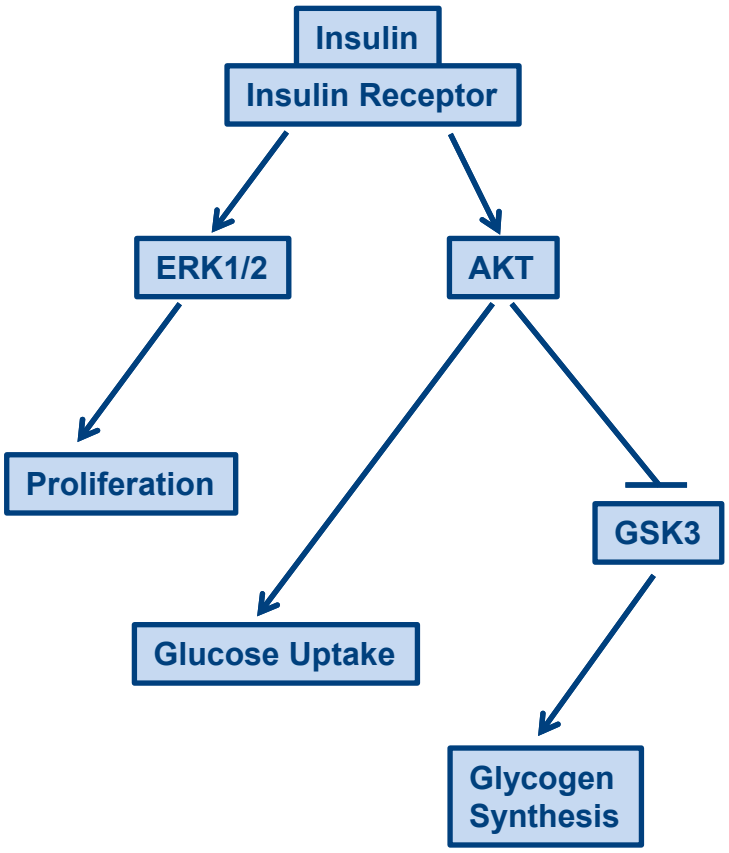


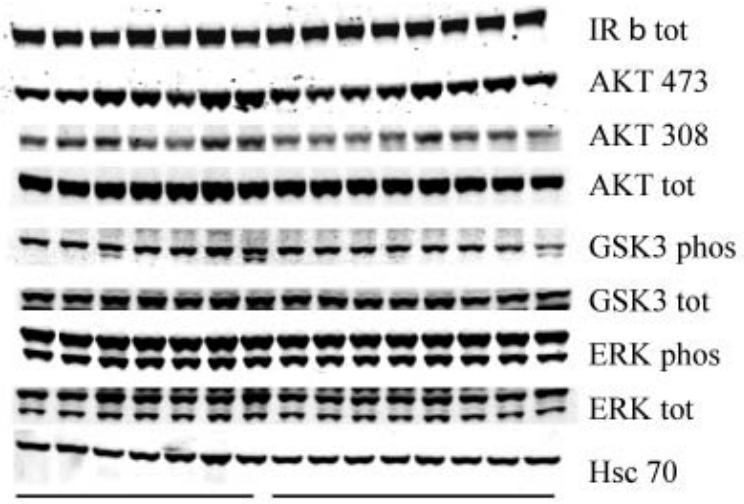
DDT and DDE Key Characteristics

EDC Characteristic	Mechanistic evidence for BPA
1. Interacts with or activates hormone receptors	DDT, and to a lesser extent DDE, activates nuclear ERs in a variety of species and tissues. DDT binds to the transmembrane domain of FSHR.
2. Antagonizes hormone receptors	DDE competitively antagonizes androgen receptor.
3. Alters hormone receptor expression	**DDT prevents the internalization of TSHR.**
4. Alters signal transduction in hormone responsive cells	**DDT and DDE reduce insulin signaling in mouse liver and adipocytes**. DDT enhances cAMP production through FSHR.
5. Induces epigenetic modifications in hormone producing or responsive cells	**DDT and DDE modify DNA methylation of mice and humans in the insulin signaling, insulin resistance, type 2 diabetes mellitus, and thermogenesis KEGG pathways.** DDT and DDE alter hypothalamic *Dnmt1* expression in rats.

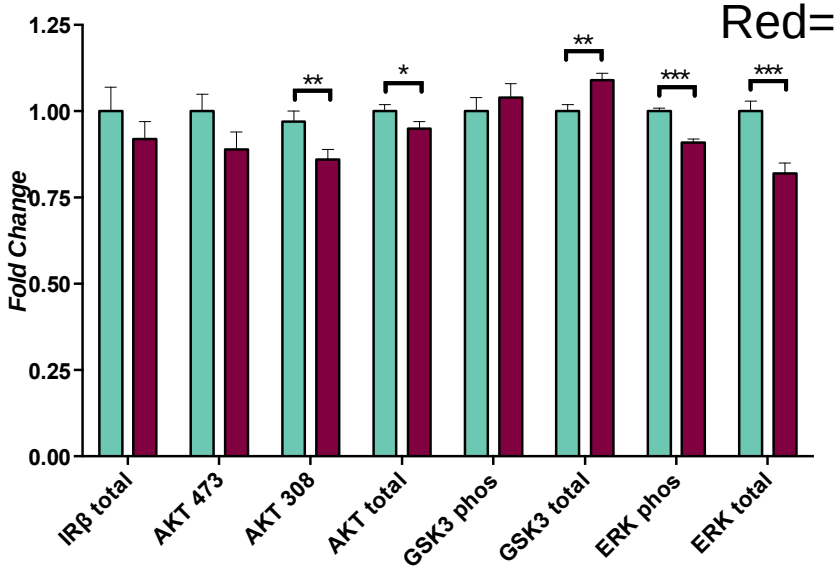
Bold, supports human and other animal diabesogen phenotypes

KC4. Impaired insulin signaling by DDT



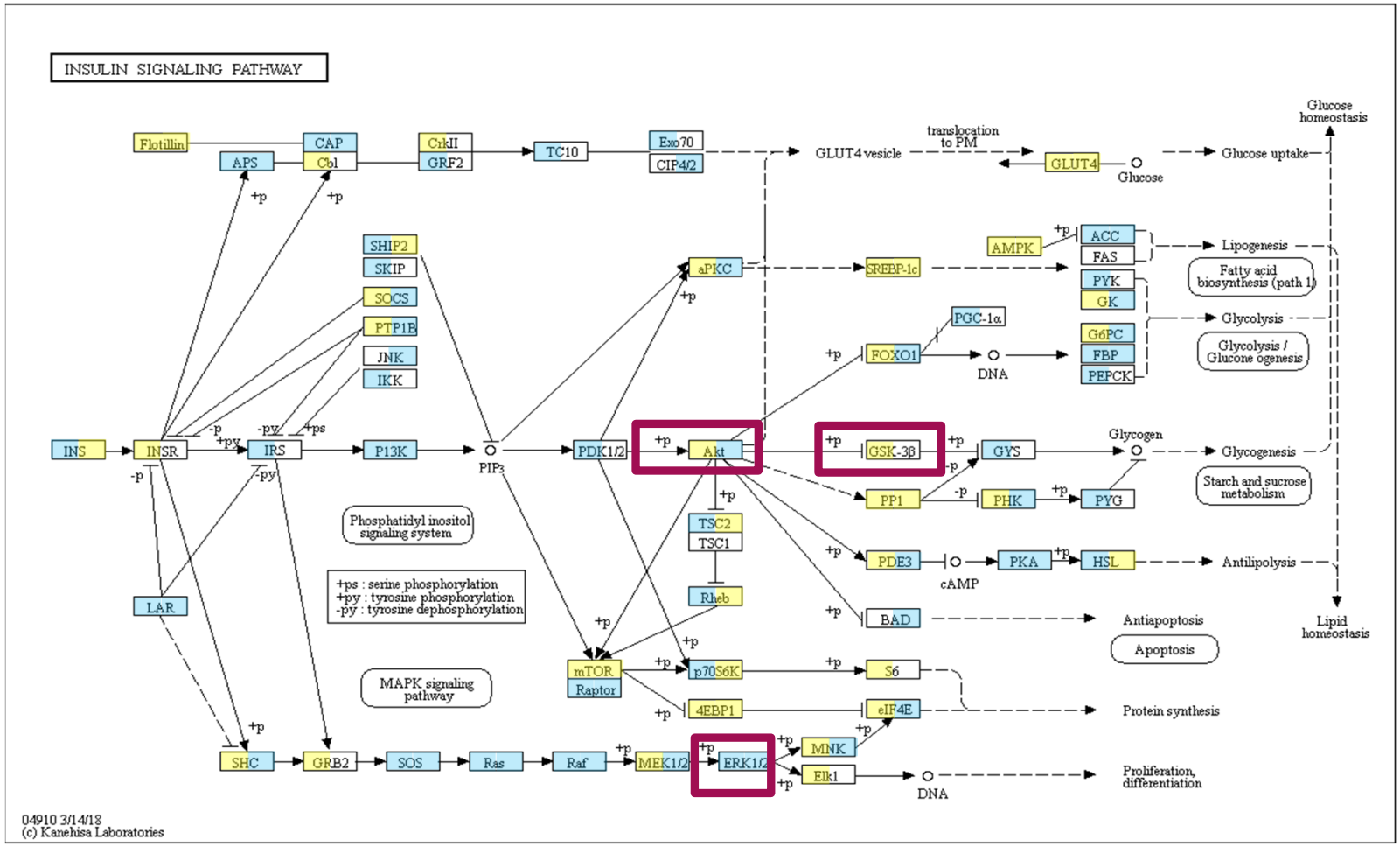


Teal=VEH
Red=DDT



La Merrill et al. 2014

KC5. Insulin signaling enriched with DMR in blood from humans and mice

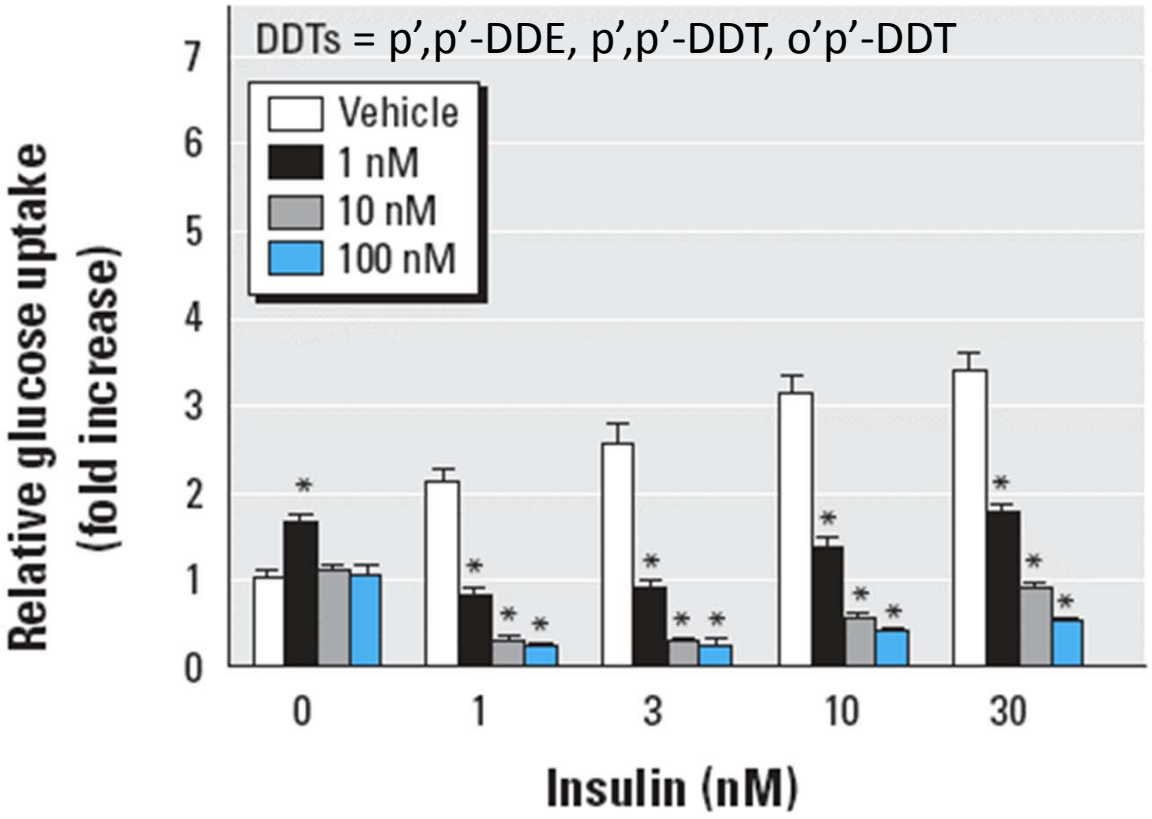


Left half of gene boxes = DMR in infant mouse blood

Right half of gene boxes = DMR in adult human blood

Increased (blue) or decreased (yellow) DNA-CH_3 in exposed mammal

KC4. DDTs decrease insulin stimulated glucose uptake by adipocytes



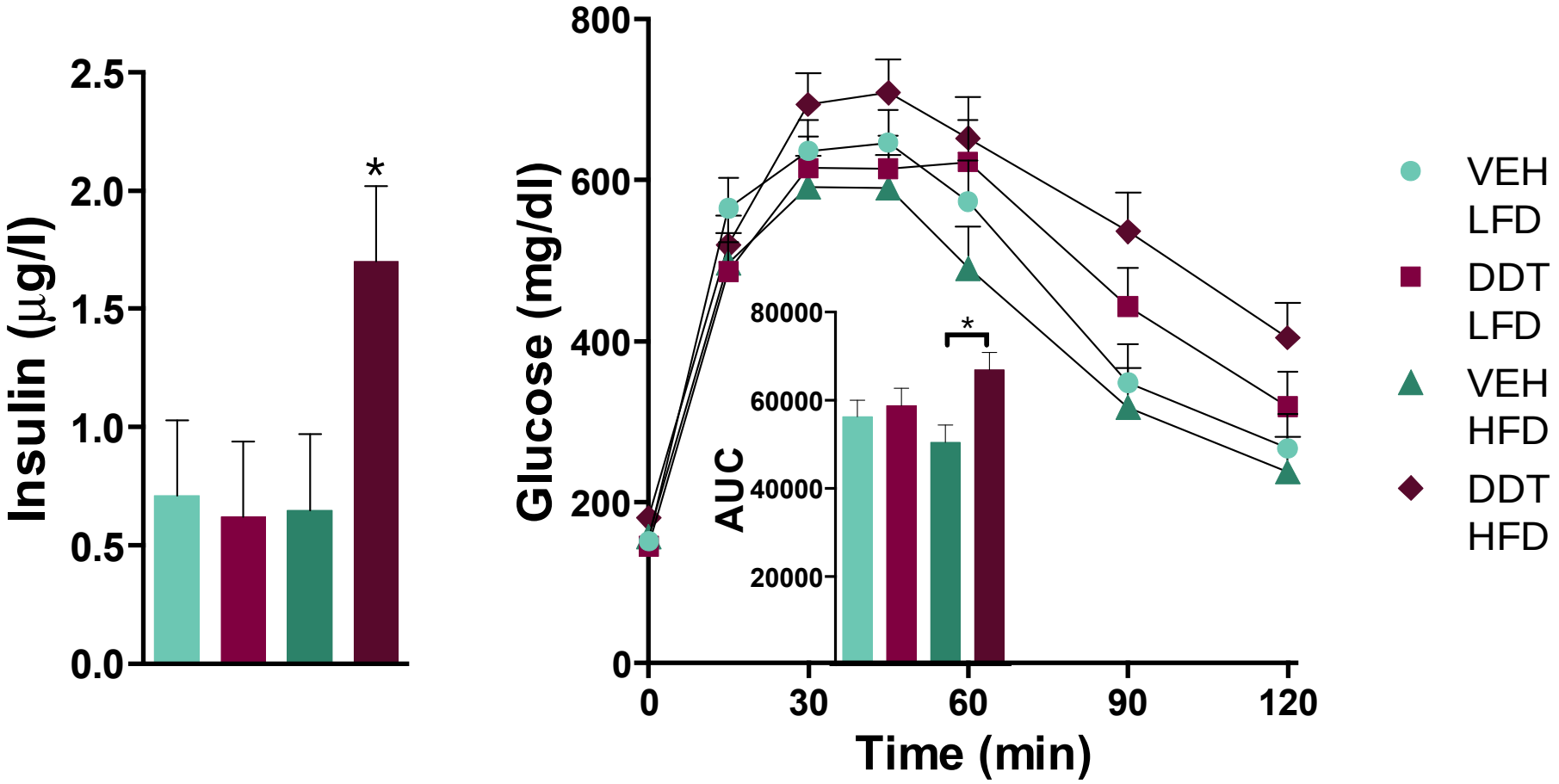
Ruzzin et al. 2010

DDT and DDE Key Characteristics

EDC Characteristic	Mechanistic evidence for BPA
6. Alters hormone synthesis	**DDT and DDE increase hepatic PC, PEPCK, FDPase, G6Pase in rats. DDT and DDE decrease *Dio2* expression in mouse brown fat.**
7. Alters hormone transport across cell membranes	**DDT and DDE reduce glucose stimulated insulin secretion.** Passive secretion of corticosterone from rodent adrenal glands is reduced by low dose DDE.
8. Alters hormone distribution or circulating hormone levels	**DDT and DDE increase circulating insulin levels in mice.** DDE increases serum LH and FSH in mice.
9. Alters hormone metabolism or clearance	DDT and DDE increase hepatic E2 hydroxylation and methylation, as well as o-methylase activity, in rats. DDT and DDE increase testosterone metabolism in rats.
10. Alters fate of hormone producing or responsive cells	**DDT and DDE increase liver fat and total mass in rodents and non-human primates.**

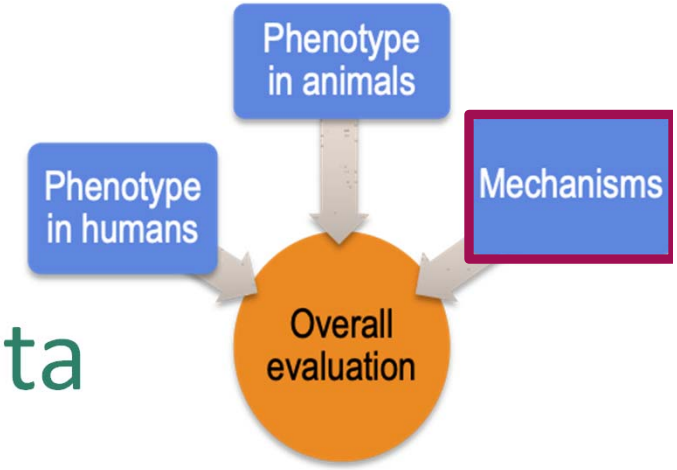
Bold, supports human and other animal diabesogen phenotypes

KC8. Mice with DDT and DDE exposure have increased levels of circulating insulin



La Merrill et al PLOS ONE 2014; unrestrained excursion also seen in Yau & Mennear, Toxicol & App Pharm 1977

KCs in data integration: DDT & DDE mechanistic data



- There are 10,000s of mechanistic scientific papers on DDT and DDE that provide substantial evidence for all of the 10 KCs.
- DDT and/or DDE
  - Prevent the internalization of TSHR and reduces the expression of *Dio2* in brown adipose tissue
  - Alter DNA methylation in the insulin signaling and T2D pathways
  - Increase circulating insulin levels
  - DDT impairs insulin signaling
- These mechanistic studies identified by the KCs approach are consistent with obesity, reduced energy expenditure, and T2D

Impaired thermogenesis is a common theme among diabesogens

Risk factor	Effect on obesity risk	Effect on T2D risk	Thermogenesis Status
PERINATAL DDT OR DDE	Positive effect	Positive effect	Impaired
CLOZAPINE AND SIMILAR DRUGS	Positive effect	Positive effect	Impaired
A GENE CALLED FTO (Intronic SNP)	Positive effect	Positive effect	Impaired
PRENATAL TOBACCO	Positive effect	Positive effect	Impaired

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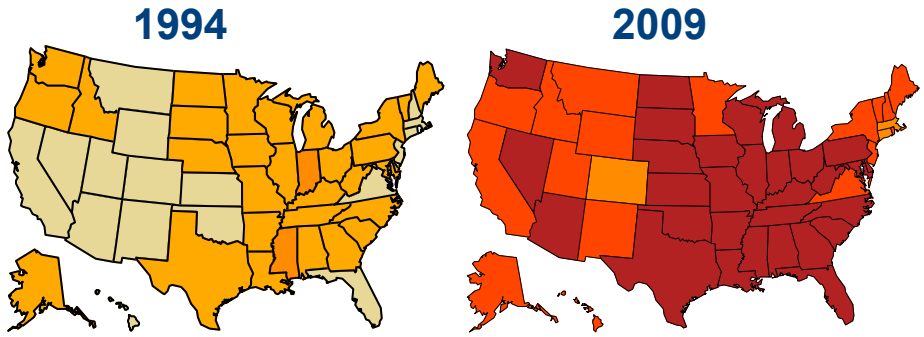
ONES R01 ES024946
P30 ES023513

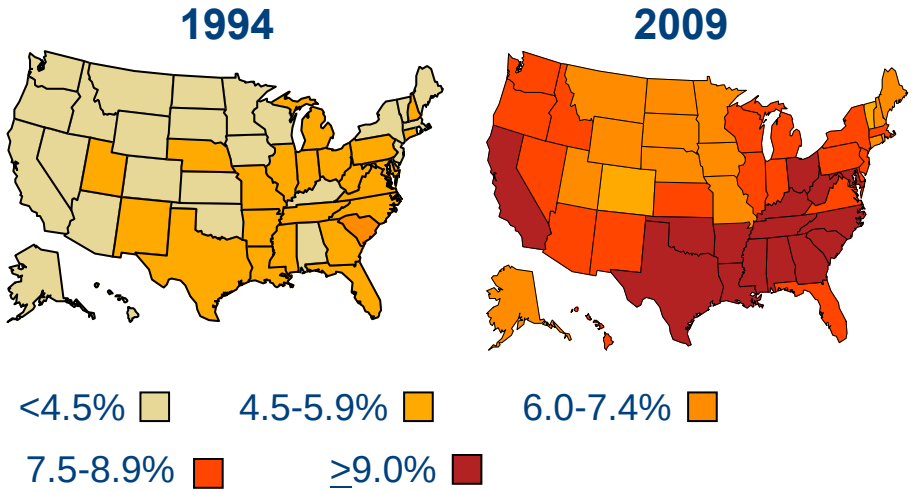
Rachel Carson; Photographer: Alfred Eisenstaedt; National Portrait Gallery, Smithsonian Institution

Widespread Insulin Resistance

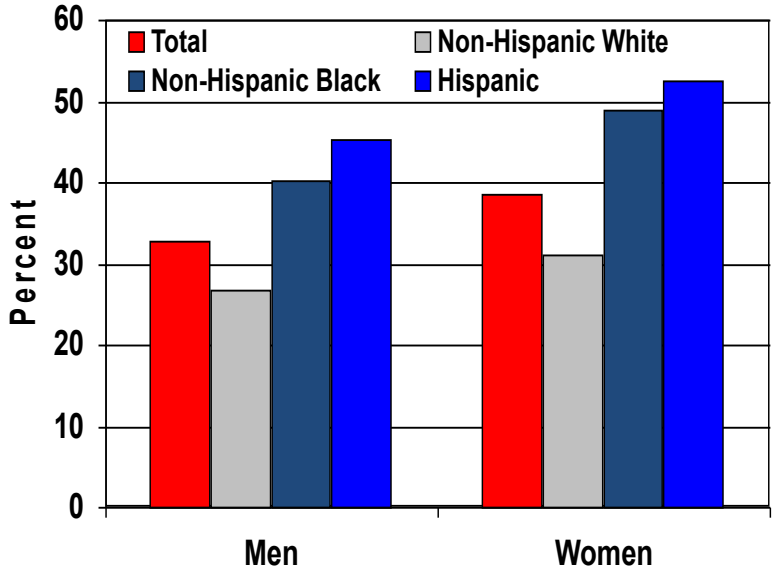
Age-adjusted Percent of Obese Adults



Age-adjusted Percent of Diabetic Adults



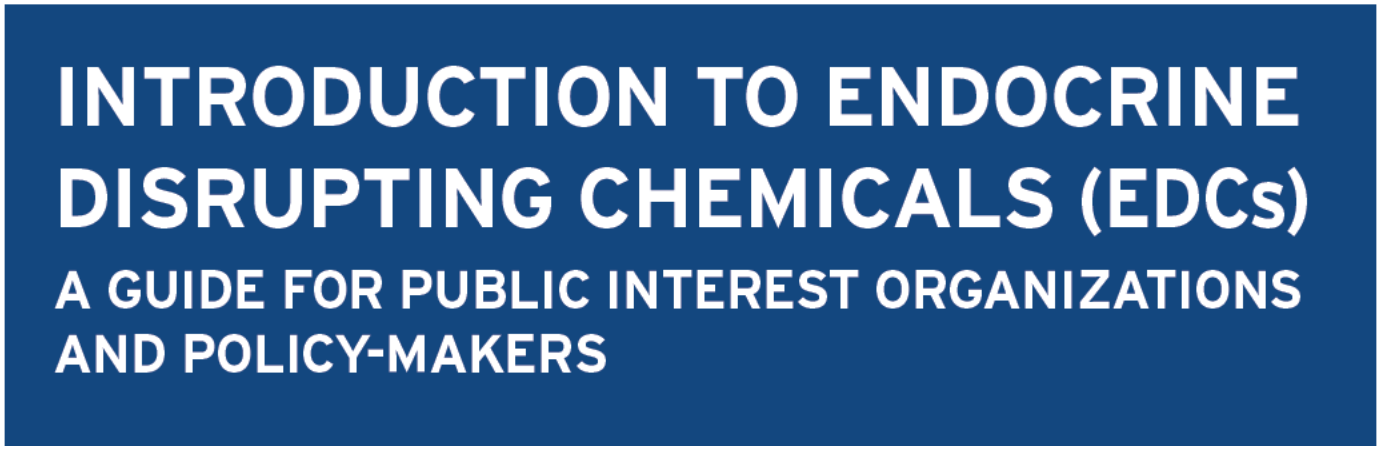
Lifetime risk of developing diabetes for individuals born in the US in 2000



Ogden 2010 & 2012, CDC's Division of Diabetes Translation. National Diabetes Surveillance System

How you can be involved

- Educate your local organizations and policy-makers about the importance of EDCs
  - Intro to EDC Guide is available in six languages
    - English, Spanish, French, Russian, Arabic and Portuguese
    - https://www.endocrine.org/topics/edc/introduction-to-edcs
  - Need to take action
    - Guideline assays (OECD, USEPA) only cover KCs 1, 2, and 6



Strategic **A**pproach to **I**nternational **C**hemicals **M**anagement (**SAICM**)

- **SAICM** is a policy framework to promote chemical safety around the world
- hosted by the United Nations Environment Programme
- Endocrine Society collaborated with non-profit organization IPEN to
  - educate conference attendees about EDCs,
    - Give out copies of the **Guide** to educate representatives about the importance of EDCs and the need to take action
  - draft and revise the text, and
  - build support for the resolution.
    - Over 120 governments

https://endocrinenews.endocrine.org/endocrine-society-influences-edc-policy-around-the-world/

Considering *Cause*: DDT and DDE as presumed obesogens

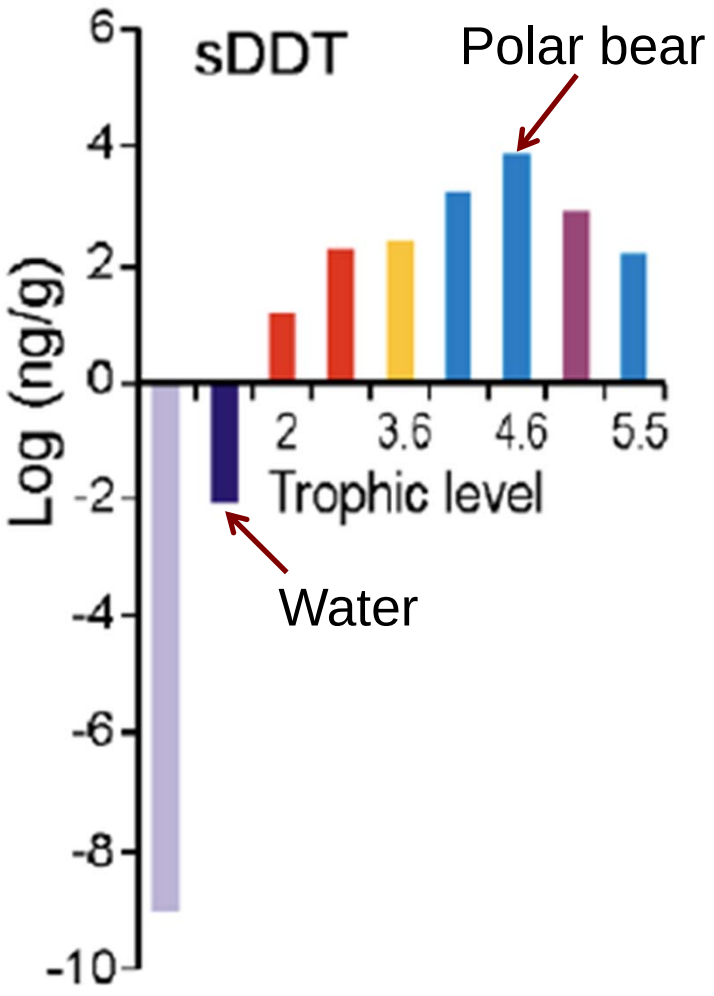
Conclusions: We classified *p,p′*-DDT and *p,p′*-DDE as "presumed" to be obesogenic for humans, based on a moderate level of primary human evidence, a moderate level of primary *in vivo* evidence, and a moderate level of supporting evidence from *in vivo* and *in vitro* studies. https://doi.org/10.1289/EHP527

Hill's Causal Considerations	Evidence
Strength:	Effect size modest
Consistency & Coherence:	Obesity consistent across at least 3 mammalian species
Specificity:	DDT and DDE have been isolated in affirmative cell culture and in rodent experiments
Temporality:	DDT/E ->impaired thermogenesis -> obesity
Biological Gradient:	DDT dose dep. decrease in bAR response and expression; DDE dose dep. decrease in uncoupled respiration
Plausibility:	Extensive: thermogenesis-EE-obesity experimentally & in humans; Extensive: DDE-obesity in humans; Few: DDT-obesity experimentally & in humans; Some: DDT/E-thermogenesis-EE experimentally & in humans
Experimental Reversibility	Extensive: thermogenesis-EE-obesity experimentally Some: DDE-thermogenesis with CL316,243 Non-existent: DDT/E-thermogenesis-EE-obesity experimentally
Analogy	Extensive: genetic/pharmaceutical/developmental exposure-SNS-thermogenesis-EE-obesity links

Melting Glaciers are a Source of DDTs

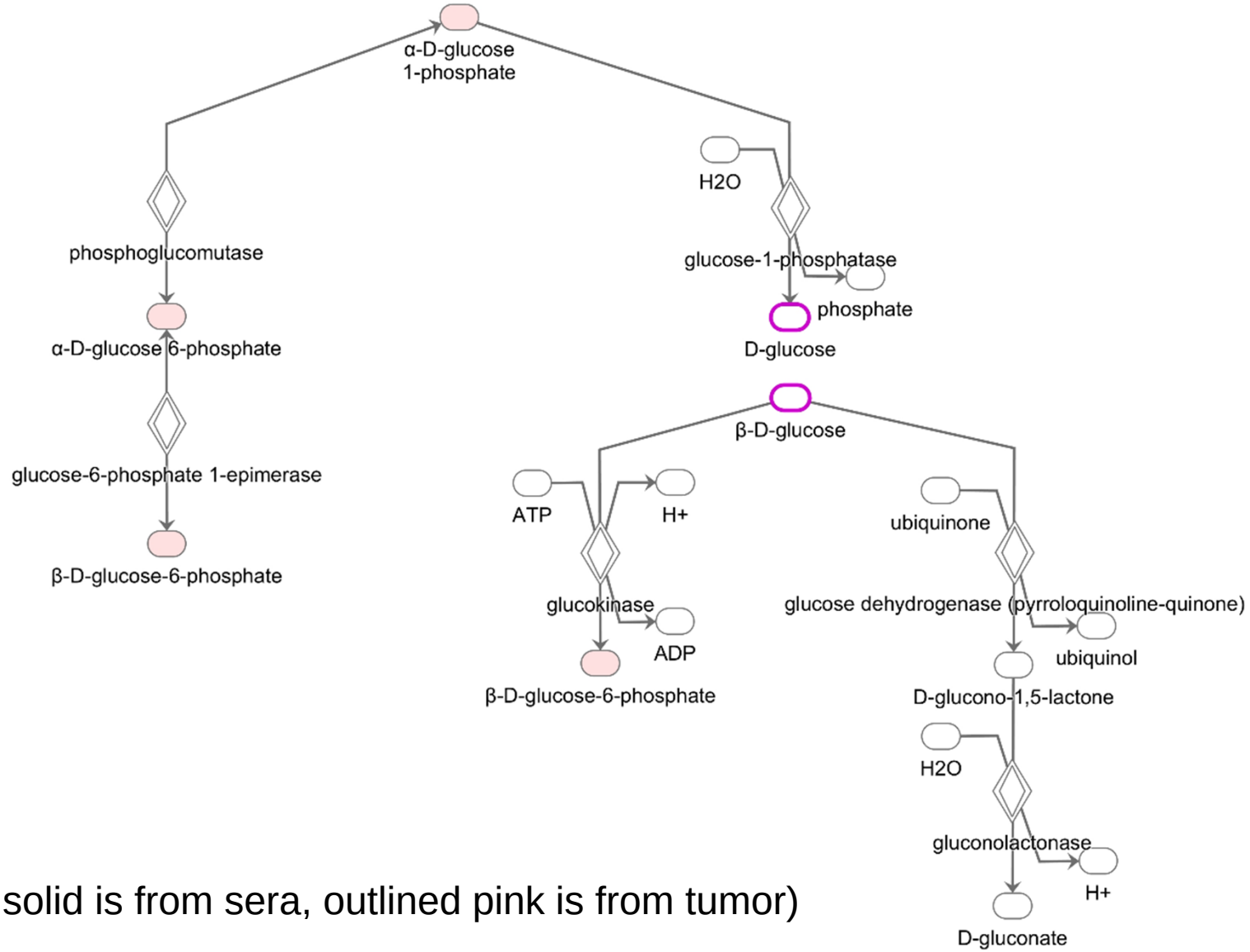
- Semi-volatile
  - Long range atmospheric transport
  - Accumulate in cold regions
  - 46% of DDTs Canadian Archipelago from melting glaciers

Compound	Concentration (pg/L)	Total glacial input (kg)	Glacial input for 1993 (kg/year)
α–HCH[b]	256	205	39
γ-HCH[b]	115	92	18
ΣDDT[b]	480	384	74
CHLOR[b]	35	28	5
HCB[b]	65	52	10
PCB[c]	3.5	2.8	0.5



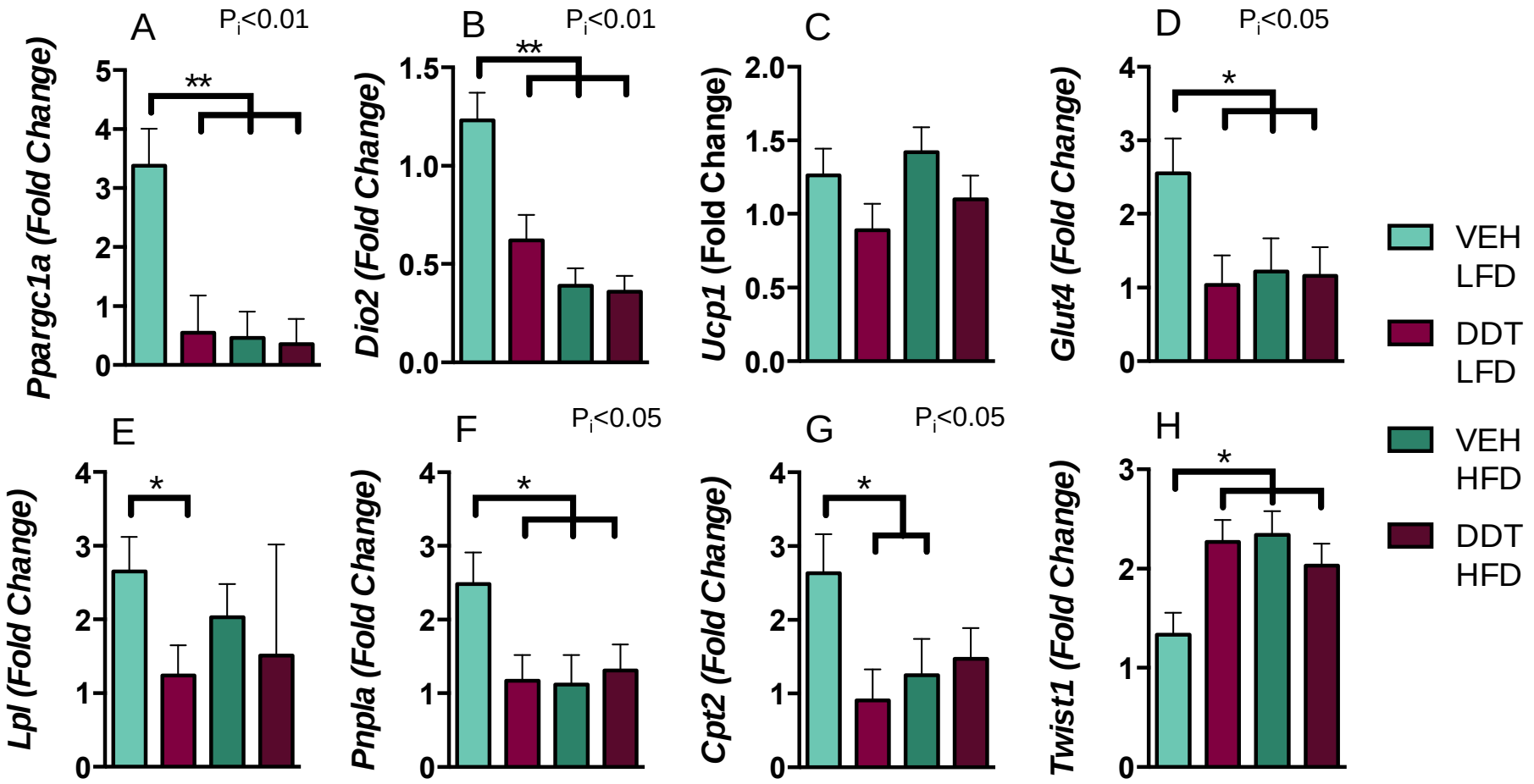
Macdonald 2005, Blais 2001

Glucose metabolism is associated with DDT in mouse serum and mammary tumors as well



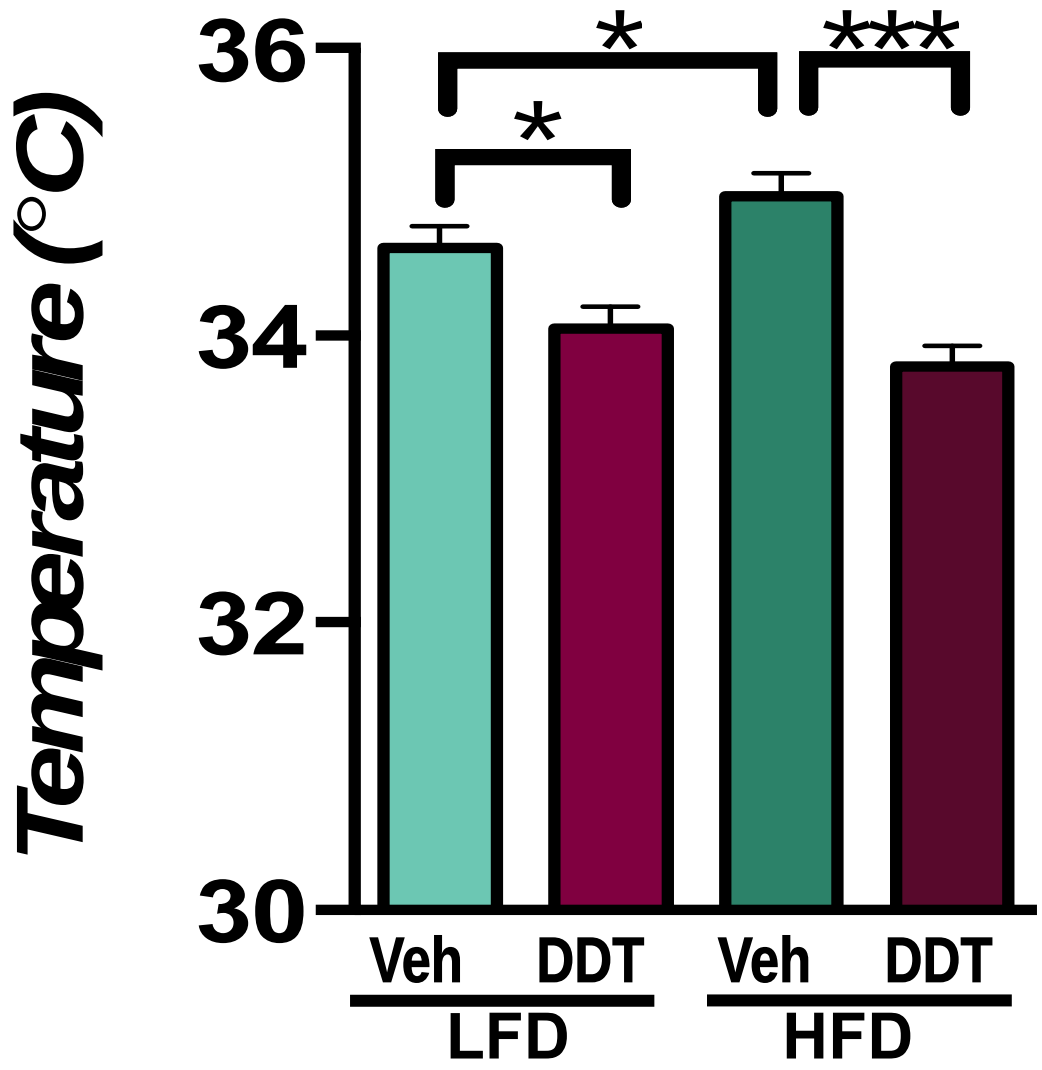
(pink solid is from sera, outlined pink is from tumor)

HFD Attenuates the Depressive Effect of Perinatal DDT on BAT Thermogenesis & Substrate Utilization in 9 mo old mice



La Merrill et al 2014

High Fat Diet Increases Susceptibility to the Effects of Perinatal DDT on Thermogenesis



P_i=0.01

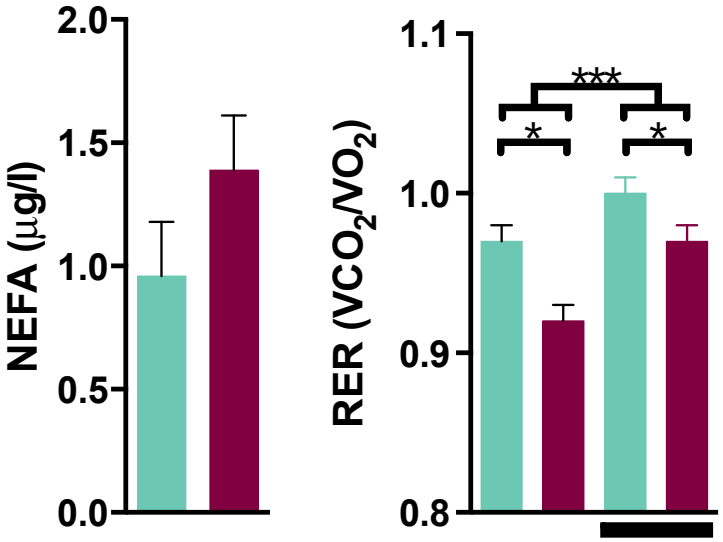
Size of perinatal DDT effect In 9 month old mice:

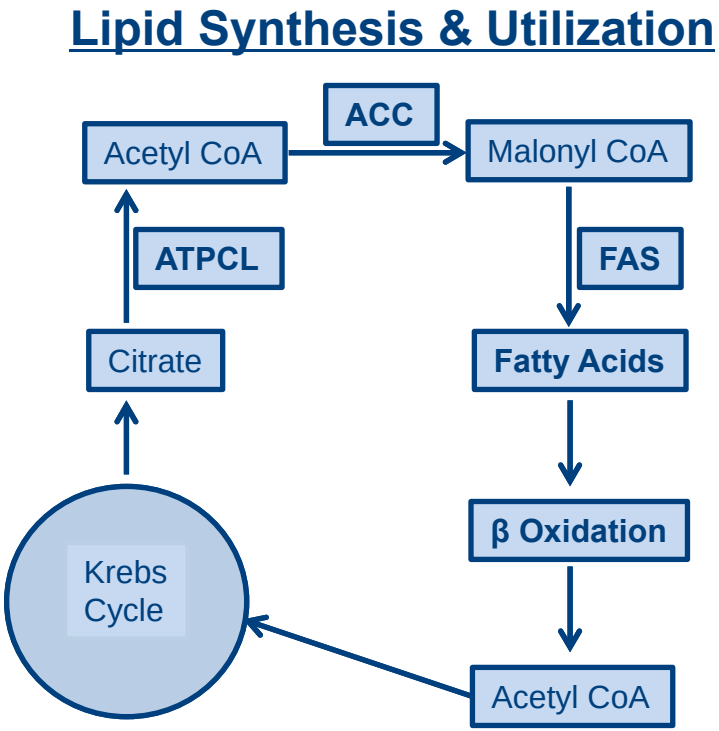
Low fat diet fed mice 0.56° C lower with DDT

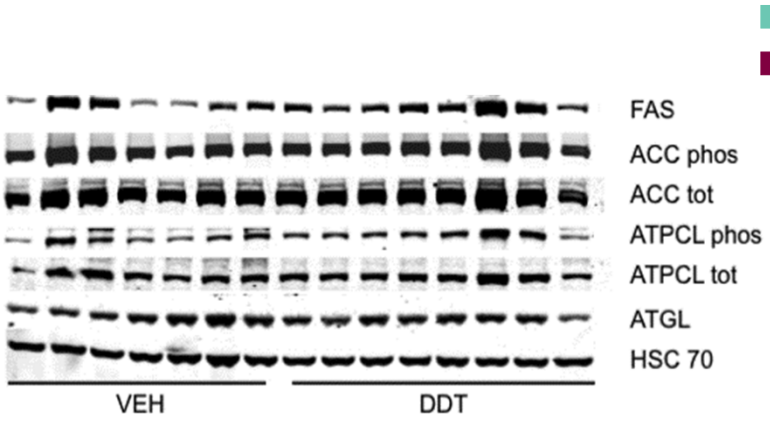
High fat diet fed mice 1.19° C lower with DDT

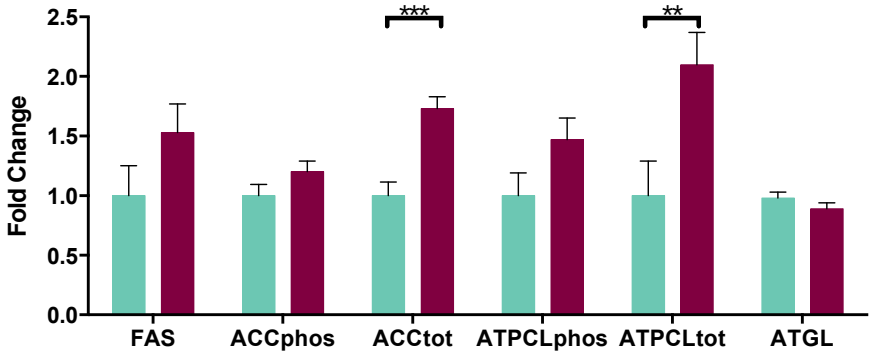
La Merrill et al 2014

Perinatal DDT Increases Lipid Utilization









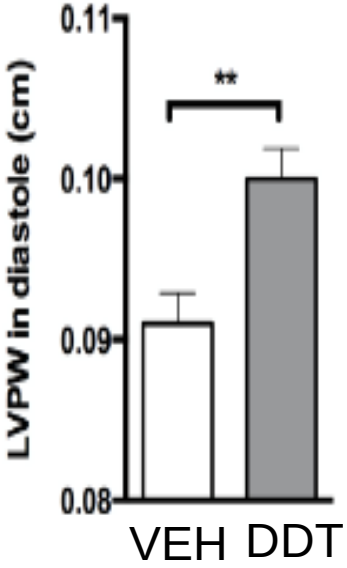
La Merrill et al 2014

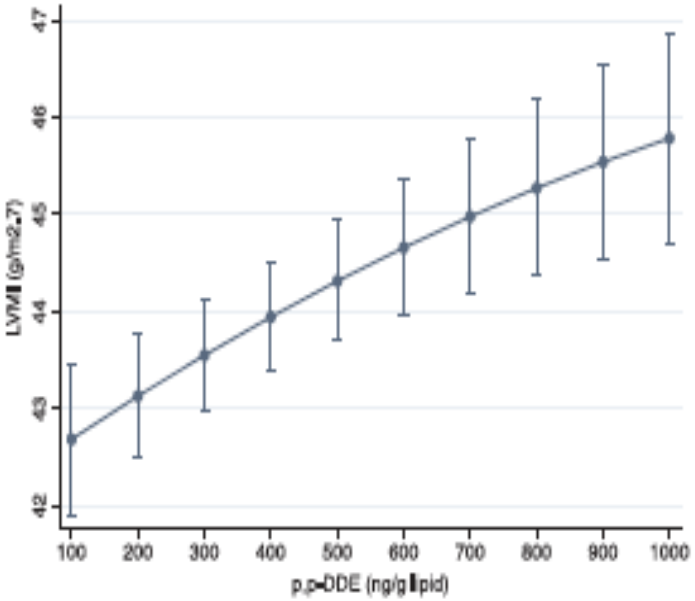
Lipid utilization a common theme in human sera metabolome too

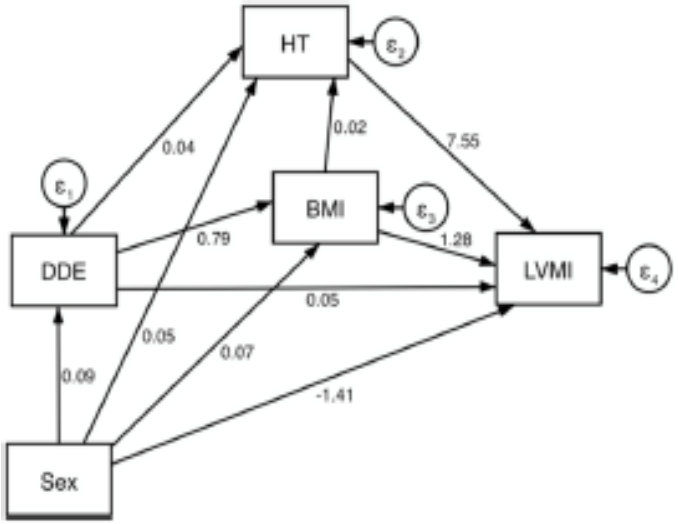
Metabolic pathways	opDDT pval	ppDDT pval	ppDDE pval	ppDDT:ppDDE pval
Carnitine shuttle	0.0006	0.3832	0.0306	0.0729
Linoleate metabolism	**0.0006**	**0.0191**	**0.0004**	0.0003
Drug metabolism - other enzymes	0.0015	0.1978	0.0009	0.0166
Arginine and Proline Metabolism	0.0020	0.0221	0.0621	0.2129
Glycosphingolipid metabolism	**0.0024**	**0.0431**	**0.0113**	0.0003
Lysine metabolism	**0.0075**	**0.0072**	**0.0039**	0.0065
Omega-3 fatty acid metabolism	0.0124	1.0000	0.0029	0.0077
Fatty Acid Metabolism	0.0131	0.1107	0.0005	0.0026
Fatty acid activation	**0.0253**	**0.0257**	**0.0007**	0.0021
Aspartate and asparagine metabolism	0.0306	0.0020	0.2304	0.0286
Saturated fatty acids beta-oxidation	0.0321	1.0000	0.1387	0.0438
Urea cycle/amino group metabolism	0.0325	0.0006	0.2550	0.2104

Do any of these metabolic effects
actually matter
in terms of
chronic diseases
that kill people?

In PIVUS people and our mouse model, we have confirmed DDT and DDE increase LV cardiac mass in mice and people - mostly mediated by obesity







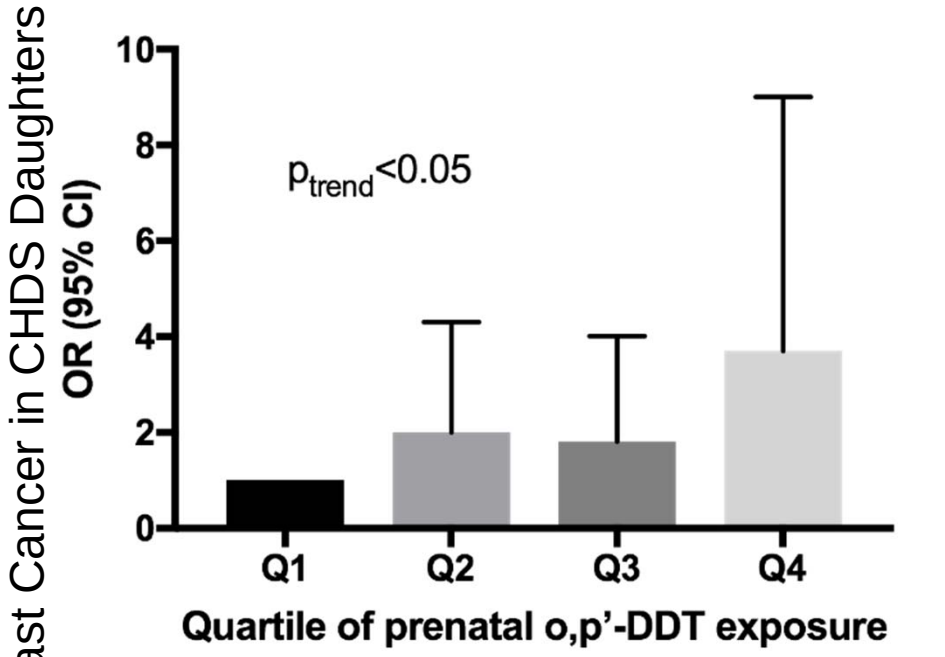
Prenatal DDT increases LV cardiac mass in adult mice.
La Merrill et al. EHP 2016

DDE exposure increase LV mass mostly mediated by obesity.
La Merrill et al. (PIVUS) Env Res 2017

In CHDS daughters and our mouse model, we have confirmed DDT increase breast cancer risk

Perhaps this is also mediated by obesity?

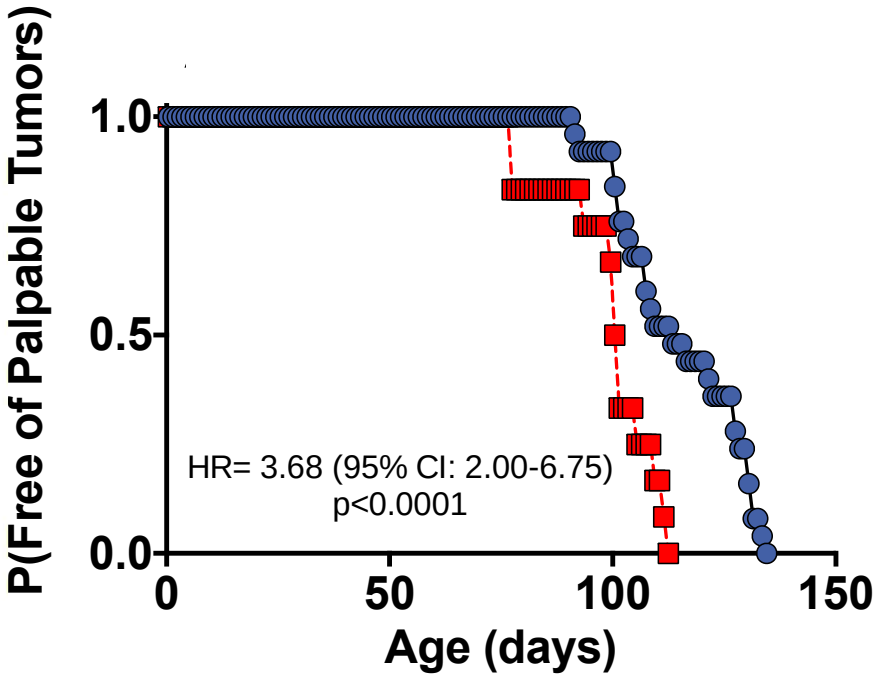
Reduced oxygen consumption could lead to
Warburg- like glycolysis in adipose aka ‘stroma’
(KC#10: Nutrient Supply; Hallmark: Deregulating cellular energetics)



DDT Exposure in Utero and Breast Cancer

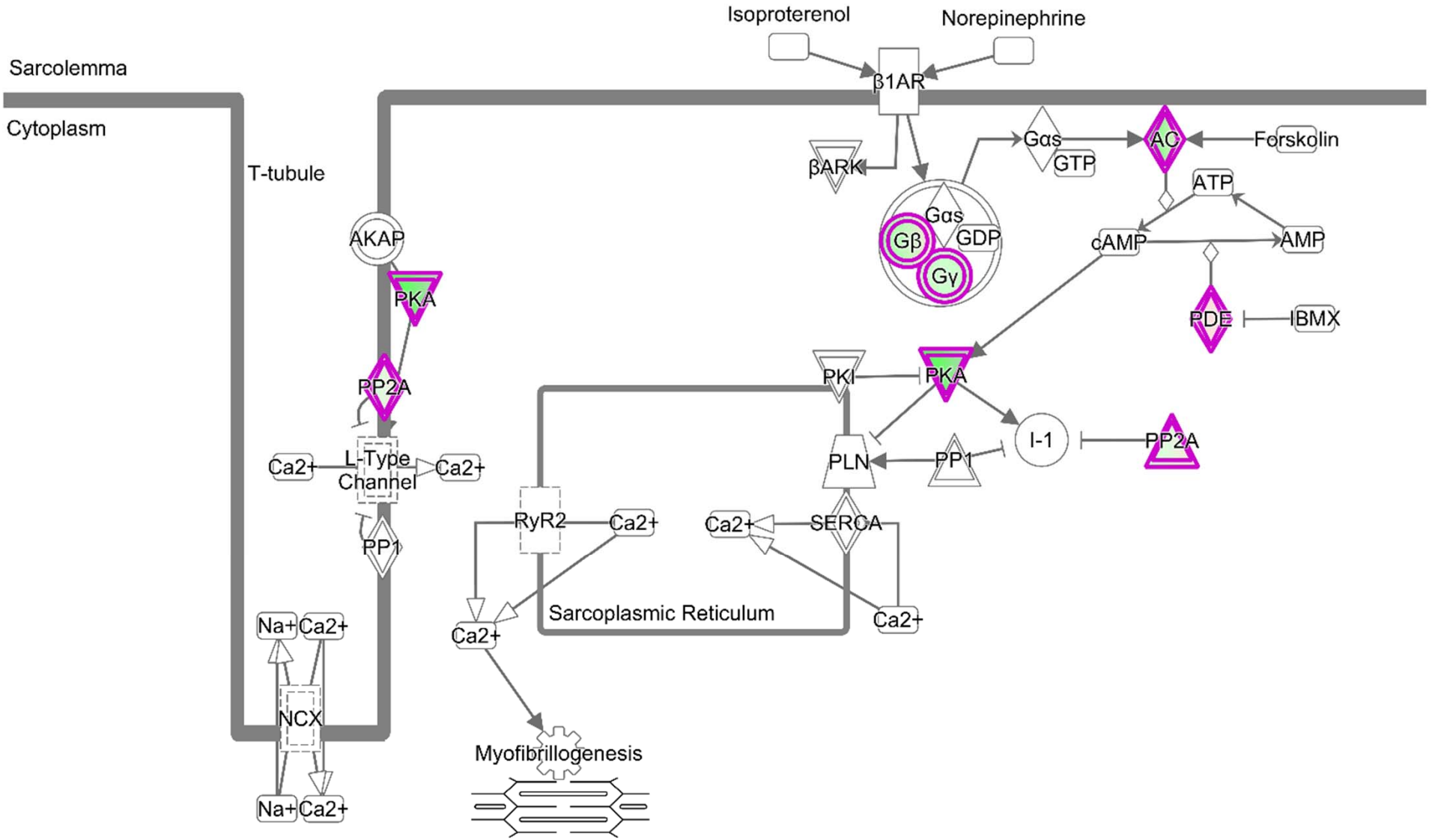
J Clin Endocrinol Metab doi: 10.1210/jc.2015-1841

Barbara A. Cohn, Michele La Merrill, Nickilou Y. Krigbaum, Gregory Yeh, June-Soo Park, Lauren Zimmermann, and Piera M. Cirillo

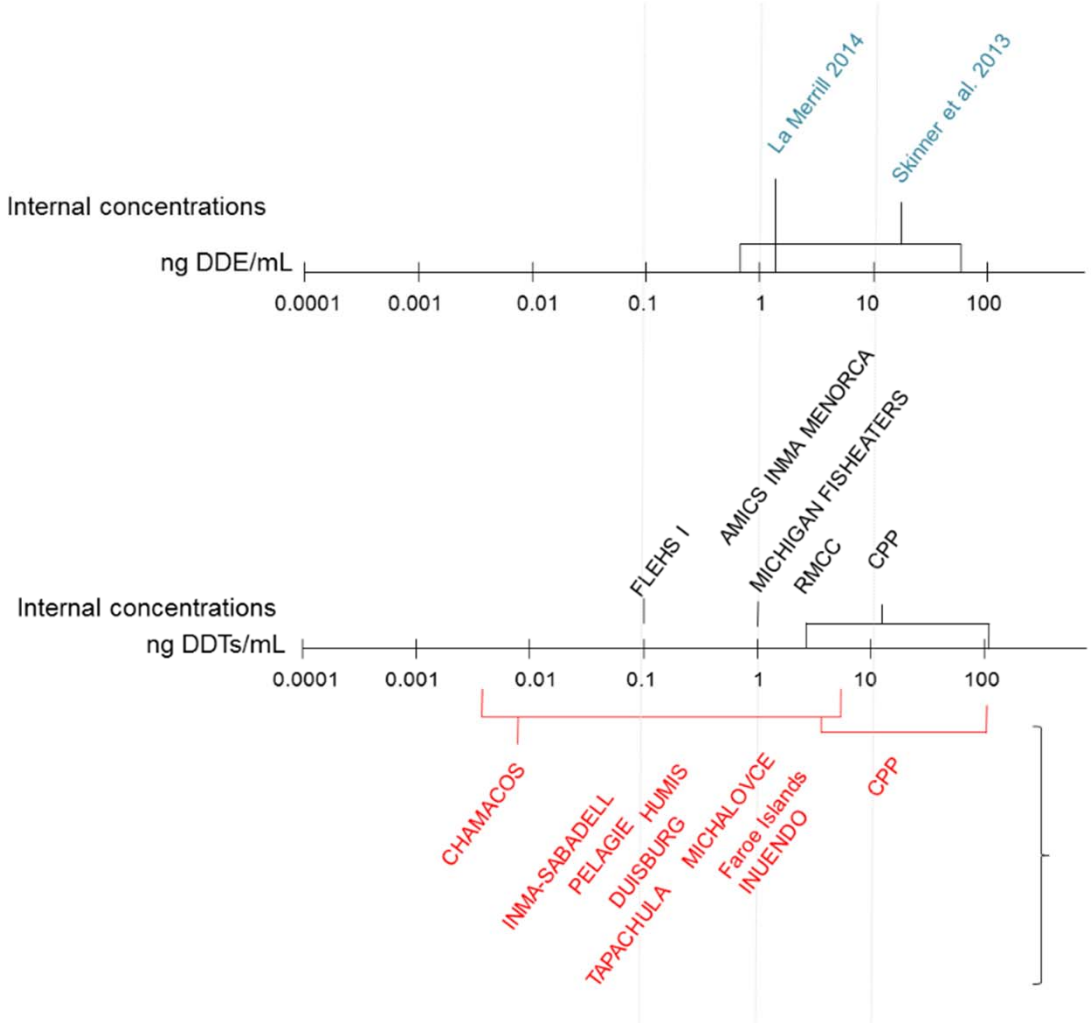


Unpublished mouse model
Ishikawa & La Merrill

B-AR canonical pathway from PIVUS and mouse blood DNA methylation



Supporting *in vivo* evidence: developmental low doses within the human DDE exposure range are also associated with obesity



Animal Studies, exposure levels wet weight

Human Studies, exposure levels wet weight

Human Studies, exposure levels lipid weight

Approached to ww using the factor 0.0077 Lopez-Cervantes 2004

Cano Sancho EHP 2017