LA GESTACIÓN COMO PERÍODO DE SUSCEPTIBILIDAD A LOS EFECTOS DE LOS DISRUPTORES ENDOCRINOS

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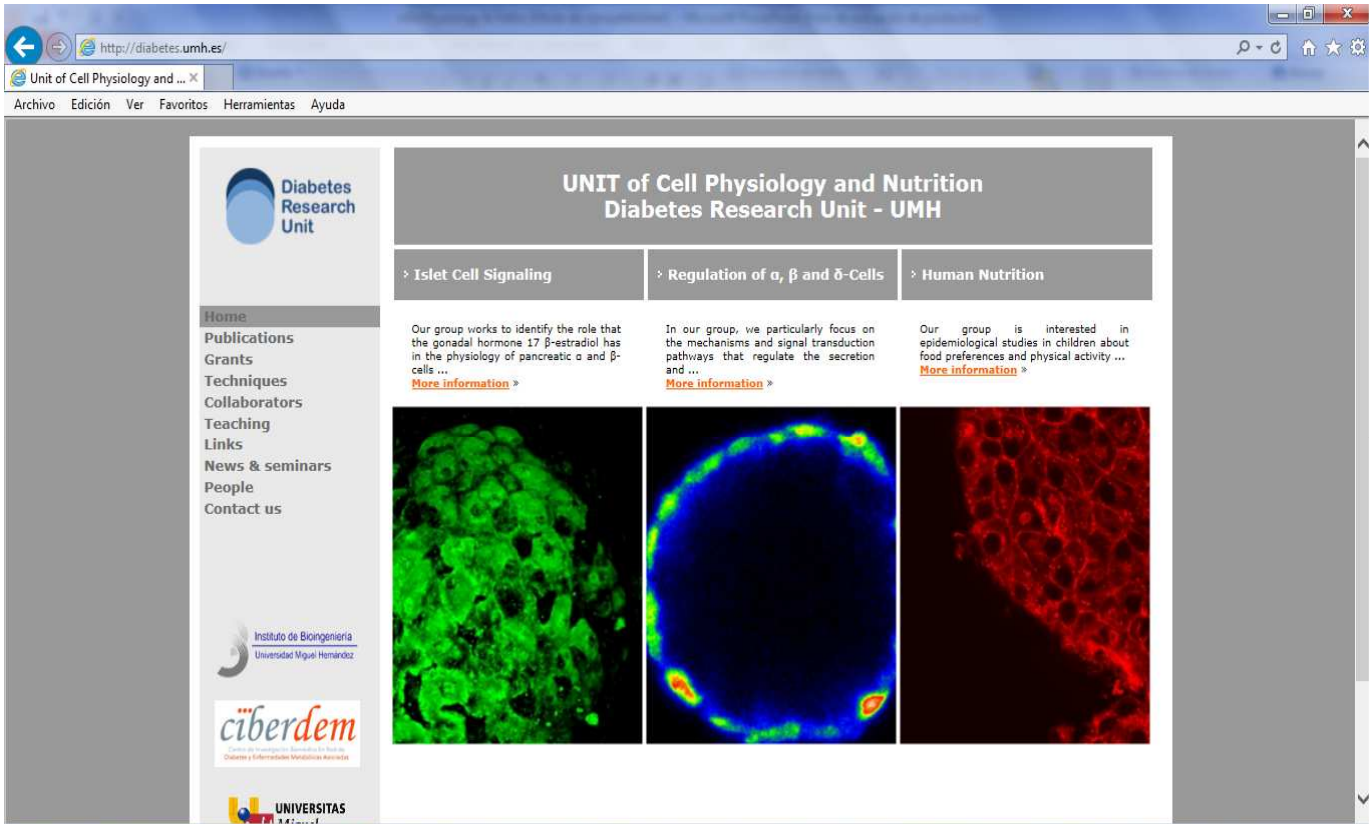
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Diabetes Research Unit
UNIT of Cell Physiology and Nutrition
Diabetes Research Unit - UMH
Islet Cell Signaling
Regulation of α, β and δ-Cells
Human Nutrition
Our group works to identify the role that the gonadal hormone 17 β-estradiol has in the physiology of pancreatic α and β-cells ...
More information »
In our group, we particularly focus on the mechanisms and signal transduction pathways that regulate the secretion and ...
More information »
Our group is interested in epidemiological studies in children about food preferences and physical activity ...
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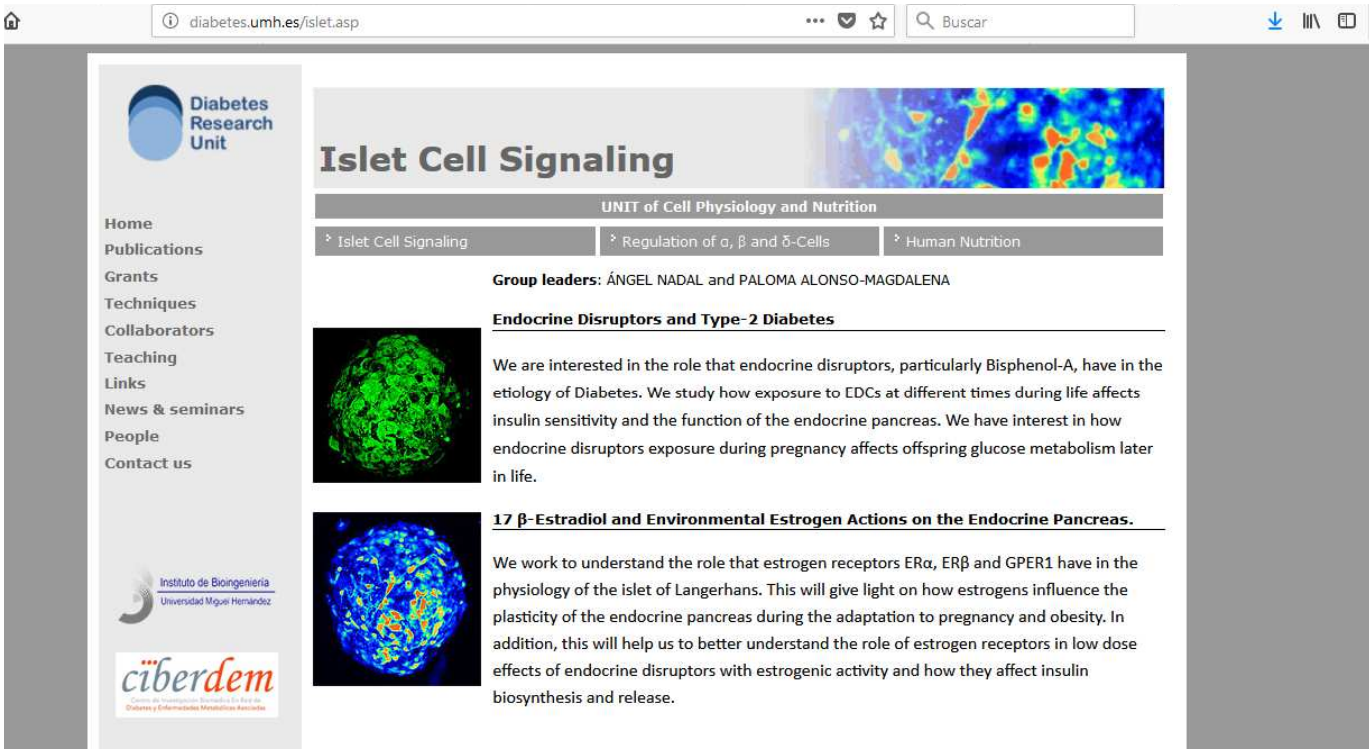
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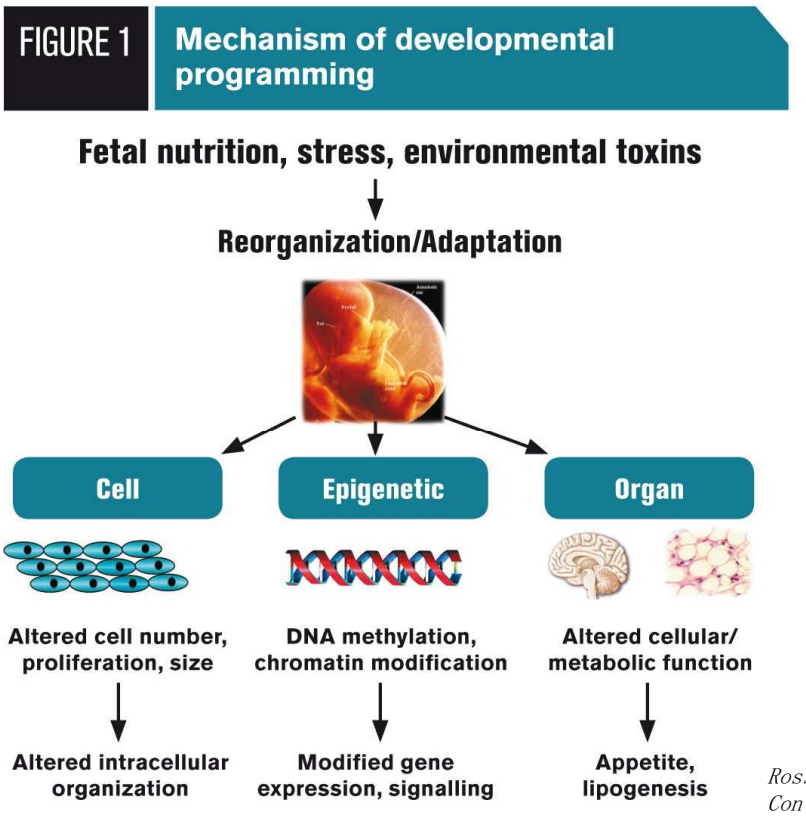
Islet Cell Signaling
Regulation of α, β and δ-Cells
Human Nutrition
Group leaders: ÁNGEL NADAL and PALOMA ALONSO-MAGDALENA
Endocrine Disruptors and Type-2 Diabetes
We are interested in the role that endocrine disruptors, particularly Bisphenol-A, have in the etiology of Diabetes. We study how exposure to EDCs at different times during life affects insulin sensitivity and the function of the endocrine pancreas. We have interest in how endocrine disruptors exposure during pregnancy affects offspring glucose metabolism later in life.
17 β-Estradiol and Environmental Estrogen Actions on the Endocrine Pancreas.
We work to understand the role that estrogen receptors ERα, ERβ and GPER1 have in the physiology of the islet of Langerhans. This will give light on how estrogens influence the plasticity of the endocrine pancreas during the adaptation to pregnancy and obesity. In addition, this will help us to better understand the role of estrogen receptors in low dose effects of endocrine disruptors with estrogenic activity and how they affect insulin biosynthesis and release.

THE STORY OF HOW A BAD START LASTS A LIFETIME……..

Developmental Origins of Health and Disease (DOHaD)

Fetal programming

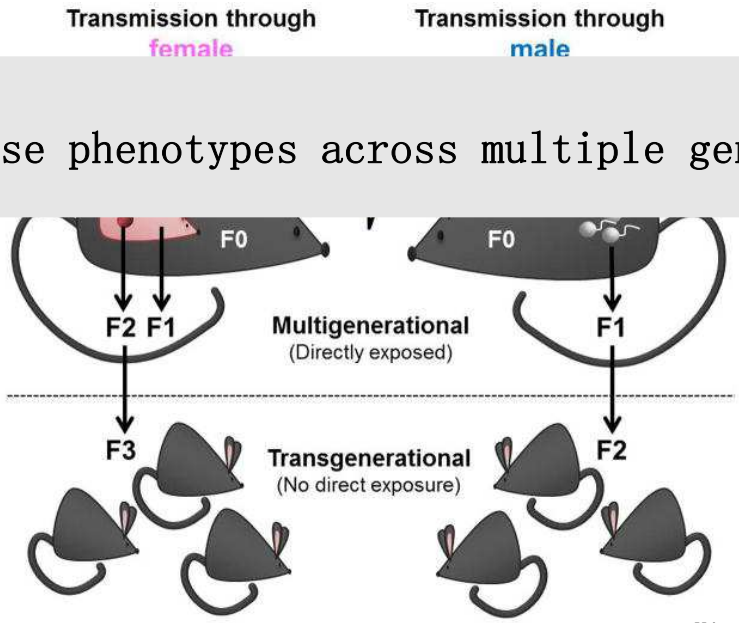
Why are there sensitive windows and persistent effects?



Ross MG and Desai M Contemporary OB/GYN

What is Transgenerational Inheritance?

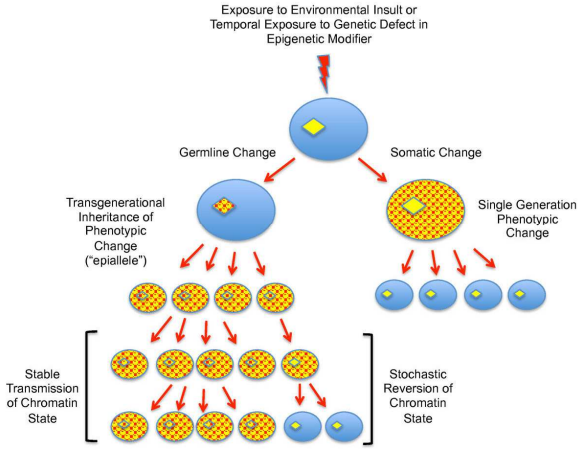
- Exposure occurs in the F0 generation
- Exposure stops-not continous, not across generations
- Health effect is evaluated in generation(s) not directly exposed



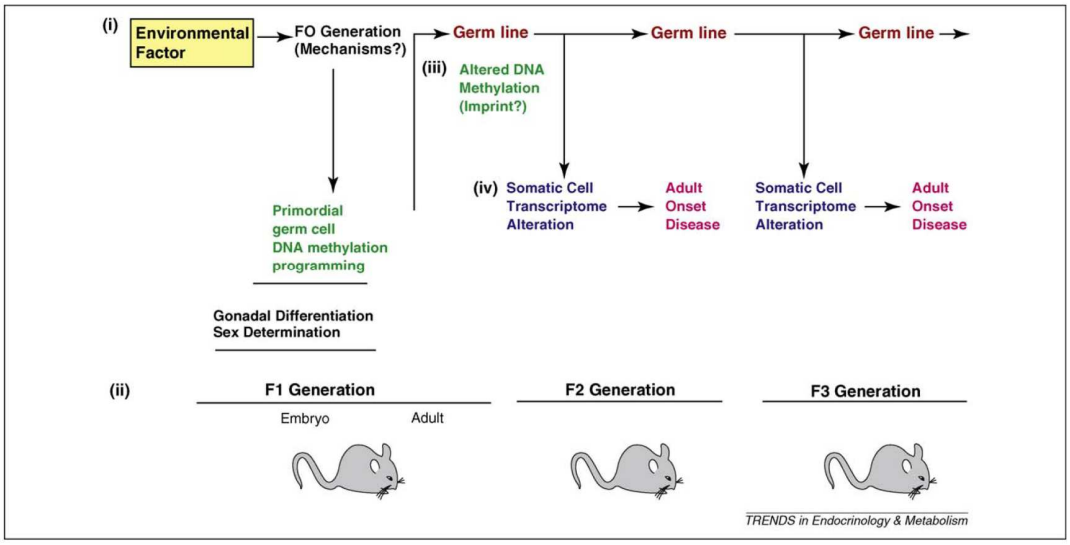
Adverse phenotypes across multiple generations!!!!

Xin et al, Semin. Cell Dev Biol 2015

How does it happen?



Kelly,
Epigenetics and Chromatin 2014



Skinner et al
TRENDS 2010

Development

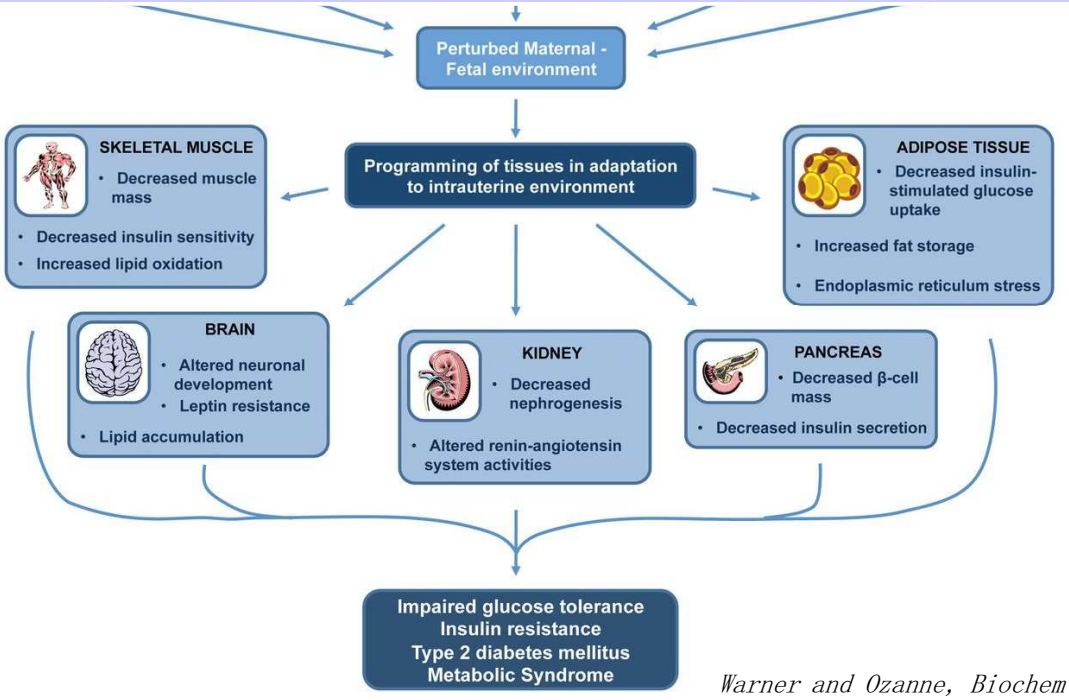
A sensitive time for environmental chemical exposures to alter programming that lasts a lifetime

We all carry a Chemical Body Burden

Every pregnant woman has a body burden of chemicals without her knowledge …with the potential of harm

PROGRAMMING OF METABOLIC DISORDERS

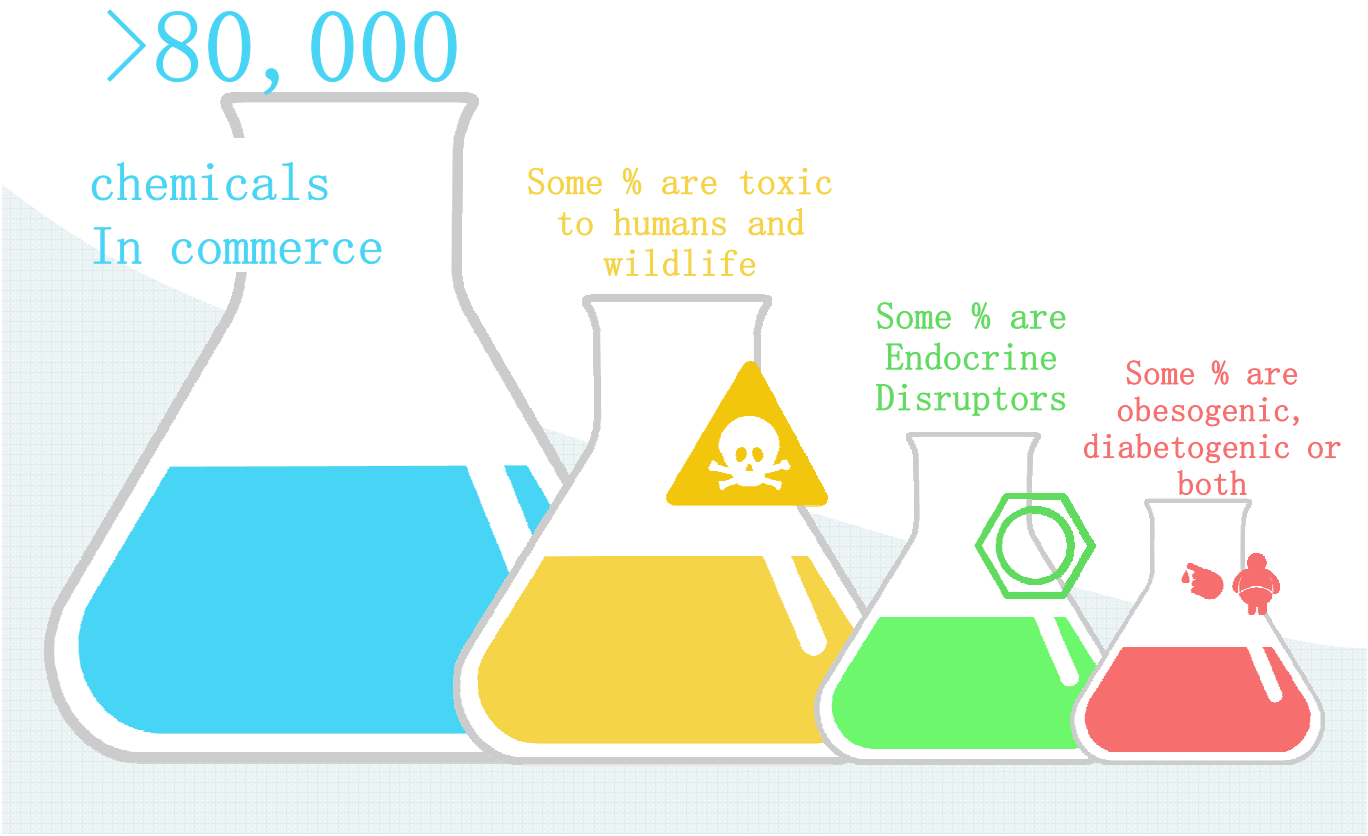
Endocrine Disruptors



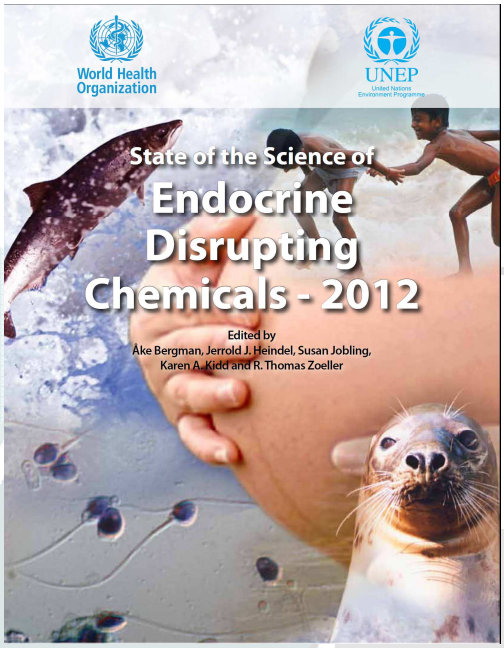
Warner and Ozanne, Biochem J 2010


Endocrine Disruptors
An endocrine disruptor is an exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action.
Zoeller et al, Endocrine Society Position Statement, Endocrinology 153: 4097–4110, 201

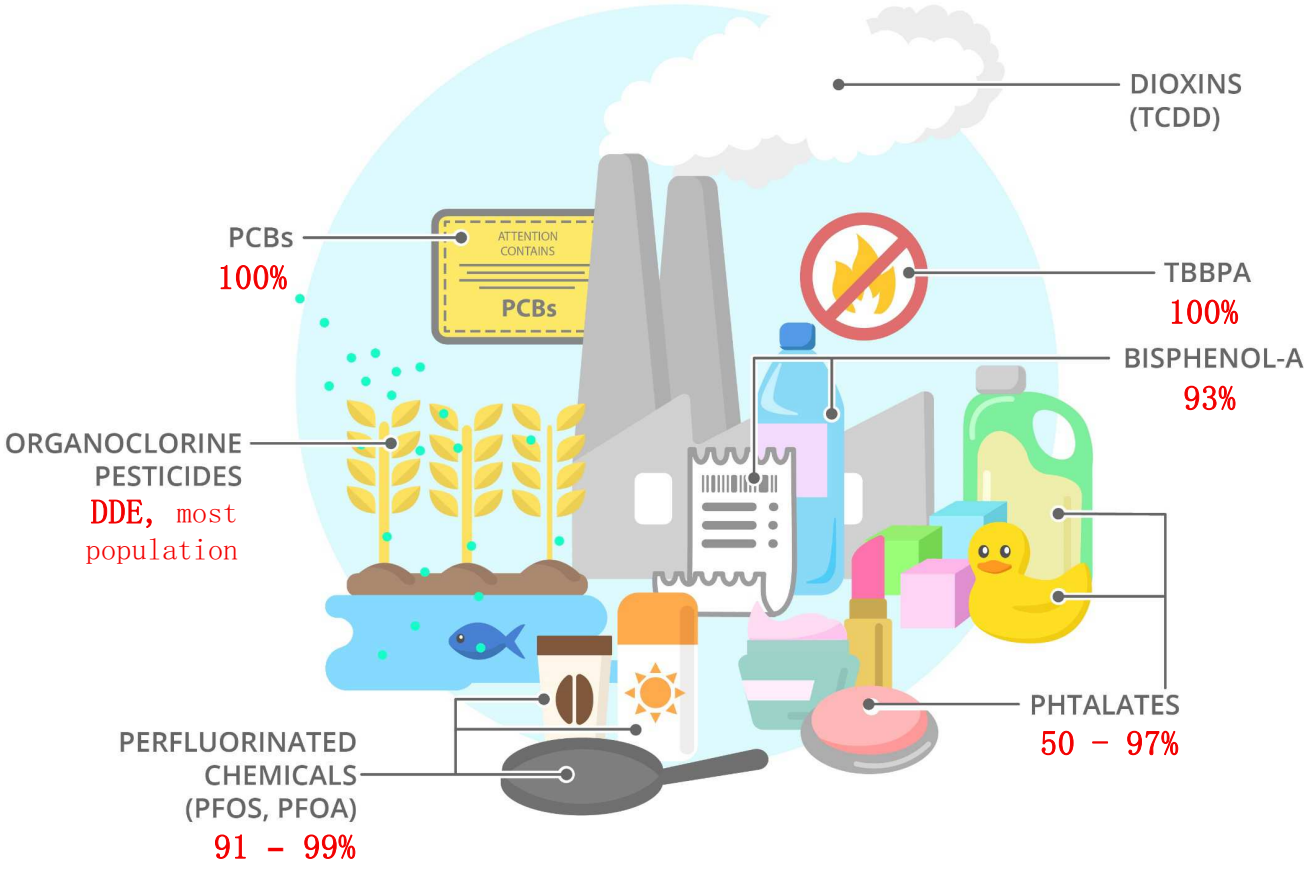
Endocrine Disruptors



Endocrine Disruptors

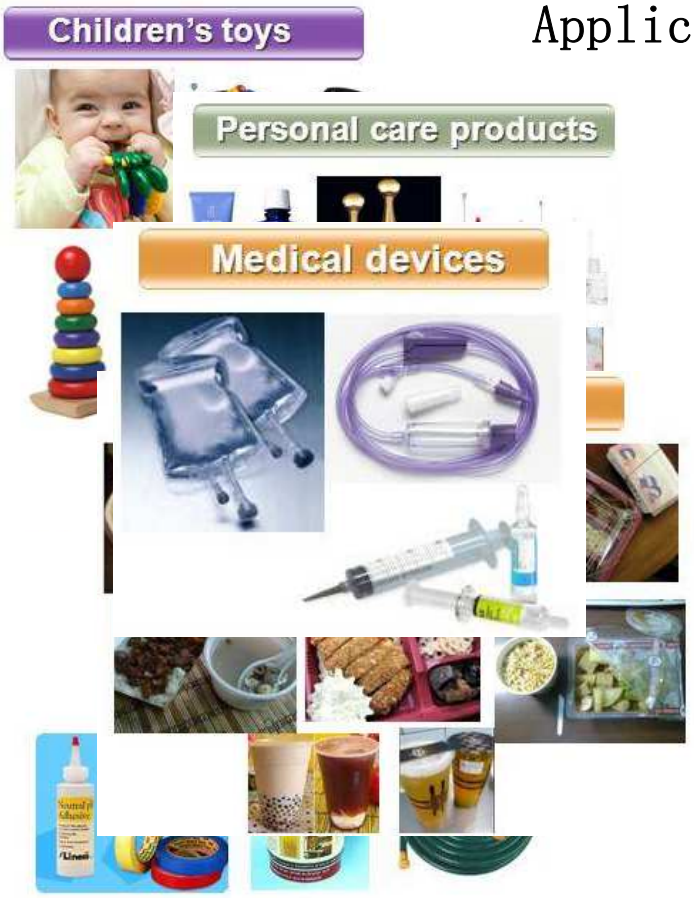


Endocrine disruptors are a matter of high concern for the World Health Organization



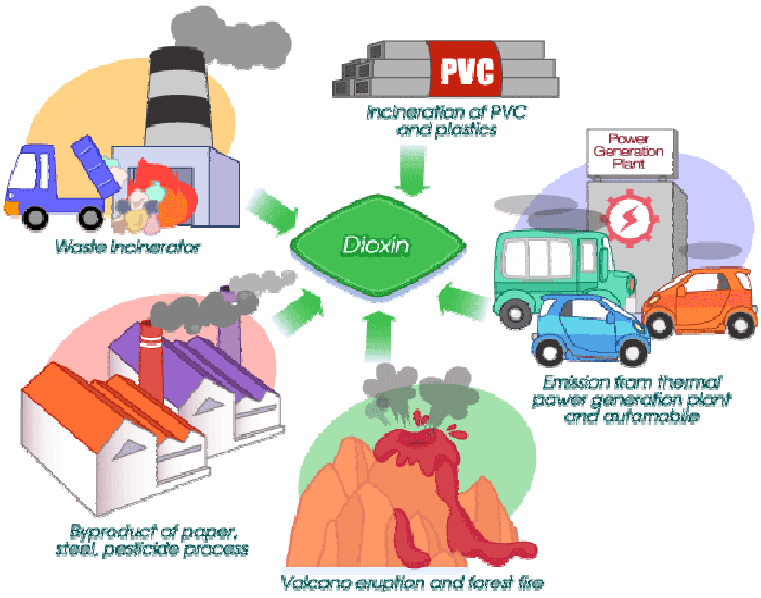
% of people tested by CDC

Applications of phtalates



- Major routes of human exposure: ingestion, inhalation and dermal contact
- DEHP daily exposure 3-30 µg/kg/d
- Urinary concentration of the DEHP metabolite MEHP is 1.5 µg/l
- The reference dose of DEHP 20 µg/kg of body weight per day

Applications of PCBs and dioxins

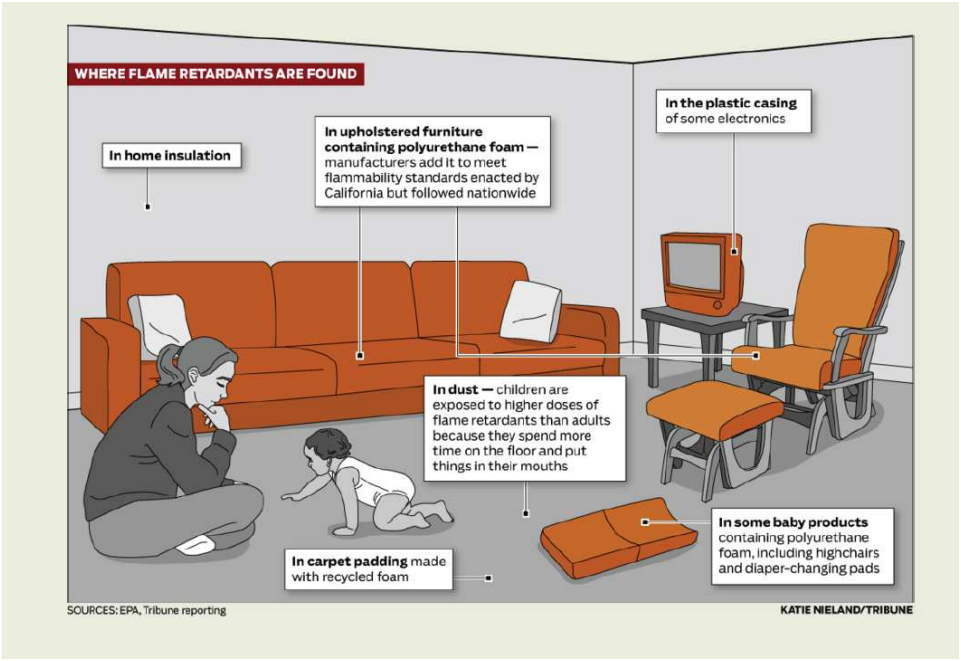


- Dioxins (PCDDs, PCDFs and certain PCBs), PCBs (209 possible PCB congeners exist)
- Thyroidogenic, estrogenic, and antiandrogenic actions
- TCDD in residents of the USA less than (20 ng/kg of lipid) but can increase up to 11 times in exposed groups.
- The reference dose (RfD) is: 7 × 10−10 mg/kg of body weight per day

Applications of PFCs (PFOA, PFOS)

- Synthetic fluorinated organic compounds
- Mean value found in serum for PFOA 2.08 ug/L and 6.31 ug/L for PFOS
- Food is thought to be the most important source of exposure. Treated carpets and floors treated with waxes and sealants that contain PFASs important source of exposure for babies and infants
- The RfD for PFOA and PFOS is 20 ng/kg of body weight per day

Applications of flame retardants



- Main sources of human exposure (indoor environments, diet, and occupational exposure)
- BDE-47 is found in the serum of 100% of the population of the USA
- Daily exposure doses of TBBPA range (0.04 ng/kg - 7.50 ng/kg of body weight per day) in adult individuals and (0.31 ng/kg - 58.54 ng/kg of body weight per day) in children

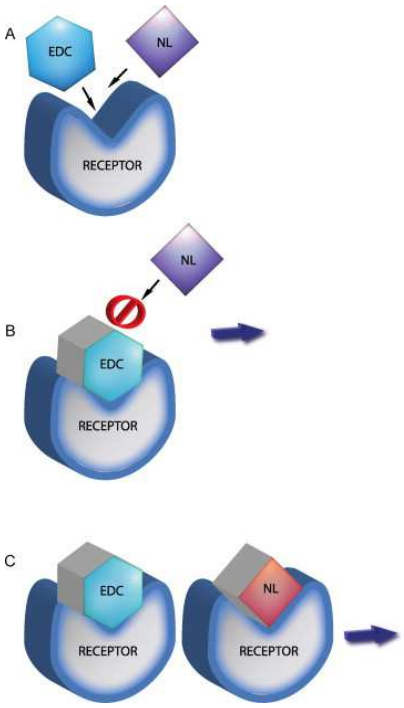
Applications of organochlorine pesticides

- DDT banned except for disease vector control
- DDT 70 μg/l in the serum of people living in countries where DDT was used to treat malaria, and in milk and adipose tissue at levels >2-3 ng/kg in China.
- OCPs are detected in human breast milk and adipose tissue
- Estrogenic, antiestrogenic, or antiandrogenic activity

Principles of Endocrine Disruptor Action (same as principles of hormone action)

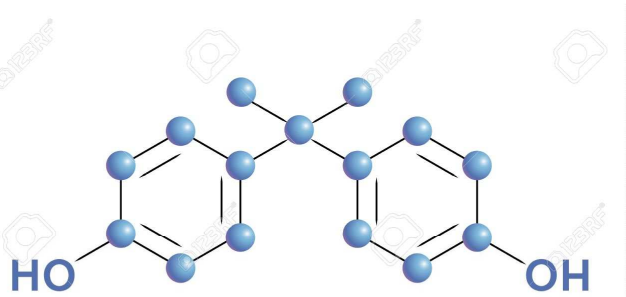
- EDCs act via receptors
- EDC responses are tissue specific
- EDC effects are sexually dimorphic
- EDCs act at low doses throughout the lifespan
- EDCs effects are life-stage specific: effects in adults but development is most sensitive lifestage

Mode of action



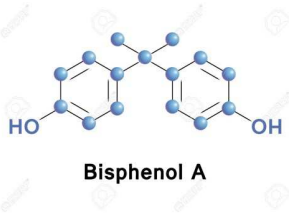
- **Mimic or partly mimic** naturally occurring hormones in the body like estrogens , androgens, and thyroid hormones.
- Bind to a receptor within a cell and **block** the endogenous hormone from binding (anti-estrogens and anti-androgens).
- **Interfere or block** the way natural hormones or their receptors are made or controlled, for example, by altering their metabolism in the liver.

ENDOCRINE DISRUPTING CHEMICAL SPOTLIGHT: BISPHENOL-A (BPA)



Bisphenol A

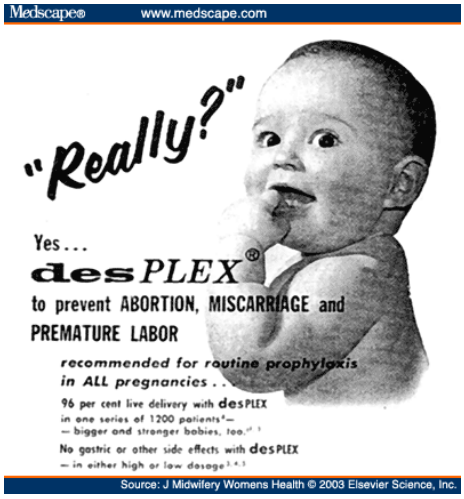
About bisphenol-A…..

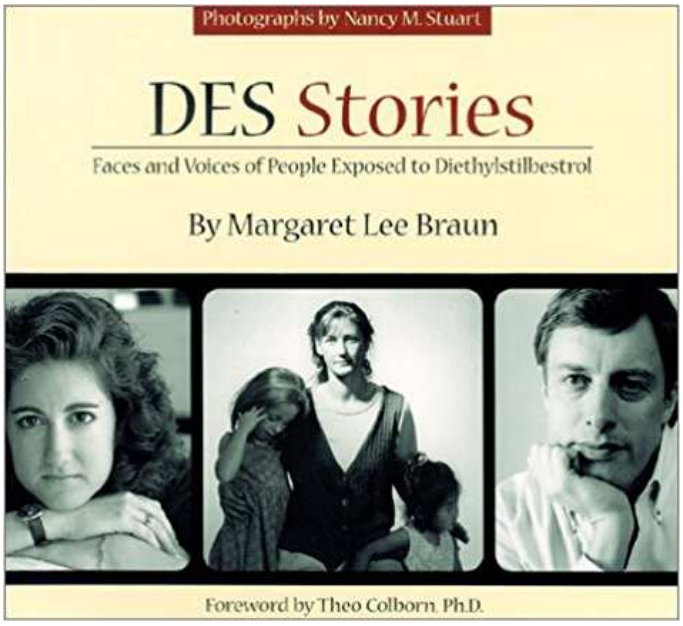


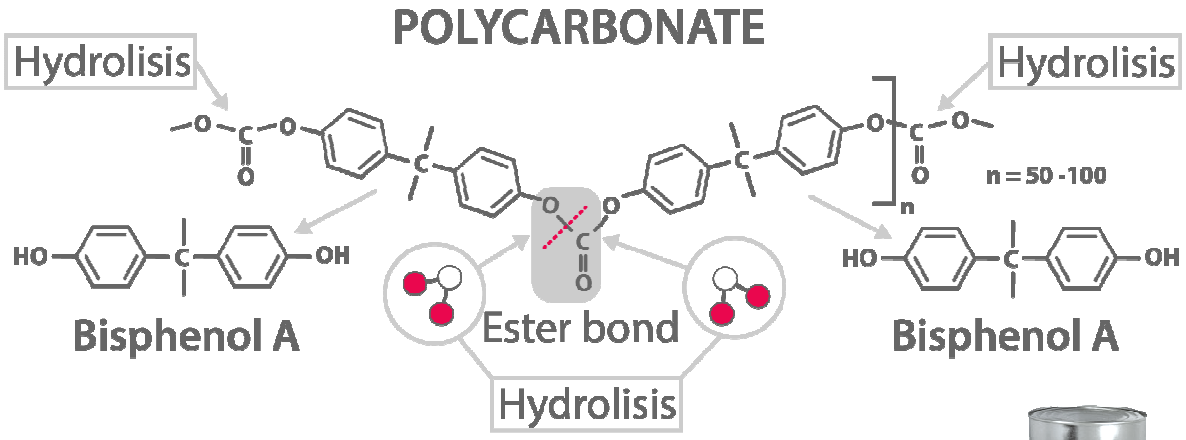
Bisphenol A

- Bisphenol A was discovered in 1891 by Russian chemist Aleksandr Dianin
- In the early 1930s, the British biochemist Edward Charles Dodds tested BPA as an artificial estrogen, but eventually developed **diethylstilbestrol (DES)** and found it to be more potent.
- 1940s and 1950s, the chemical industry discovered that BPA was an excellent hardener for epoxy resins and plastic polycarbonate
- Estimated use per year of 6 billion pounds-used in consumer products
- Effects on the endocrine system occur at very low doses

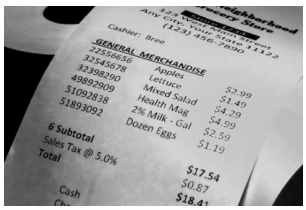
- "DES Daughters", are at an increased risk for clear cell adenocarcinoma (CCA) of the vagina and cervix, reproductive tract structural differences, pregnancy complications, and infertility.

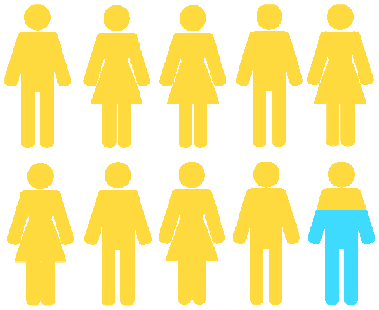






Adapted from Welshons, W. V. et al. Endocrinology 2006





BISPHENOL-A is
found in **urine** of

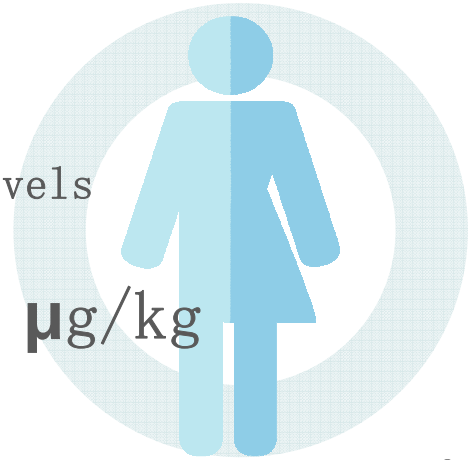
93% US citizens

(Calafat et al, EHP 2008)

BISPHENOL-A
exposure levels
on humans

0.07-12 µg/kg bw/day

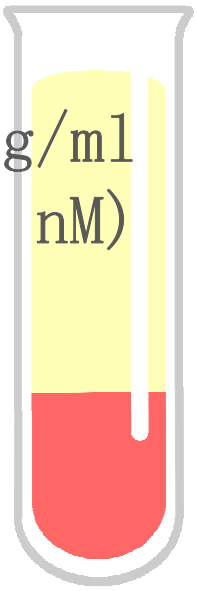
(Joint Research Center. Institute for Health and Consumer Protection. European Commission)



0.3-4 ng/ml (1.3-18 nM)

Unconjugated
BISPHENOL-A
concentration
in **human serum**
from adult men and women

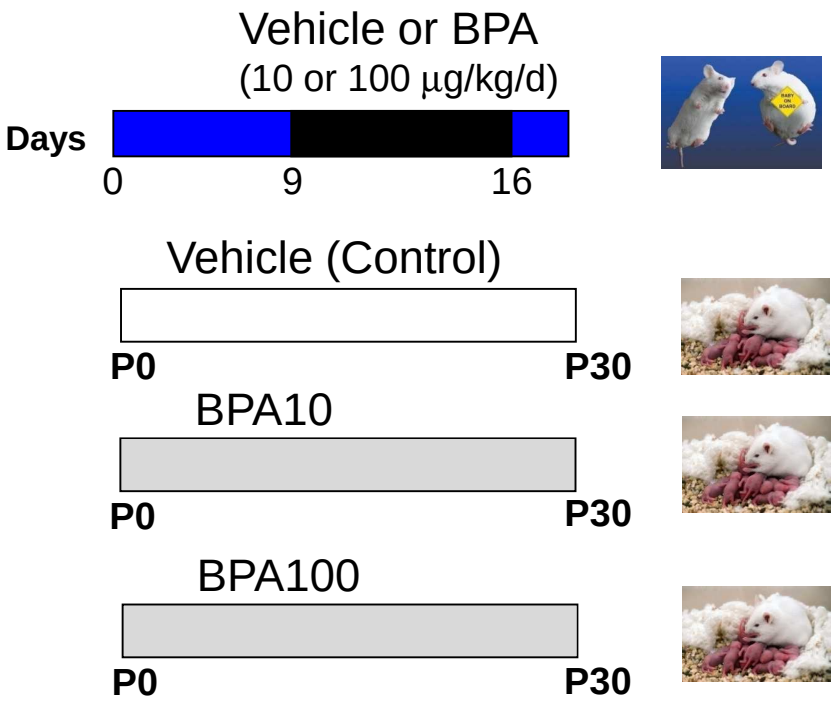
(Vandenberg et al, EHP 2010)



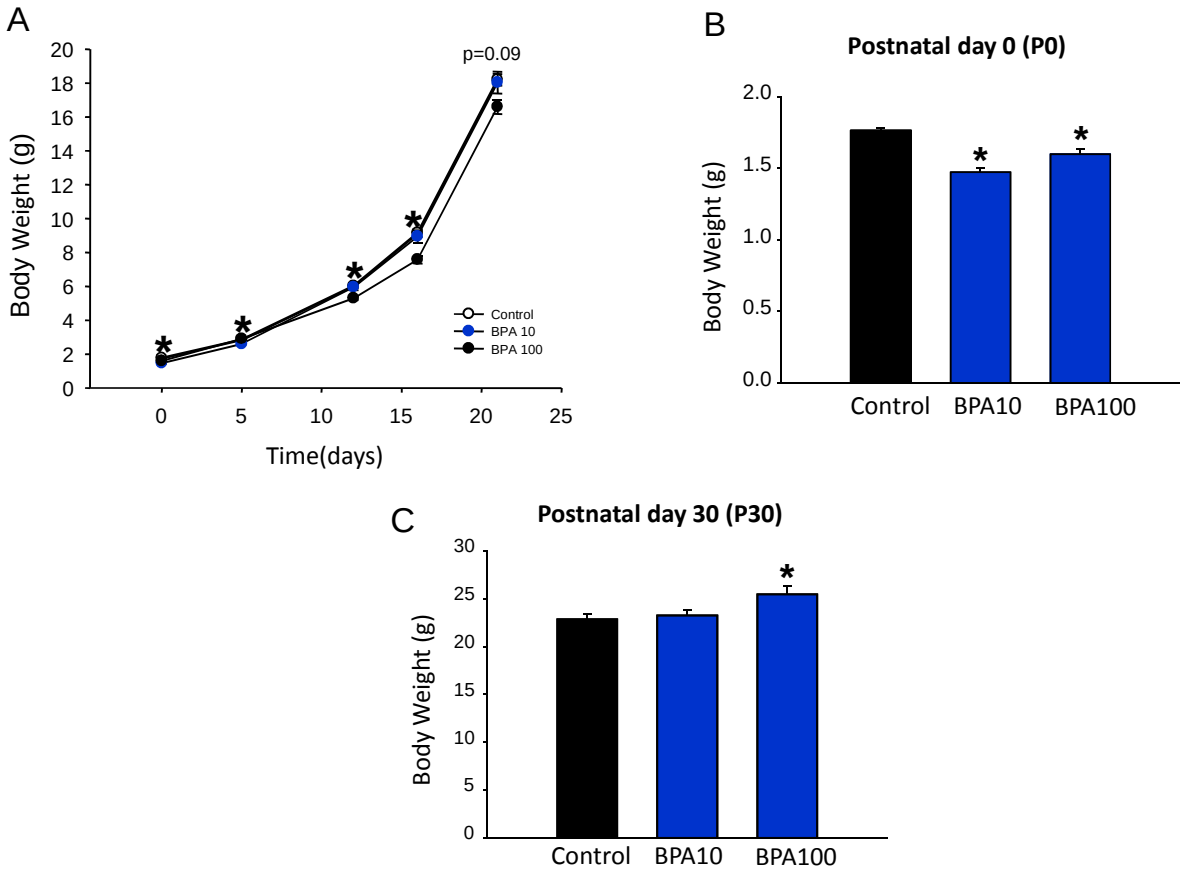
PREGNANCY

AS A SENSITIVE WINDOW FOR THE OFFSPRING

End points measured in offspring



Evolution of body weight



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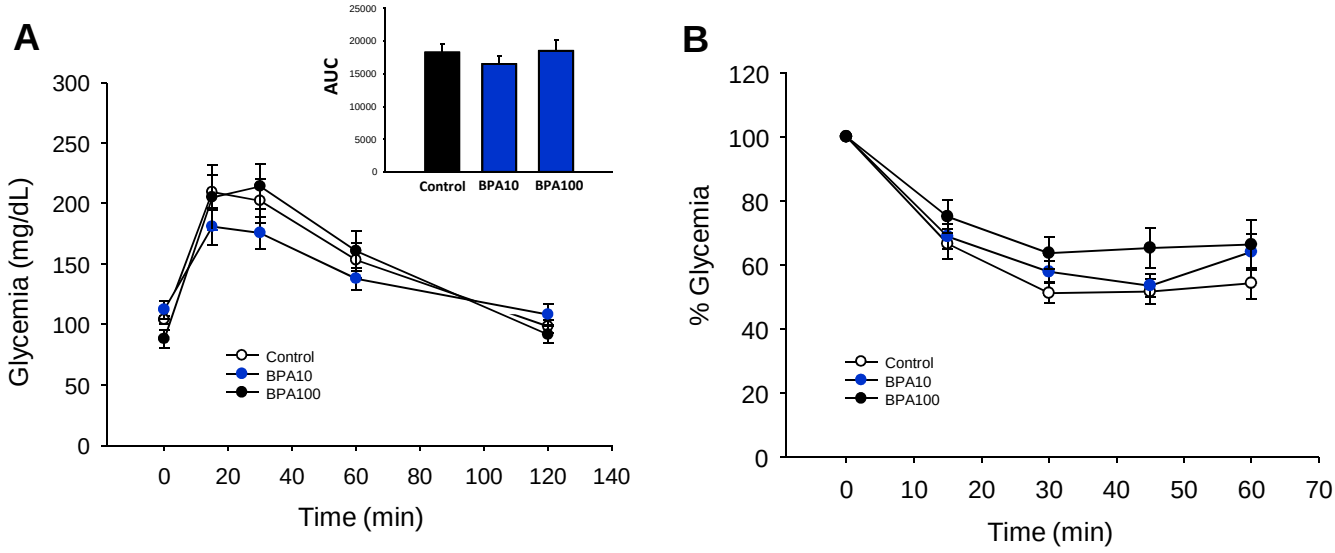
Glucose and insulin sensitivity in P30 animals



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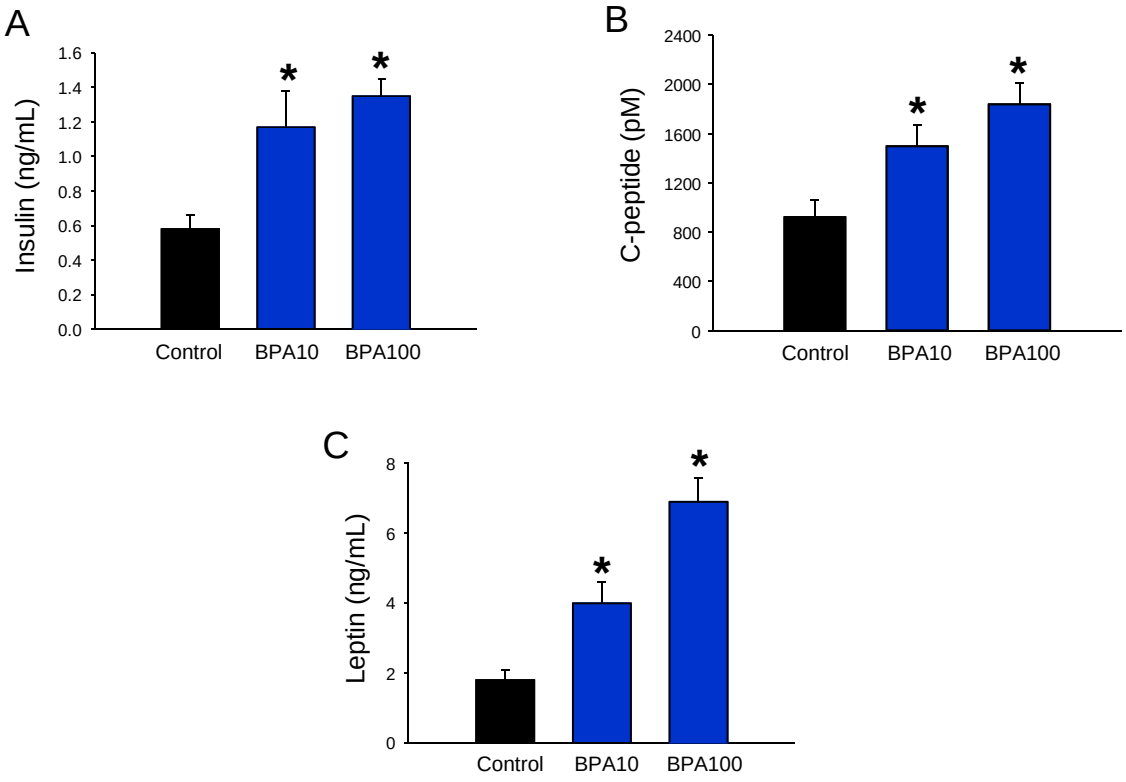
Hyperinsulinemia and hyperleptinemia in BPA-mice at P30



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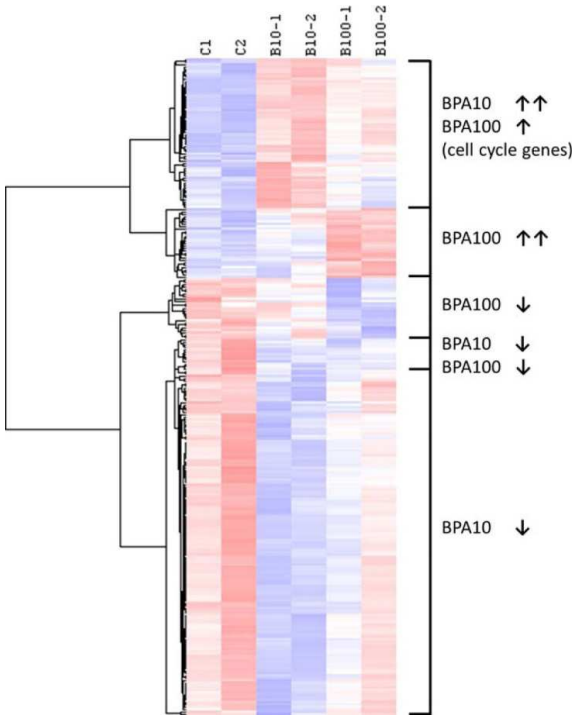

325 genes upregulated most of them related to cell cycle, mitosis, cell division

The gene cluster representations illustrate the changes in gene expression in pancreatic islets from controls, BPA10, and BPA100 mice (intense blue indicates the lowest expression and intense red, the highest expression). Genes were clustered according to their pattern of expression across the different samples analyzed. The arrows indicate whether genes were up-regulated (↑) or down-regulated (↓) in the BPA10 and BPA100 samples with respect to the control samples.

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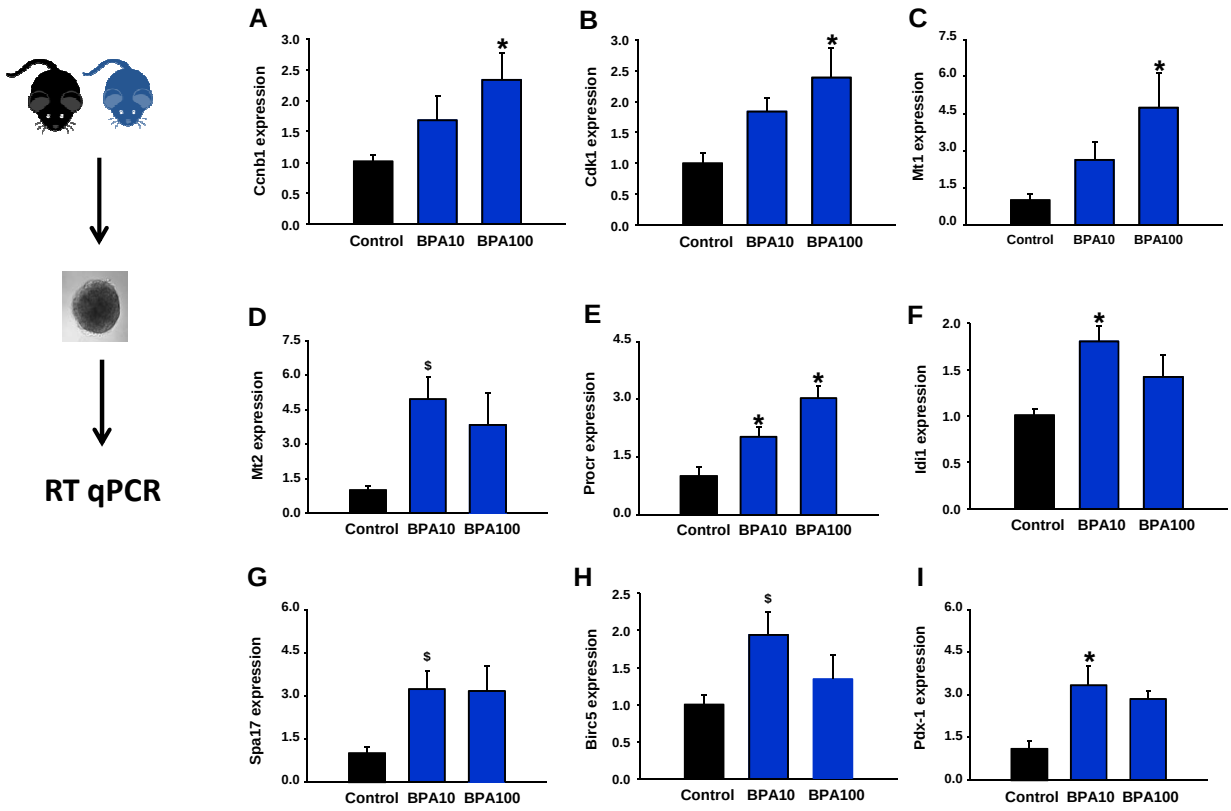
DOI: 10.1210/en.2016-1390

Upregulated gene expression of cell cycle-related genes in P30 BPA mice



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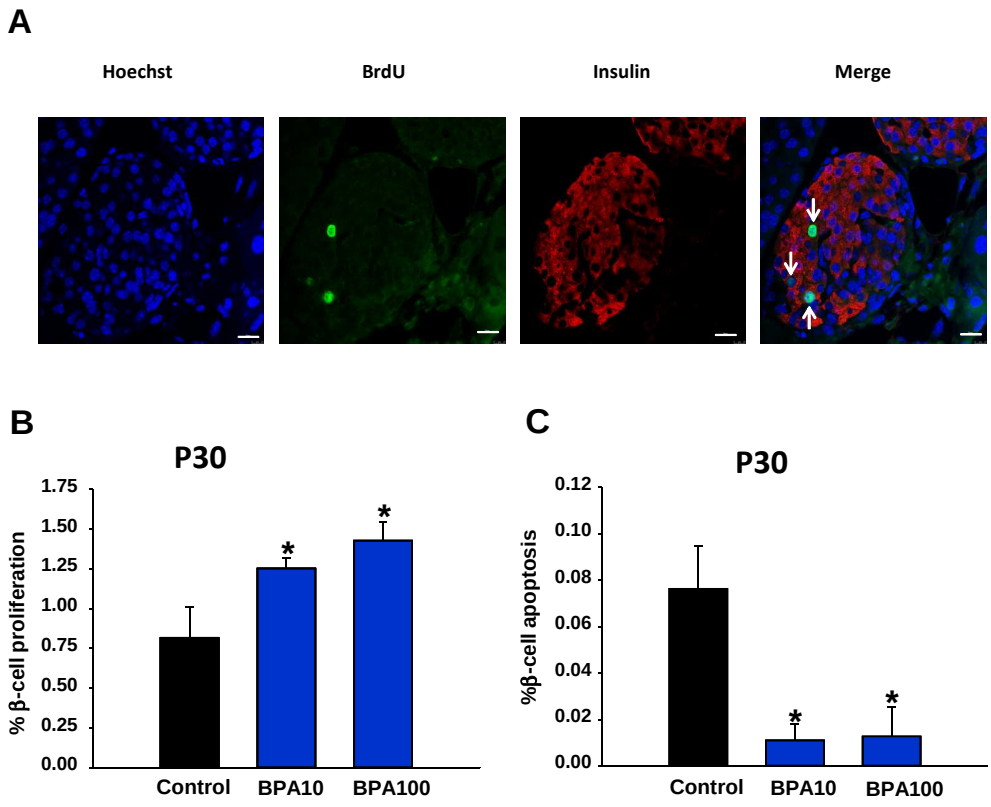
Increased pancreatic β-cell proliferation, decreased apoptosis in BPA mice at P30



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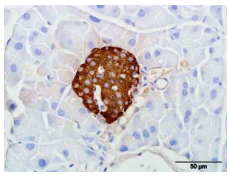
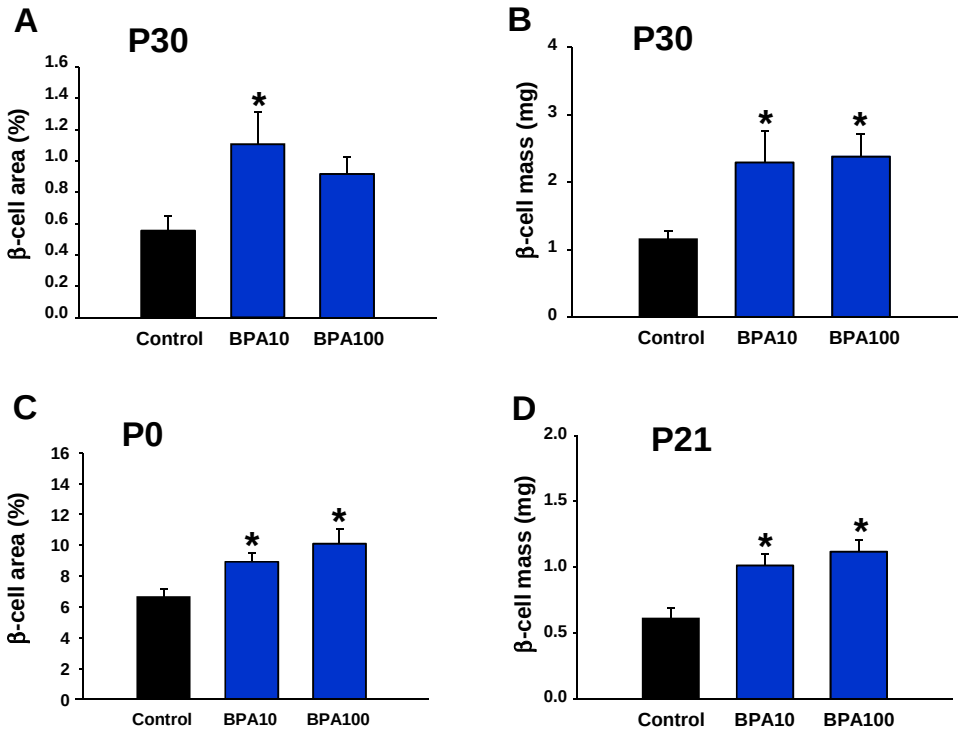


Quantificacion of pancreatic β-cell mass

Increased pancreatic β-cell mass



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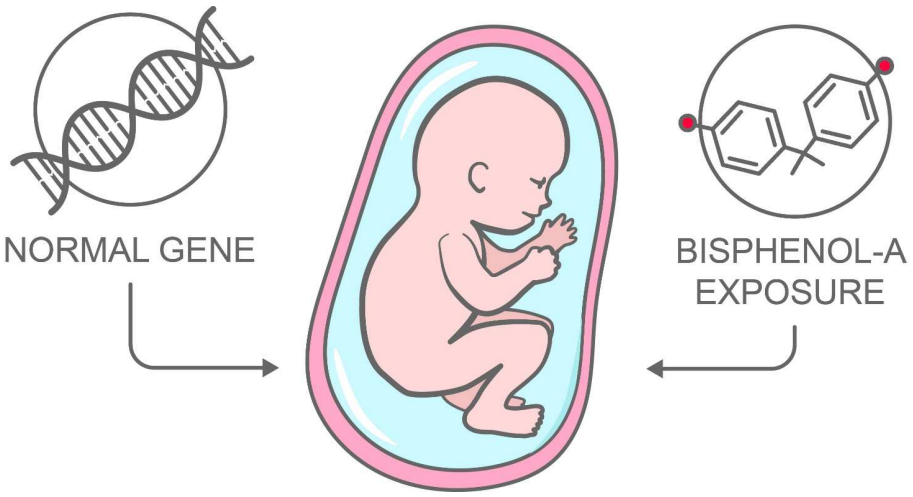


ABNORMAL GENE EXPRESSION

↓

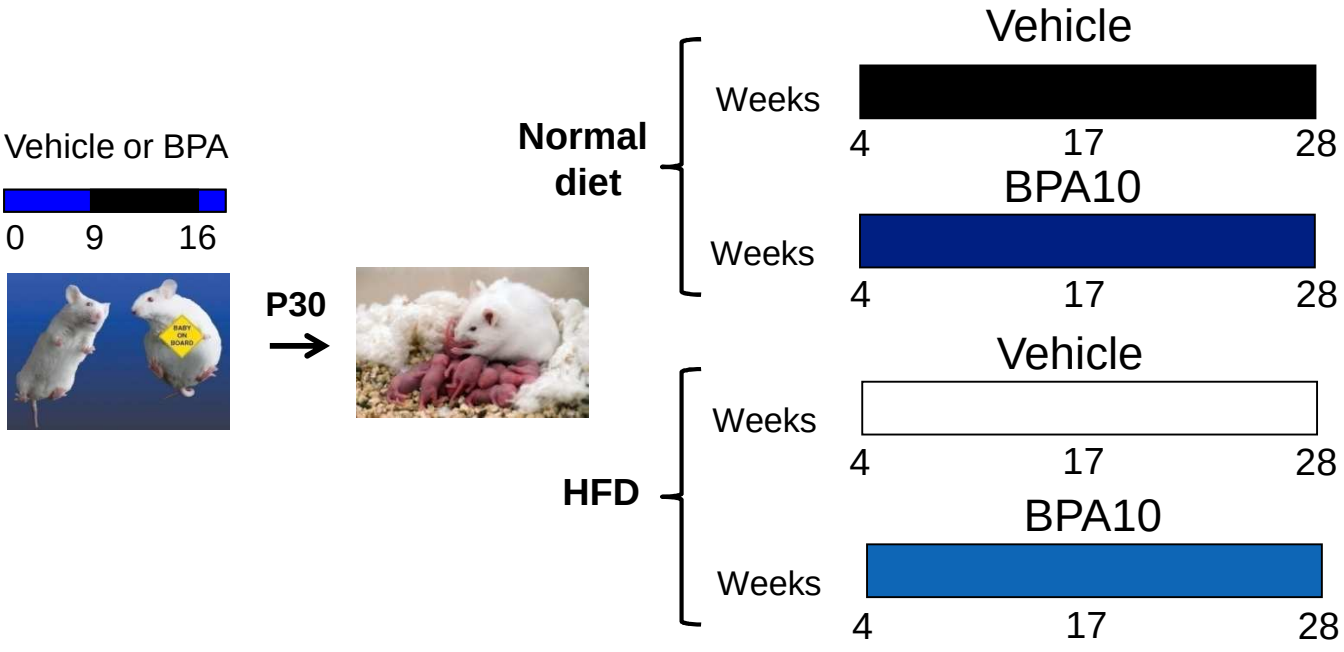
INCREASED BETA CELL MASS

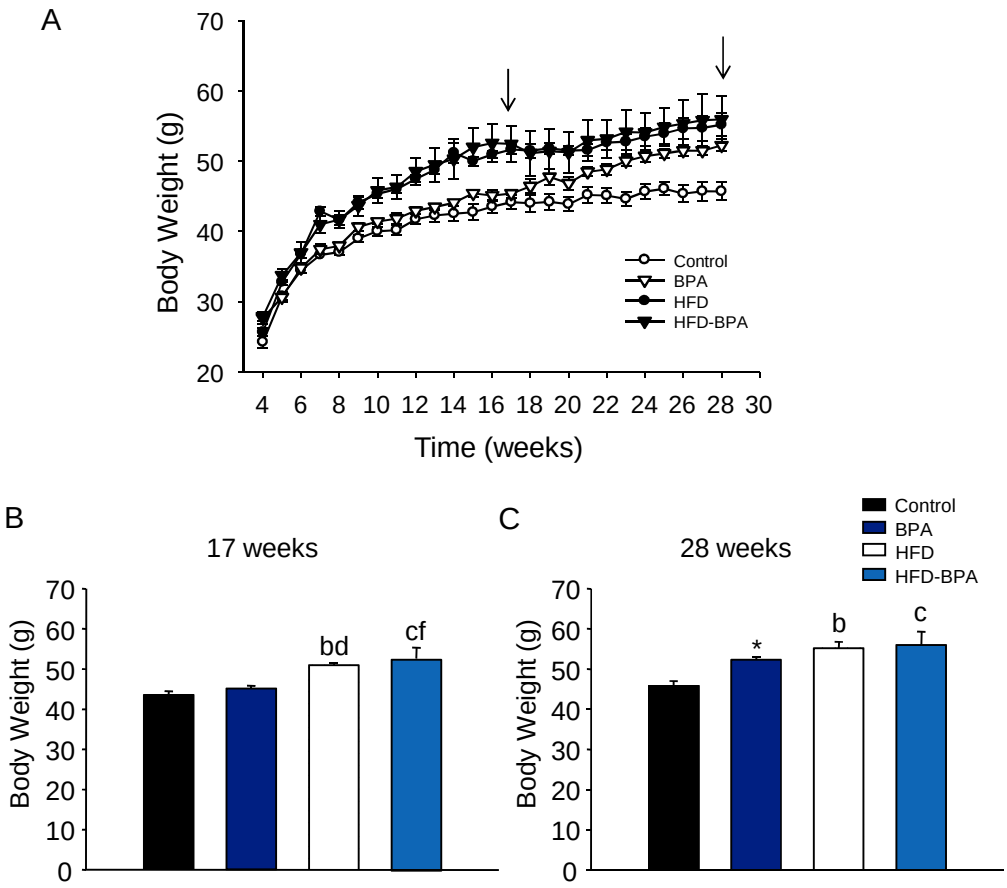
↓

EARLY HYPERINSULINEMIA

LONG-TERM CONSEQUENCES?

End points measured in offspring





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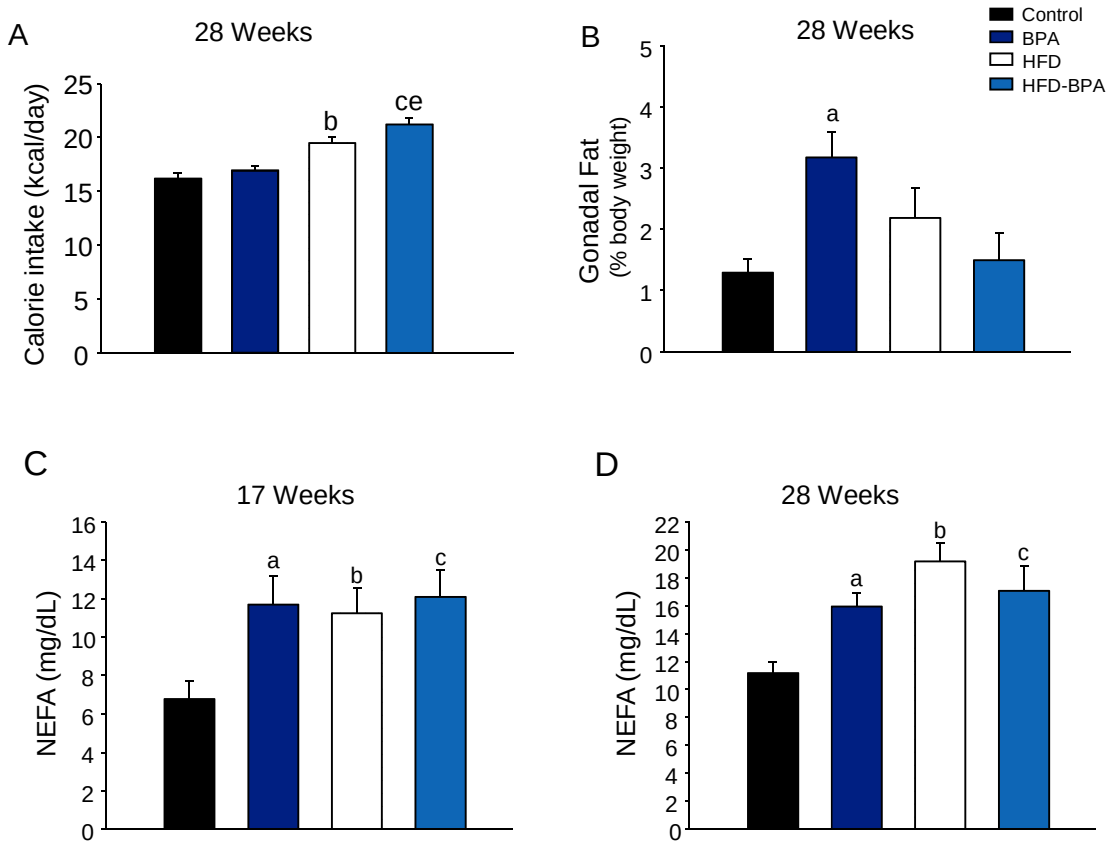

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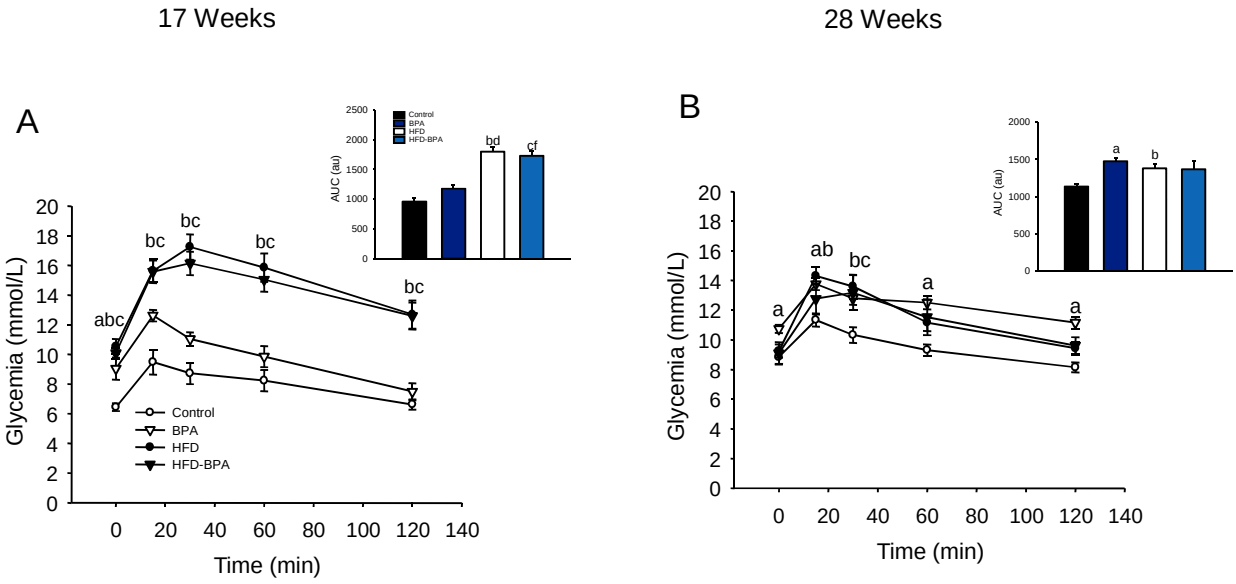
BPA provoked glucose intolerance in a similar manner than HFD



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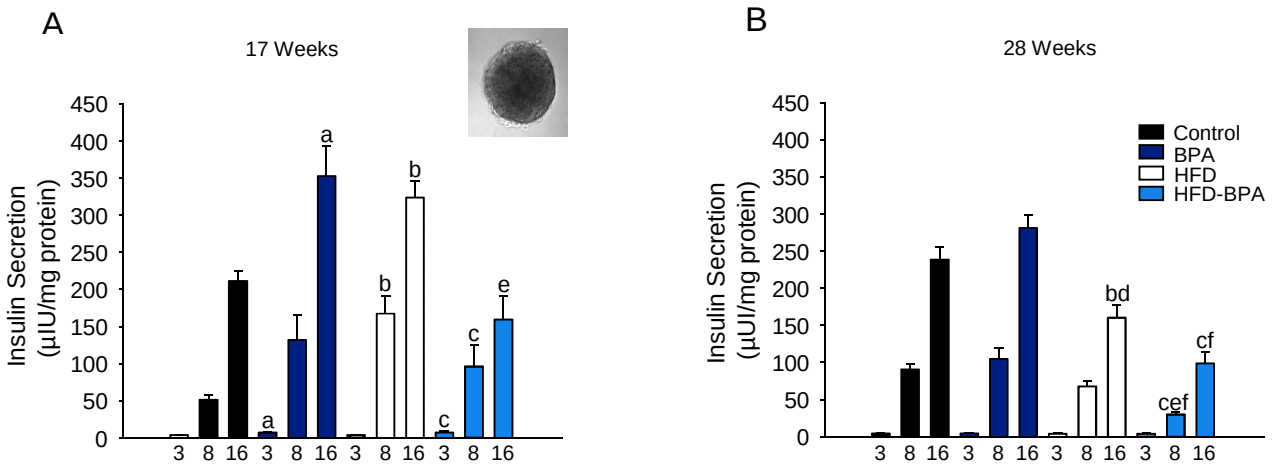
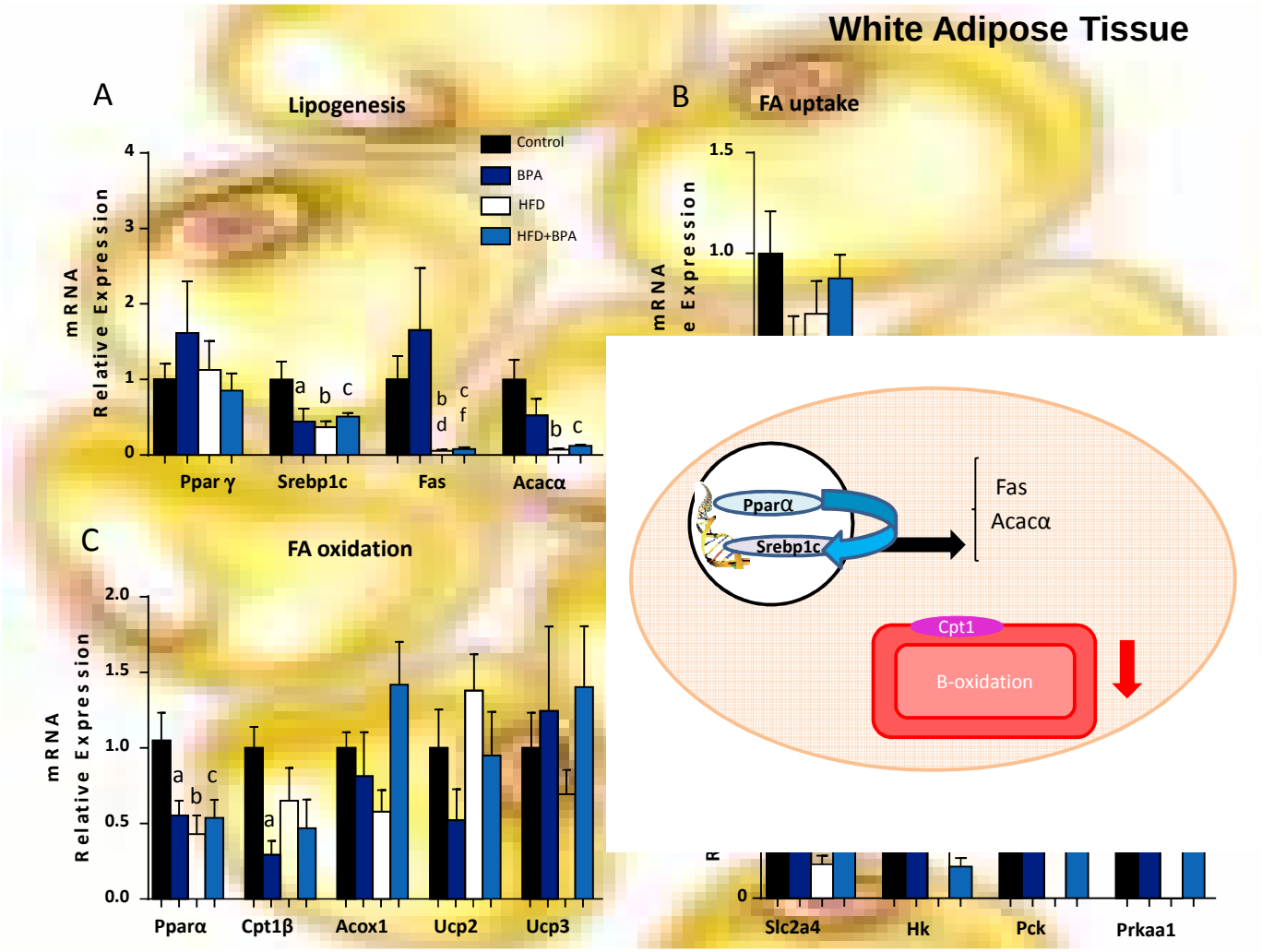
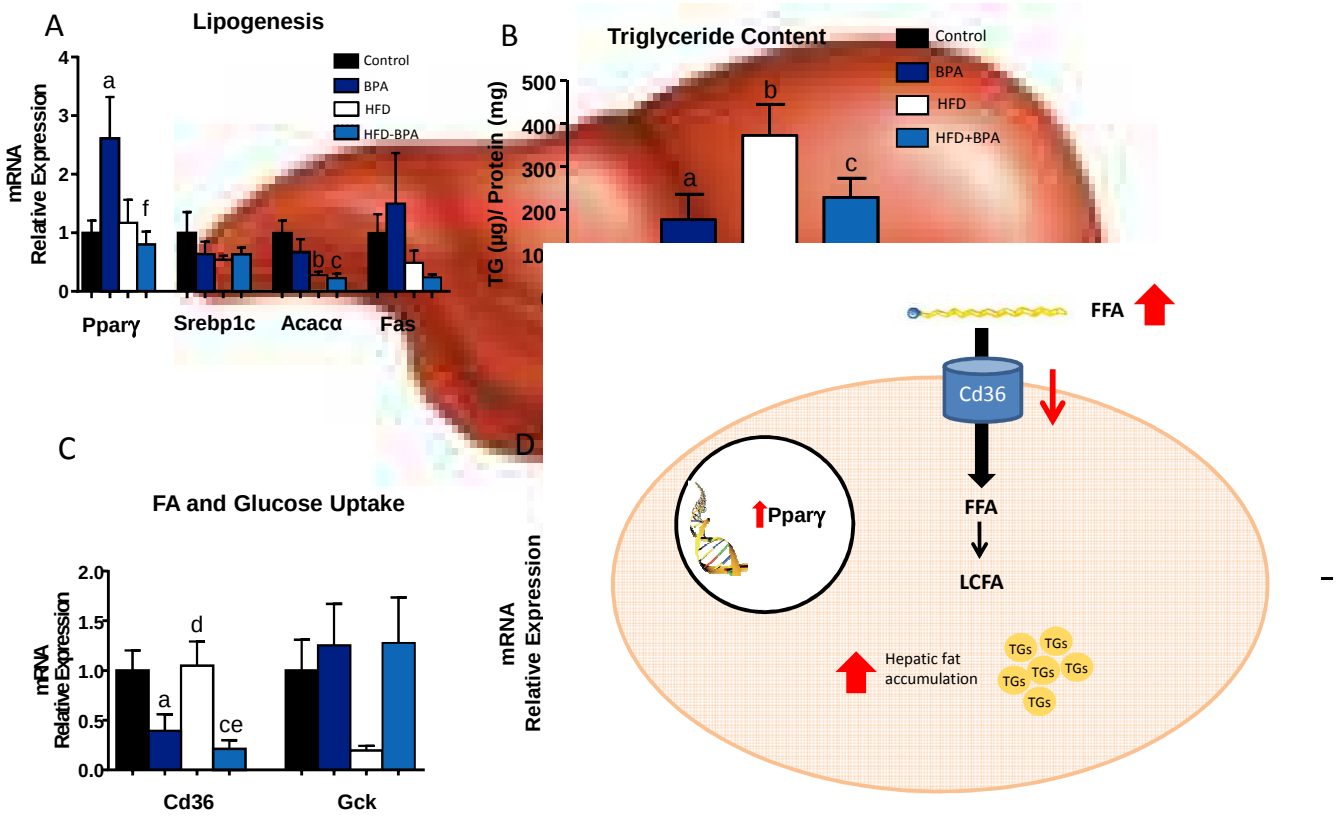
Glucose-stimulated insulin secretion: altered pancreatic β-cell function



Published in Garcia-Arevalo M, Alonso-Magdalena P, Rebelo DosSantosJ, Quesada I, Carneiro EM, Nadal. A Exposure to bisphenol-A during pregnancy partially mimics the effects of a high-fat diet altering glucose homeostasis and gene expression in adult male mice. PLoS One. 2014

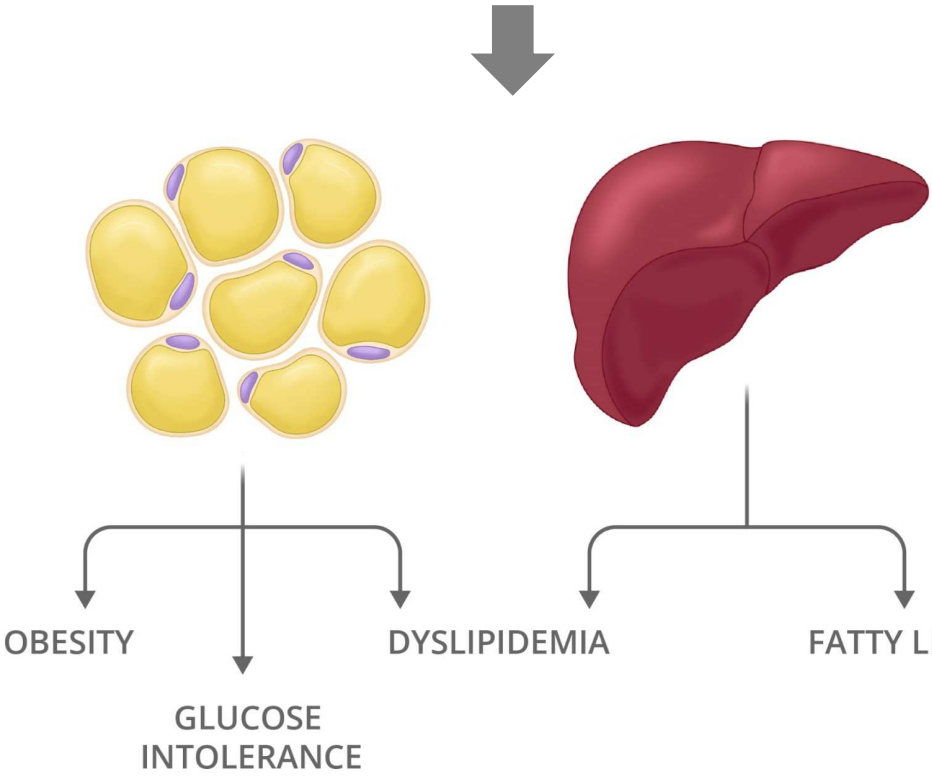

White Adipose Tissue
A
Lipogenesis
Control
BPA
HFD
HFD+BPA
mRNA Relative Expression
Ppar γ
Srebp1c
Fas
Acacα
B
FA uptake
mRNA Expression
C
FA oxidation
mRNA Relative Expression
Pparα
Cpt1β
Acox1
Ucp2
Ucp3
PparΟ±
Srebp1c
Fas
Acacα
Cpt1
B-oxidation
Slc2a4
Hk
Pck
Prkaa1

Liver



García-Arévalo et al, PlosOne 2014

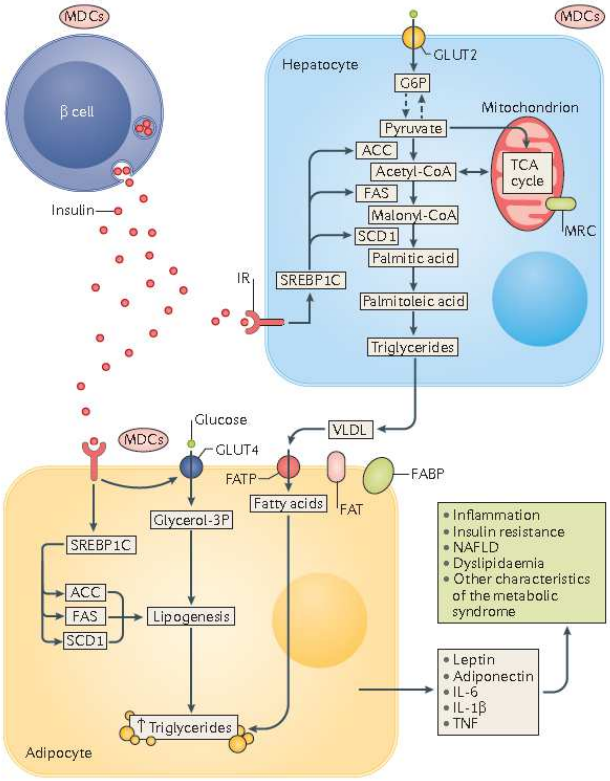
Early Hyperinsulinemia



ADULT OFFSPRING

Alonso-Magdalena, EHP 2010
Wei et al, Endocrinology 2011
Rubin et al, 2001
Somm et al, EHP2009
Liu et al, Plos One 2013
Angle et al, Reprod Toxicol 2013
MacKay et al, Endocrinology 2013
Ma et al, Diabetologia 2013
Garcia-Arevalo et al, Plos One 2014
Ding et al, J Endocrinol 2014
Li et al, Toxicol Letter 2014
Jiang et al, Toxicology letters 2014
Li et al, Toxicology letters 2014
Susiarjo et al, Endocrinology 2015

nature REVIEWS ENDOCRINOLOGY



Nadal A, Quesada I, Tuduri E, Nogueiras R and Alonso-Magdalena P (2017) Nature Rev Endocrinol

FROM ANIMAL TO HUMAN EVIDENCE: EPIDEMIOLOGICAL STUDIES LINKING EDCs DIABETES AND/OR OBESITY

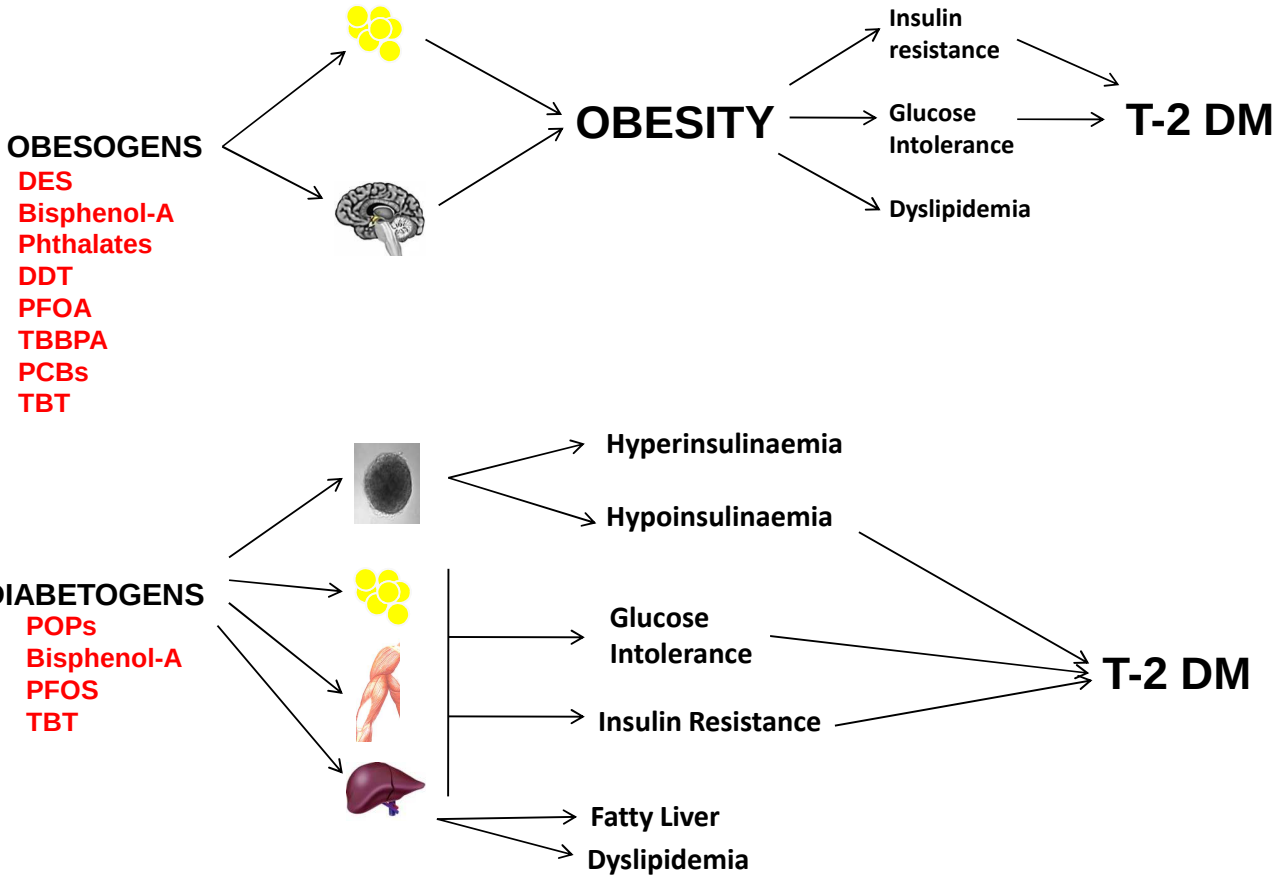
EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller

Pharmacology and Toxicology (A.C.G.), College of Pharmacy, The University of Texas at Austin, Austin, Texas 78734; Division of the National Toxicology Program (V.A.C., S.E.F.), National Institute of Environmental Health Sciences, National Institutes of Health, Research Triangle Park, North Carolina 27709; Department of Comparative Biosciences (J.A.F.), University of Illinois at Urbana-Champaign, Urbana, Illinois 61802; Institute of Bioengineering and CIBERDEM (A.N.), Miguel Hernandez University of Elche, 03202 Elche, Alicante, Spain; Departments of Urology, Pathology, and Physiology & Biophysics (G.S.P.), College of Medicine, University of Illinois at Chicago, Chicago, Illinois 60612; Departments of Physiology and Pediatrics (J.T.), University of Turku and Turku University Hospital, 20520 Turku, Finland; and Biology Department (R.T.Z.), University of Massachusetts at Amherst, Amherst, Massachusetts 01003

Endocrine Reviews 36: E1-E150, 2015

ENDOCRINE SOCIETY


OBESOGENS
DES
Bisphenol-A
Phthalates
DDT
PFOA
TBBPA
PCBs
TBT
OBESITY
Insulin resistance
Glucose Intolerance
Dyslipidemia
T-2 DM
DIABETOGENS
POPs
Bisphenol-A
PFOS
TBT
Hyperinsulinaemia
Hypoinsulinaemia
Glucose Intolerance
Insulin Resistance
Fatty Liver
Dyslipidemia
T-2 DM

Endocrine Reviews 36: E1-E150, 2015

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Based on 1322 studies from peer-reviewed literature

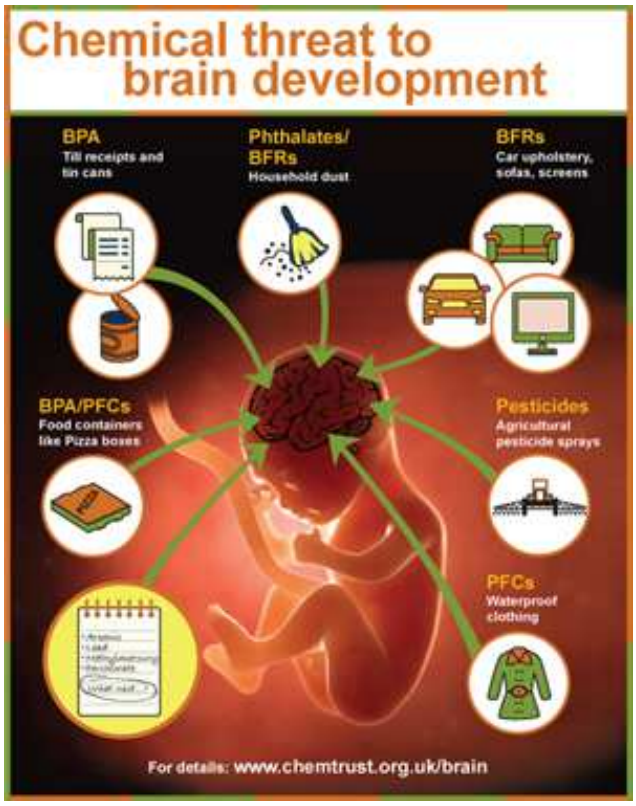
- Diabetes, obesity and cardiovascular disease
- Neurodevelopment and neuroendocrine systems
- Thyroid gland dysfunctions
- Female reproductive health
- Male reproductive health
- Hormone sensitive cancers

in females and in males

ENDOCRINE SOCIETY

1916-2016
100 YEARS
OF HORMONE SCIENCE TO HEALTH

These three scientific societies, as scientific and medical professional societies, recognize that EDs contribute to serious health problems such as **diabetes, obesity and neurodevelopmental and reproductive disorders**



CHEMTrust
Protecting humans and wildlife from harmful chemicals

No Brainer

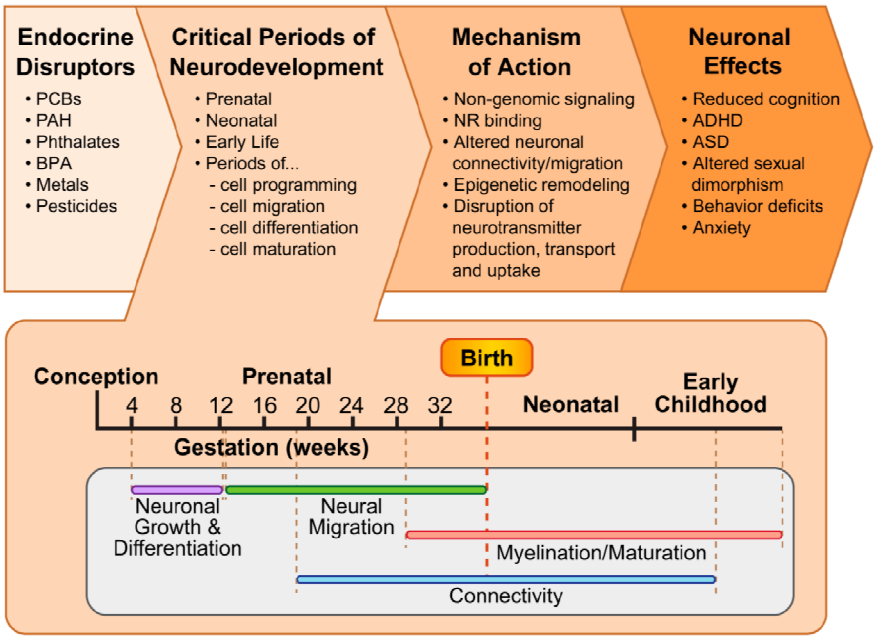
The impact of chemicals on children's brain development: a cause for concern and a need for action

Lead, methylmercury, and PCBs associated with adverse effects on child's developing brain and nervous system in multiple studies.

The National Toxicology Program (NTP) childhood exposure is associated with **reduced cognitive function**, including lower intelligence quotient (IQ) and reduced academic achievement, **attention-related behavioral problems** (including inattention, hyperactivity, and diagnosed attention-deficit/hyperactivity disorder)

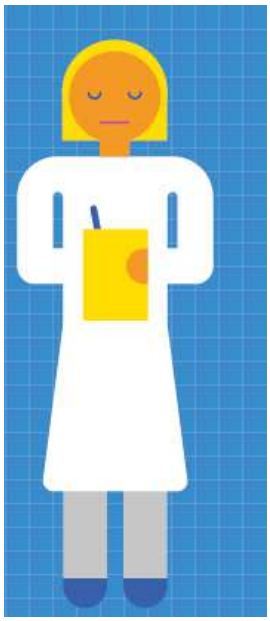
Table 1. Environmental chemicals associated with impaired neurodevelopment outcomes.

Chemical	Commercial Use	Neurodevelopmental Effects	Potential Mechanism	References
Polychlorinated biphenyls (PCBs)	coolants, plasticizers, and flame retardants	impaired learning, memory, and IQ as well as behavioral deficits such as inattention and impulsiveness	altered neuronal connectivity; thyroid hormone disruption	20–28
Polycyclic aromatic hydrocarbons (PAHs)	result from incomplete fossil fuel combustion	lower mental development index, negative associations with IQ, adverse effects on fetal growth, cognitive development, and behavioral disorders	AhR cross-talk and activation	29–42
Phthalates	plasticizers, adhesives, personal care products	Impaired concentration in girls, diminished motor function and masculine behavior in boys	inhibition of testosterone synthesis	43–50
Bisphenol A (BPA)	plastics and epoxy resins	aggression, hyperactivity, anxiety, social behavior	estrogenic effects, non-specific signaling pathways	54–60
Metals	many commercial applications	neurodevelopment, cognition, impaired cortisol metabolism	alteration of sex hormone levels, non-direct effects	14, 61–71
Pesticides	pest deterrent, biocide	lower mental developmental index, attention deficits, reduced childhood IQ	alteration of inhibition/excitation, disruption of thyroid hormones, iodine uptake disruption	72–88



From: Elucidating the Links Between Endocrine Disruptors and Neurodevelopment
Endocrinology. 2015;156(6):1941-1951. doi:10.1210/en.2014-1734

MOVING FROM RESEARCH TO PREVENTION!!



Good News: Windows of Susceptibility are also Windows of Prevention

© Olivier Bonhomme, Le Monde

Reduce **exposures to environmental chemicals** prior to and during **pregnancy**

Suggestions for Reducing Exposures to Chemicals Linked to Adverse Health Effects

Food and Water

- ✓ Don't microwave polycarbonate plastic food containers or use them for storing hot liquids
- ✓ Avoid plastic containers designated #3, #6, and #7
- ✓ Eat fresh and frozen foods while reducing consumption of canned and processed foods
- ✓ Opt for glass, porcelain, or stainless steel containers when possible, especially for hot food and drinks
- ✓ Prepare more meals at home and emphasize fresh ingredients
- ✓ Wash fruits and vegetables before consuming them
- ✓ Consider using a water filter
- ✓ If possible, purchase organic produce, meat, and dairy products
- ✓ Eat a diversified diet with plenty of variety

CÓDIGOS DE IDENTIFICACIÓN DE RESINAS DE PLÁSTICO

PETE PET	HDPE PEAD	PVC V	LDPE PELD	PP	PS	O OTROS
POLIETILENO TEREFTALATO	POLIETILENO DE ALTA	POLICLORURO DE VINILO	POLIETILENO DE BAJA	POLIPROPILENO	POLIESTIRENO	OTROS

PRODUCTOS PLÁSTICOS MÁS SEGUROS 2, 4 y 5

Las botellas marcadas con el código 1. PET o PETE se deben utilizar solamente una vez, después podrían desprender DEHP, un ftalato tóxico.

PLÁSTICOS QUE HAY QUE EVITAR 3, 6 y 7

PVC o vinilos pueden contener ftalatos y bisfenol-A	espuma de poliestireno	puede contener bisfenol-A

Personal Care

- ✓ Read labels and avoid products containing phthalates
- ✓ Choose products labeled "Phthalate-Free" and "BPA-Free"
- ✓ Avoid fragrances and opt for cosmetics labeled "no synthetic fragrance", "scented only with essential oils", or "phthalate-free"
- ✓ Wash your hands often, especially before preparing and eating food
- ✓ Minimize handling of receipts and thermal paper

For Children

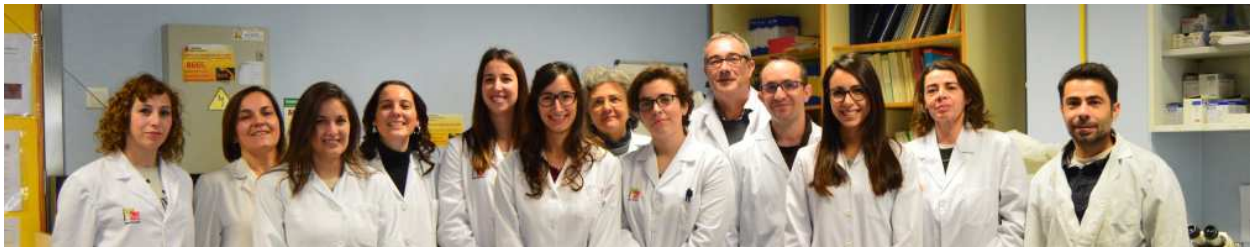
- ✓ Avoid hand-me-down plastic toys
- ✓ Opt for infant formula bottles and toys that are labeled "BPA-Free"

Exercise and Activity

- ✓ Check air quality in your area [https://airnow.gov]
- ✓ Avoid outdoor exercise when pollution levels are high
- ✓ Avoid exercise near high traffic areas. Instead, choose routes away from busy roads and vehicles

Instituto de Bioingeniería
Universidad Miguel Hernández de Elche

ciberdem
Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas



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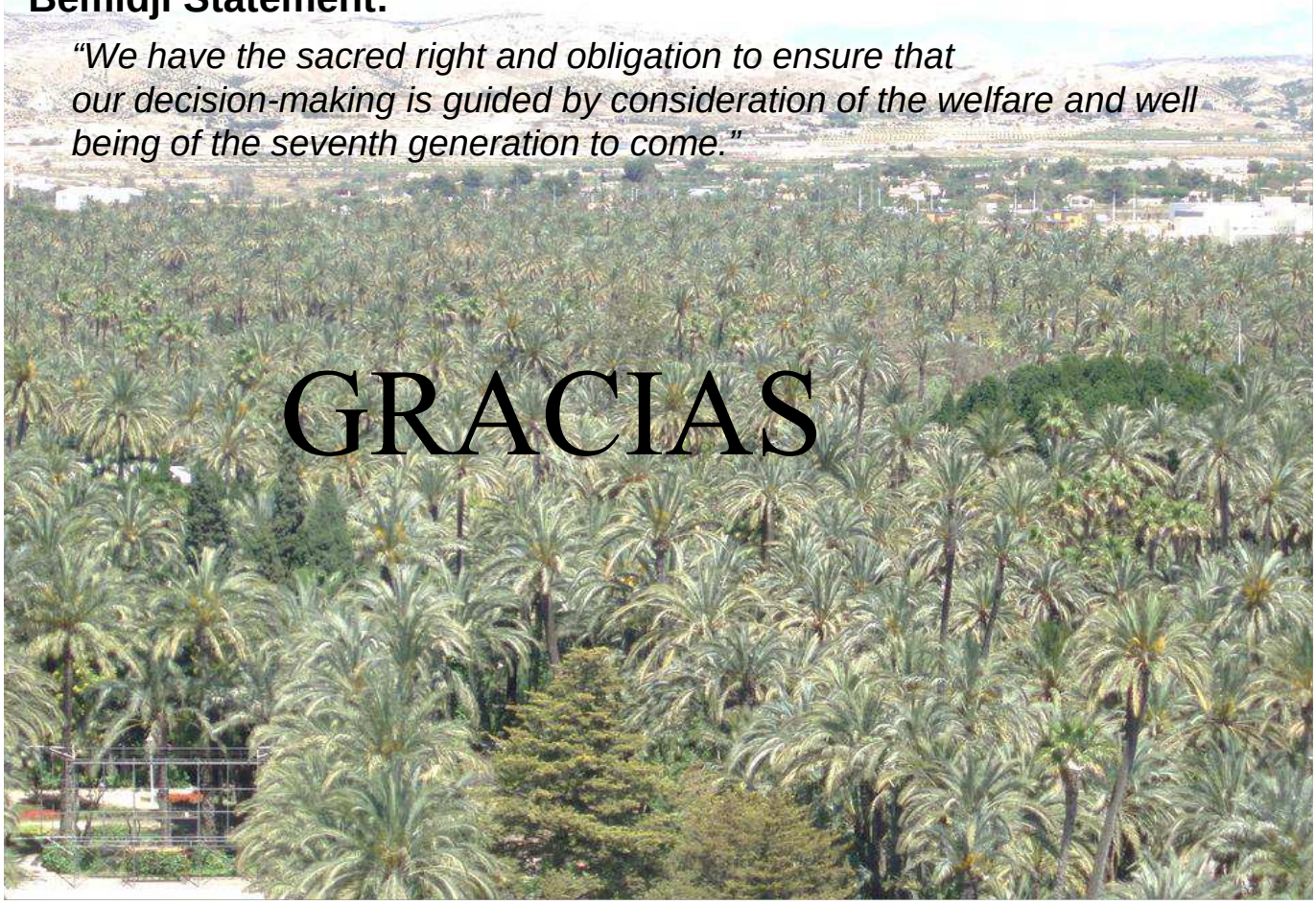
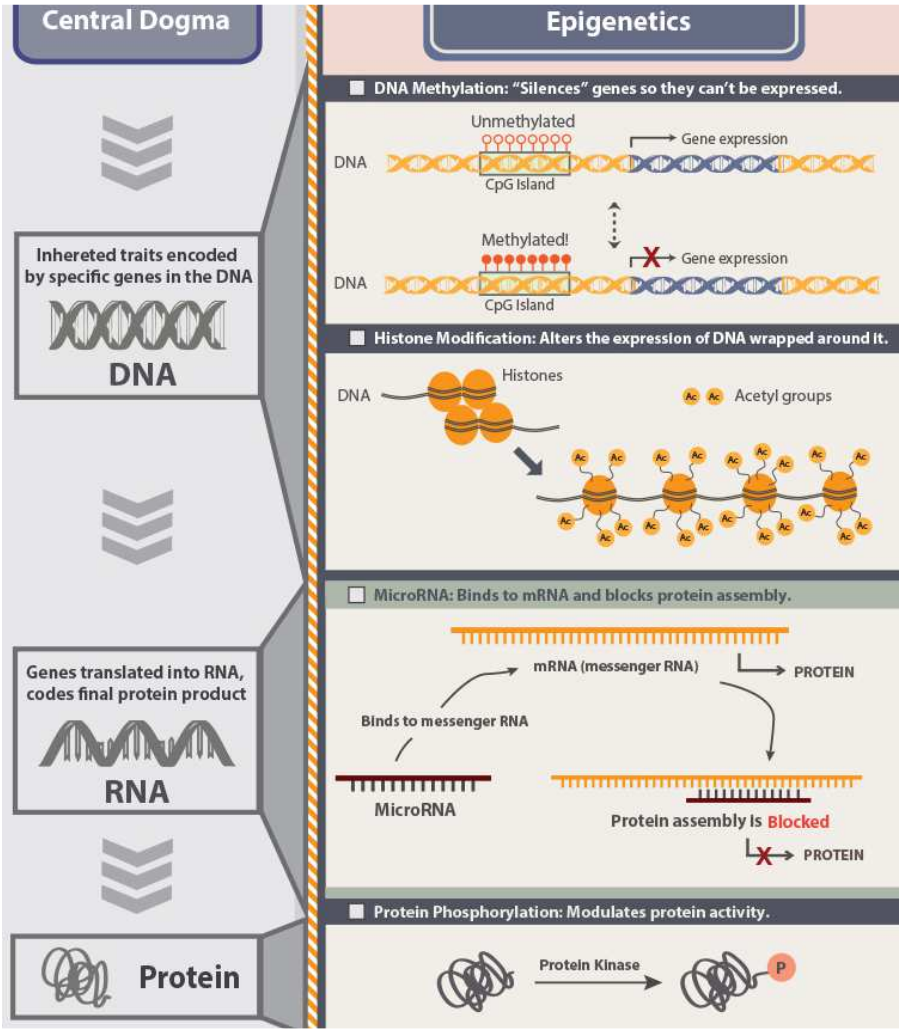
Juan Martinez-Pinna and Sergi Soriano, *Universitat d'Alacant, Alicante*
Bernat Soria, CIBERDEM and CABIMER, *Sevilla*

Grant Support: MINECO, Generalitat Valenciana, ISCarlos III and EFSD

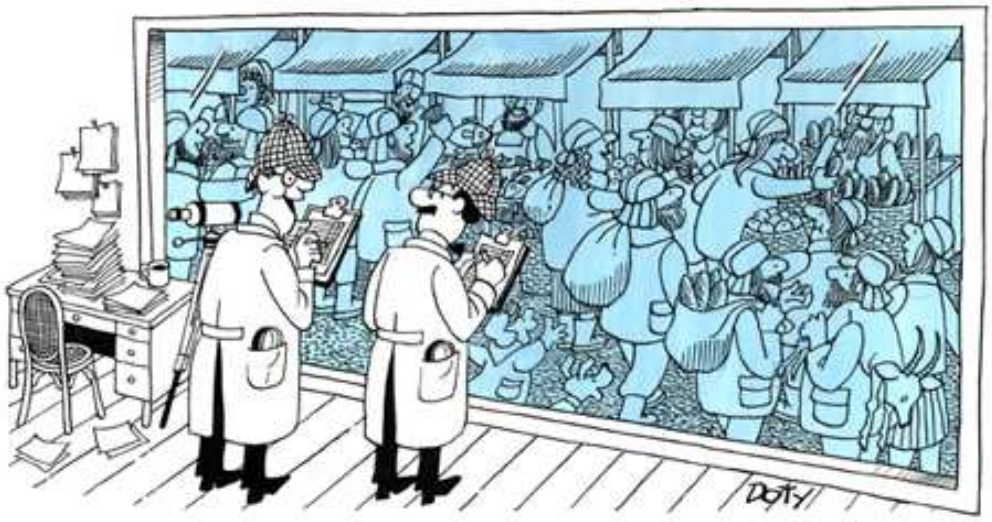
Bemidji Statement:

"We have the sacred right and obligation to ensure that our decision-making is guided by consideration of the welfare and well being of the seventh generation to come."




Central Dogma
Inhereted traits encoded by specific genes in the DNA
DNA
Genes translated into RNA, codes final protein product
RNA
Protein
Epigenetics
DNA Methylation: "Silences" genes so they can't be expressed.
Unmethylated
Gene expression
DNA
CpG Island
Methylated!
Gene expression
DNA
CpG Island
Histone Modification: Alters the expression of DNA wrapped around it.
DNA
Histones
Acetyl groups
MicroRNA: Binds to mRNA and blocks protein assembly.
mRNA (messenger RNA)
PROTEIN
Binds to messenger RNA
MicroRNA
Protein assembly is Blocked
PROTEIN
Protein Phosphorylation: Modulates protein activity.
Protein Kinase
P

BPA AND METABOLIC DISORDERS: EPIDEMIOLOGICAL EVIDENCE



"These studies always remind me of an ant colony I had as a kid!"

From http://preventcancer.aicr.org/site/PageServer?pagename=cancer_diet_mystery_epidemiological

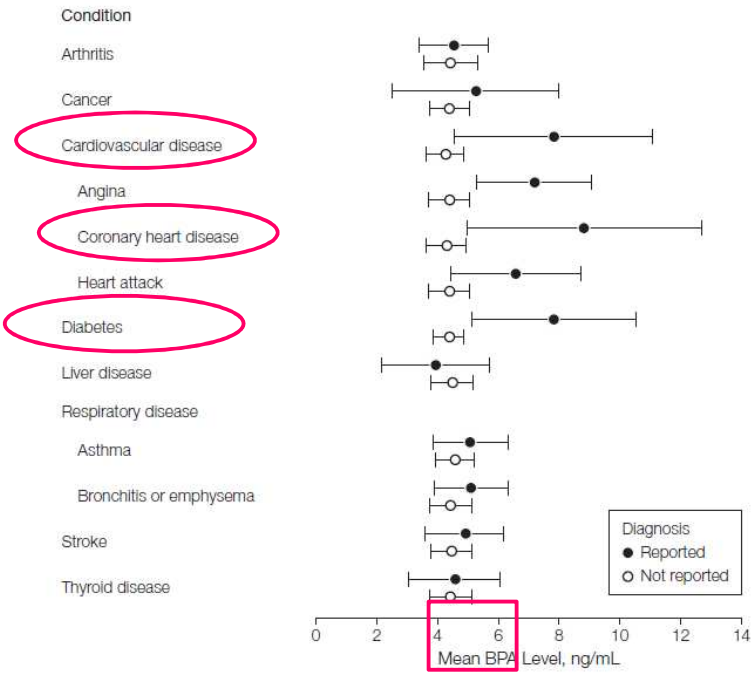
ORIGINAL CONTRIBUTION

(Reprinted) JAMA, September 17, 2008—Vol 300, No. 11

Association of Urinary Bisphenol A Concentration With Medical Disorders and Laboratory Abnormalities in Adults

Estimated Mean Bisphenol A (BPA) Concentrations in Relation to Reported Diseases and Conditions

Figure. Estimated Mean Bisphenol A (BPA) Concentrations in Relation to Reported Diseases and Conditions



Estimates adjusted for age and sex. Error bars indicate 95% confidence intervals.

CONCLUSIONS

Using data representative of the adult US population, we found that higher urinary concentrations of BPA were associated with an increased prevalence of cardiovascular disease, diabetes, and liver-enzyme abnormalities. These findings add to the evidence suggesting adverse effects of low-dose BPA in animals.

Iain A. Lang, PhD
Tamara S. Galloway, PhD
Alan Scarlett, PhD
William E. Henley, PhD
Michael Depledge, PhD, DSc
Robert B. Wallace, MD
David Melzer, MB, PhD

Urinary Bisphenol A and Type-2 Diabetes in U.S. Adults: Data from NHANES 2003-2008

Monica K. Silver[1], Marie S. O'Neill[1,2], MaryFran R. Sowers[2†], Sung Kyun Park[1,2*]

1 Department of Environmental Health Sciences, School of Public Health, University of Michigan, Ann Arbor, Michigan, United States of America, **2** Department of Epidemiology, School of Public Health, University of Michigan, Ann Arbor, Michigan, United States of America

PLoS ONE 6(10): e26868. doi:10.1371/journal.pone.0026868

Conclusions: Although higher urinary BPA was associated with elevated HbA1c and T2DM in the pooled analysis, it was driven by data from only one NHANES cycle. Additional studies, especially of a longitudinal design with repeated BPA measurements, are needed to further elucidate the association between BPA and T2DM.

J Clin Endocrin Metab. First published ahead of print September 28, 2011 as doi:10.1210/jc.2011-1682

ORIGINAL ARTICLE

Endocrine Research

Relationship between Urinary Bisphenol A Levels and Diabetes Mellitus

Anoop Shankar and Srinivas Teppala

Department of Community Medicine, West Virginia University School of Medicine, Morgantown, West Virginia 26506

TABLE 2. Association between urinary BPA and diabetes mellitus

BPA quartiles (ng/ml)	Sample size (diabetes %)	Age-, sex-adjusted, OR (95% CI)	Multivariable-adjusted, OR (95% CI)[a]
Quartile 1 (<1.10)	1121 (8.3)	1 (referent)	1 (referent)
Quartile 2 (1.10–2.10)	905 (10.8)	1.55 (1.19–2.02)	1.42 (1.03–1.96)
Quartile 3 (2.11–4.20)	977 (11.2)	1.60 (1.25–2.05)	1.48 (1.05–2.08)
Quartile 4 (>4.20)	964 (12.8)	1.81 (1.36–2.43)	1.68 (1.22–2.30)
p-trend		<0.0001	0.002

[a] Adjusted for age (years), gender, race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican-Americans, others), education categories (below high school, high school, above high school), smoking (never, former, current), alcohol intake (never, former, current), BMI (normal, overweight, obese), systolic and diastolic blood pressure (mm Hg), urinary creatinine (mg/dl), and total cholesterol (mg/dl).

TABLE 3. Association between urinary BPA and diabetes mellitus by BMI

	Normal weight		Overweight/obese	
BPA quartiles (ng/ml)	Sample size	Multivariable-adjusted, OR (95% CI)[a]	Sample size	Multivariable-adjusted, OR (95% CI)[a]
Quartile 1 (<1.10)	408	1 (referent)	713	1 (referent)
Quartile 2 (1.10–2.10)	276	2.75 (1.03–7.33)	629	1.27 (0.90–1.79)
Quartile 3 (2.11–4.20)	272	2.14 (0.79–5.81)	705	1.41 (1.00–1.98)
Quartile 4 (>4.20)	283	3.17 (1.23–8.18)	681	1.56 (1.09–2.24)
p-trend		0.03		0.01

[a] Adjusted for age (years), gender, race-ethnicity (non-Hispanic whites, non-Hispanic blacks, Mexican-Americans, others), education categories (below high school, high school, above high school), smoking (never, former, current), alcohol intake (never, former, current), systolic and diastolic blood pressure (mm Hg), urinary creatinine (mg/dl), and total cholesterol (mg/dl).

Acta Diabetol
DOI 10.1007/s00592-013-0472-z

ORIGINAL ARTICLE

Relationship between urinary bisphenol A levels and prediabetes among subjects free of diabetes

Charumathi Sabanayagam · Srinivas Teppala · Anoop Shankar

Sex differences in the association of urinary bisphenol-A concentration with selected indices of glucose homeostasis among U.S. adults

Hind A. Beydoun PhD [a], Suraj Khanal MBBS [a], Alan B. Zonderman PhD [b], May A. Beydoun PhD [b,*]

[a] *Graduate Program in Public Health, Eastern Virginia Medical School, Norfolk, VA*
[b] *Laboratory of Behavioral Neuroscience, National Institute on Aging/National Institutes of Health/Intramural Research Program, Baltimore, MD*

Annals of Epidemiology xxx (2013) 1–8

Results: Taking the first quartile as a referent, the third quartile of BPA level was positively associated with log-transformed level of insulin and β-cell function (homeostasis model assessment for β-cell function) as well as insulin resistance (log-transformed homeostasis model assessment for insulin resistance; homeostasis model assessment for insulin resistance ≥2.5), with significant BPA-by-sex interaction; these associations were stronger among males than among females. Irrespective of sex, the ratio of BPA-to-creatinine level was not predictive of indices of glucose homeostasis.

Research | Children's Health

A Section 508–conformant HTML version of this a
is available at http://dx.doi.org/10.1289/EHF

Bisphenol A and Adiposity in an Inner-City Birth Cohort

Lori A. Hoepner,[1,2,3] Robin M. Whyatt,[1,2] Elizabeth M. Widen,[4,5,6,7] Abeer Hassoun,[8] Sharon E. Oberfield,[8] Noel T. Mueller,[9] Diurka Diaz,[1,2] Antonia M. Calafat,[10] Frederica P. Perera,[1,2] and Andrew G. Rundle[1,2,4]

Prenatal exposure to BPA positively associated with increased BMI and adiposity in children

ELSEVIER

Environmental Research

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

Association of early life exposure to bisphenol A with obesity and cardiometabolic traits in childhood

Marina Vafeiadi [a,*], Theano Roumeliotaki [a], Antonis Myridakis [b], Georgia Chalkiadaki [a], Eleni Fthenou [a], Eirini Dermitzaki [c], Marianna Karachaliou [a], Katerina Sarri [a], Maria Vassilaki [a], Euripides G. Stephanou [b], Manolis Kogevinas [d,e,f], Leda Chatzi [a]

JAMA
The Journal of the American Medical Association

Association Between Urinary Bisphenol Concentration and Obesity Prevalence in Children and Adolescents

Leonardo Trasande, MD, MPP
Teresa M. Attina, MD, PhD, MPH
Jan Blustein, MD, PhD

OPEN ACCESS Freely available online

PLOS | ONE

Urine Bisphenol A Level in Relation to Obesity and

BPA levels in children associated with overweight and obesity

Urinary Bisphenol A and Obesity in US Children

Ruchi Bhandari*, Jie Xiao, and Anoop Shankar

Wang et al. Environmental Health 2012, 11:79
http://www.ehjournal.net/content/11/1/79

ENVIRONMENTAL HEALTH

RESEARCH Open Access

Association between bisphenol A exposure and body mass index in Chinese school children: a cross-sectional study

He-xing Wang[1], Ying Zhou[1*], Chuan-xi Tang[2], Jin-gui Wu[2], Yue Chen[3] and Qing-wu Jiang[1]

Toxicol. Res.
Vol. 30, No. 1, pp. 39-44 (2014)
Open Access http://dx.doi.org/10.5487/TR.2014.30.1.039
pISSN: 1976-8257 eISSN: 2234-2753 **Original Article**

Toxicological Research
Official Journal of
Korean Society of Toxicology
Available online at http://www.toxmut.or.kr

Association between Urinary Bisphenol A and Waist Circumference in Korean Adults

Ahra Ko†, Myung-Sil Hwang†, Jae-Hong Park, Hui-Seung Kang, Hee-Seok Lee and Jin-Hwan Hong

Research Article

Urinary Bisphenol A Levels and Measures of Obesity:

BPA levels in adults associated with overweight and obesity

Srinivas Teppala,[1] Suresh Madhavan,[2] and Anoop Shankar[1]

JCEM ONLINE

Brief Report—Endocrine Research

Urinary Bisphenol A (BPA) Concentration Associates with Obesity and Insulin Resistance

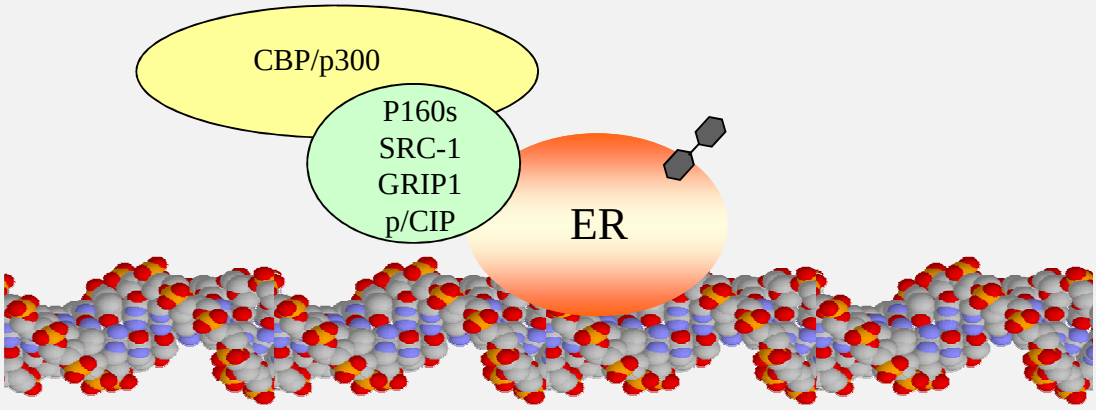
Tiange Wang,* Mian Li,* Bing Chen, Min Xu, Yu Xu, Yun Huang, Jieli Lu, Yuhong Chen, Weiqing Wang, Xiaoying Li, Yu Liu, Yufang Bi, Shenghan Lai, and Guang Ning

- **Modes of action/causality/vulnerable phases**

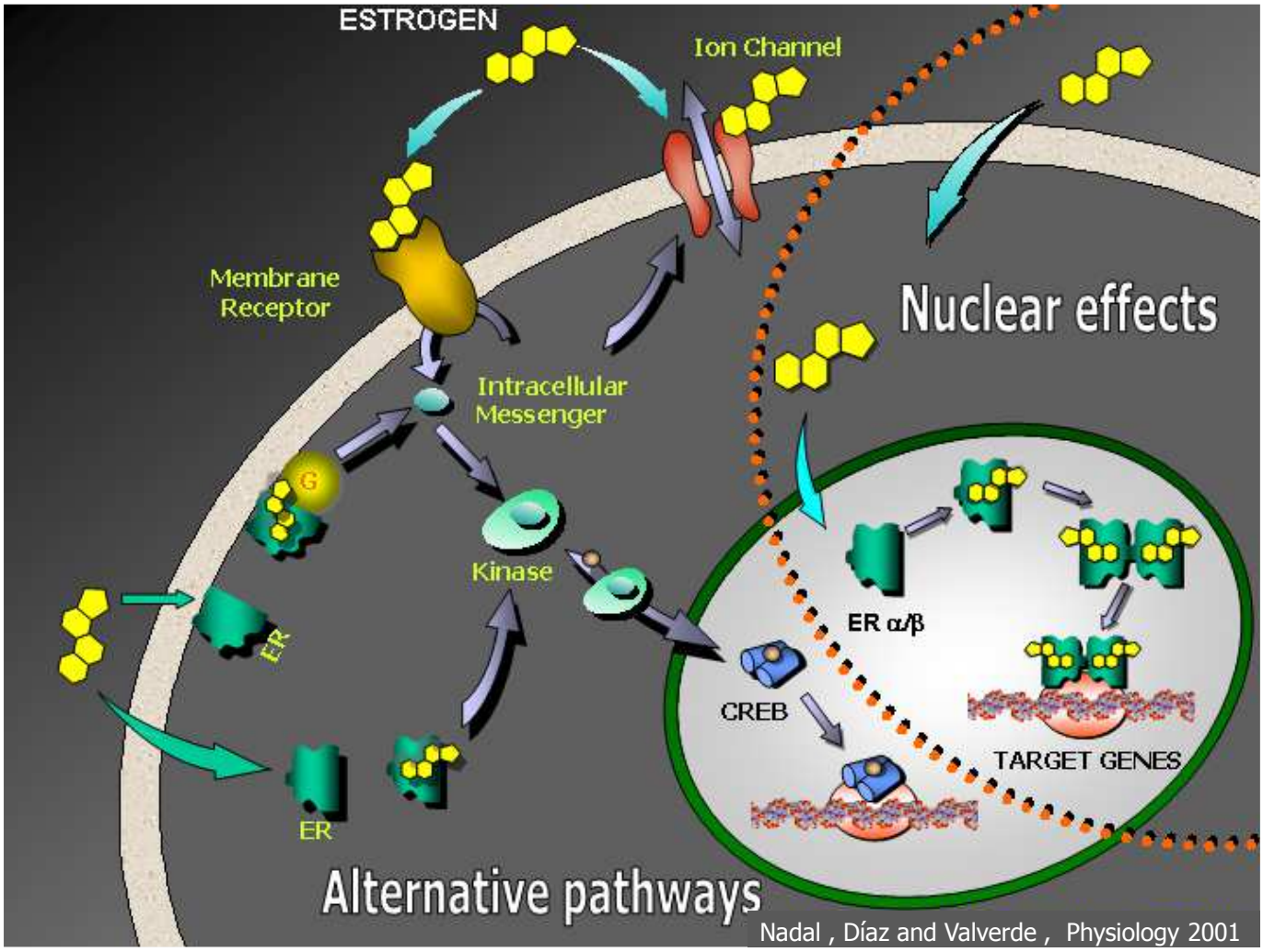
BASED ON EXISTING EVIDENCE, WE ARE CONFIDENT OF THE FOLLOWING:

- **BPA can act as an estrogen**
- **Timing of exposure and exposure dose/concentration are critical**
- **The effects of BPA might be different in individual cell types and these effects can vary depending on intrinsic and extrinsic influences**
- **When BPA binds to clasic nuclear estrogen receptors and induce specific ERE binding, BPA is usually less potent than estradiol**
- **When BPA action is mediated by estrogen receptors outside the nucleus, its potency is as high as that of estradiol, ranging within the pico-nano molar concentrations**
- **BPA exerts pleiotropic cellular and tissue-type specific effects and non-monotonic dose-response at the cellular and intracellular level at low physiological relevant concentrations**

The concept of estrogenicity of an exogenous chemical is based on the property of these compounds to bind ERα and ERβ, and to act subsequently as transcription factors when binding to the ERE in the DNA



Matthews JB, Twomey K, Zacharewski TR. In vitro and in vivo interactions of bisphenol A and its metabolite, bisphenol A glucuronide, with estrogen receptors alpha and beta. Chem Res Toxicol 2001;14(2):149-157.



Nadal , Díaz and Valverde , Physiology 2001

In the case of EDCs, the dose does not make the poison

Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses

Laura N. Vandenberg, Theo Colborn, Tyrone B. Hayes, Jerrold J. Heindel, David R. Jacobs, Jr., Duk-Hee Lee, Toshi Shioda, Ana M. Soto, Frederick S. vom Saal, Wade V. Welshons, R. Thomas Zoeller, and John Peterson Myers

Center for Regenerative and Developmental Biology and Department of Biology (L.N.V.), Tufts University, Medford, Massachusetts 02155; The Endocrine Disruption Exchange (T.C.), Paonia, Colorado 81428; Laboratory for Integrative Studies in Amphibian Biology (T.B.H.), Molecular Toxicology, Group in Endocrinology, Energy and Resources Group, Museum of Vertebrate Zoology, and Department of Integrative Biology, University of California, Berkeley, California 94720; Division of Extramural Research and Training (J.J.H.), National Institute of Environmental Health Sciences, National Institutes of Health, U.S. Department of Health and Human Services, Research Triangle Park, North Carolina 27709; Division of Epidemiology and Community Health (D.R.J.), School of Public Health, University of Minnesota, Minneapolis, Minnesota 55455; Department of Preventive Medicine (D.-H.L.), School of Medicine, Kyungpook National University, Daegu 702-701, Korea; Molecular Profiling Laboratory (T.S.), Massachusetts General Hospital Center for Cancer Research, Charlestown, Massachusetts 02129; Department of Anatomy and Cellular Biology (A.M.S.), Tufts University School of Medicine, Boston, Massachusetts 02111; Division of Biological Sciences (F.S.v.S.) and Department of Biomedical Sciences (W.V.W.), University of Missouri-Columbia, Columbia, Missouri 65211; Biology Department (T.Z.), University of Massachusetts-Amherst, Amherst, Massachusetts 01003; and Environmental Health Sciences (J.P.M.), Charlottesville, Virginia 22902

Endocrine Reviews, June 2012, 33(3):378–455

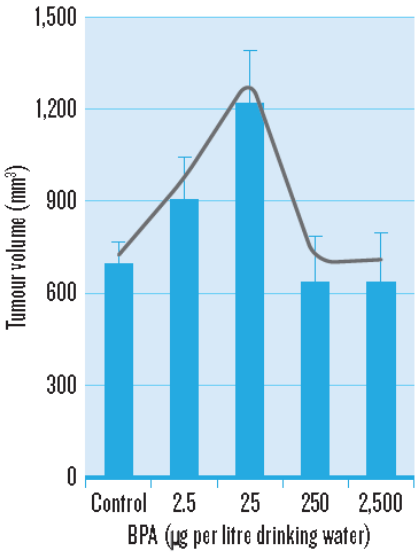
462 | NATURE | VOL 490 | 25 OCTOBER 2012

NEWS FEATURE

THE LEARNING CURVE

NON-MONOTONIC CURVES

Mice exposed to moderate doses of bisphenol A develop the largest tumours. Moderate and high doses are thought to induce tumour-cell proliferation, but high doses also trigger cell death.



SOURCE: Jenkins, S. *et al. Environ. Health Perspect.* **119**, 1604–1609 (2011)

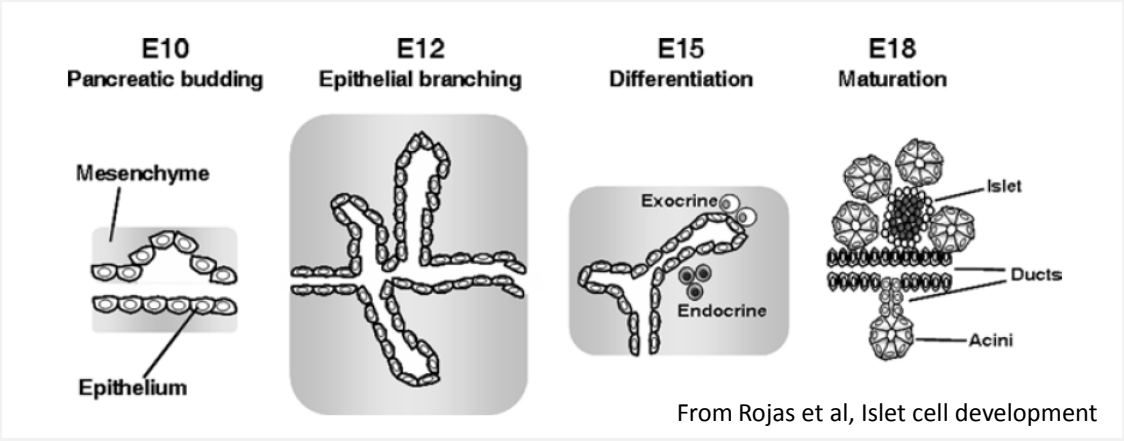
June 15, 2017

Dear Minister,

On behalf of The Endocrine Society, the European Society of Endocrinology and the European Society for Paediatric Endocrinology, representing the world's leaders in endocrinology and endocrine science, we express our serious concern with the European Commission's proposed criteria on Endocrine Disruptors (EDs). As scientific and medical professional societies devoted to the study of hormone-related diseases and disorders, we recognize that EDs contribute to serious health problems such as diabetes, obesity, and neurodevelopmental and reproductive disorders. These diseases affect the health and quality of life for people around the world and scientific criteria to effectively identify and regulate EDs are critical to ensure the health and well-being of the public, for this and next generations.

Fetal life: a critical “window” in which the appropiate number of beta cells are set in place

Embryogenesis



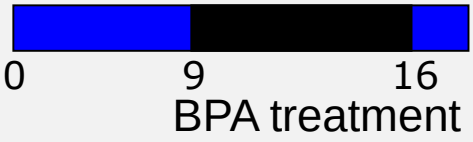
From Rojas et al, Islet cell development

Fetal growth → Late fetal gestation, fastest expansion of β-cell mass

Postnatal growth → Growth of β-cell mass but at reduced rate


PREGNANCY
AS A SENSITIVE WINDOW
FOR THE MOTHER

Bisphenol-A action on pregnant mice

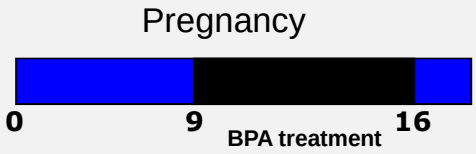


End points measured at pregnancy days 17 and 18

BPA 10 μg/kg/day

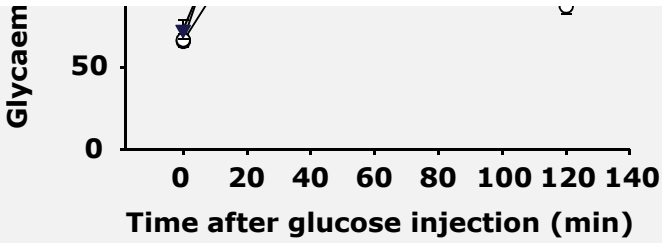
BPA 100 μg/kg/day

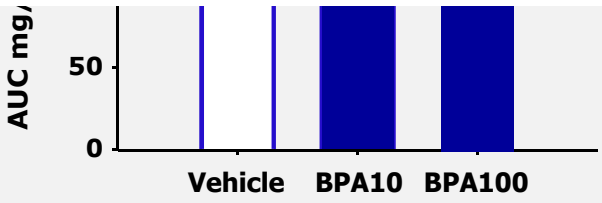
Alonso-Magdalena et al, EHP 2010



End points measured at pregnancy days 17 and 18

BPA-exposed pregnant females developed glucose intolerance which resembles gestational diabetes





GLUCOSE TOLERANCE TEST

Alonso-Magdalena et al, EHP 2010

CONSEQUENCES OF GESTATIONAL DIABETES IN THE LONG TERM FOR THE MOTHER

Delivery

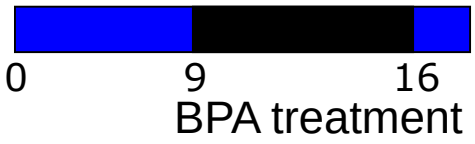
Diabetes

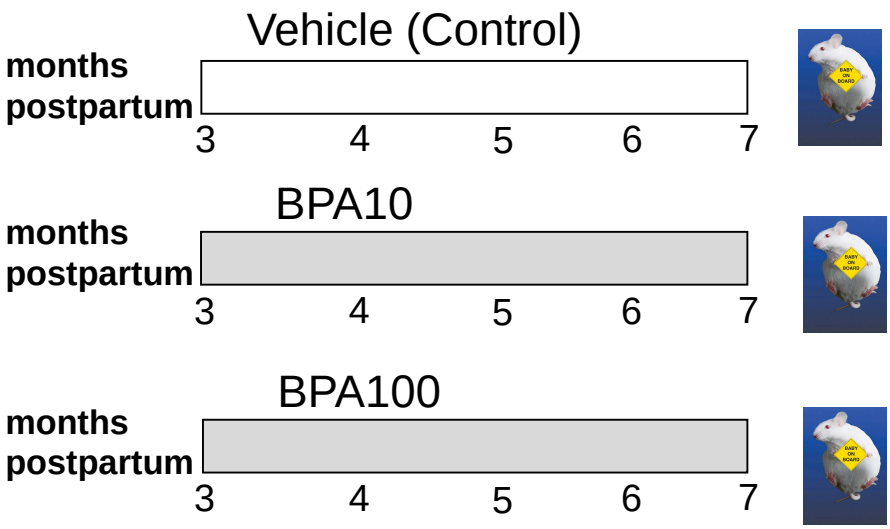
GESTATIONAL DIABETES: Any degree of glucose intolerance with onset or first recognition during pregnancy

Normally remission after delivery

- Increased risk for the development of **diabetes** usually type 2.
- Approximately 10% of women with GDM will have diabetes soon after delivery, rising to 20-60 % within 5-10 years

Animal model: Consequences in the long term for the mother?

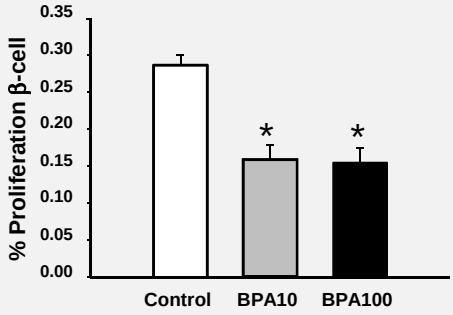


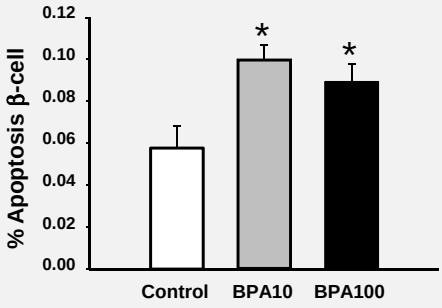


Alonso-Magdalena et al, Endocrinology 2015

BPA-exposed pregnant mums seven months after labour

- ❖ Glucose intolerance
- ❖ Decline of pancreatic β-cell function
- ❖ Decreased pancreatic β-cell mass
- ❖ Decreased β-cell proliferation
- ❖ Increased β-cell apoptosis

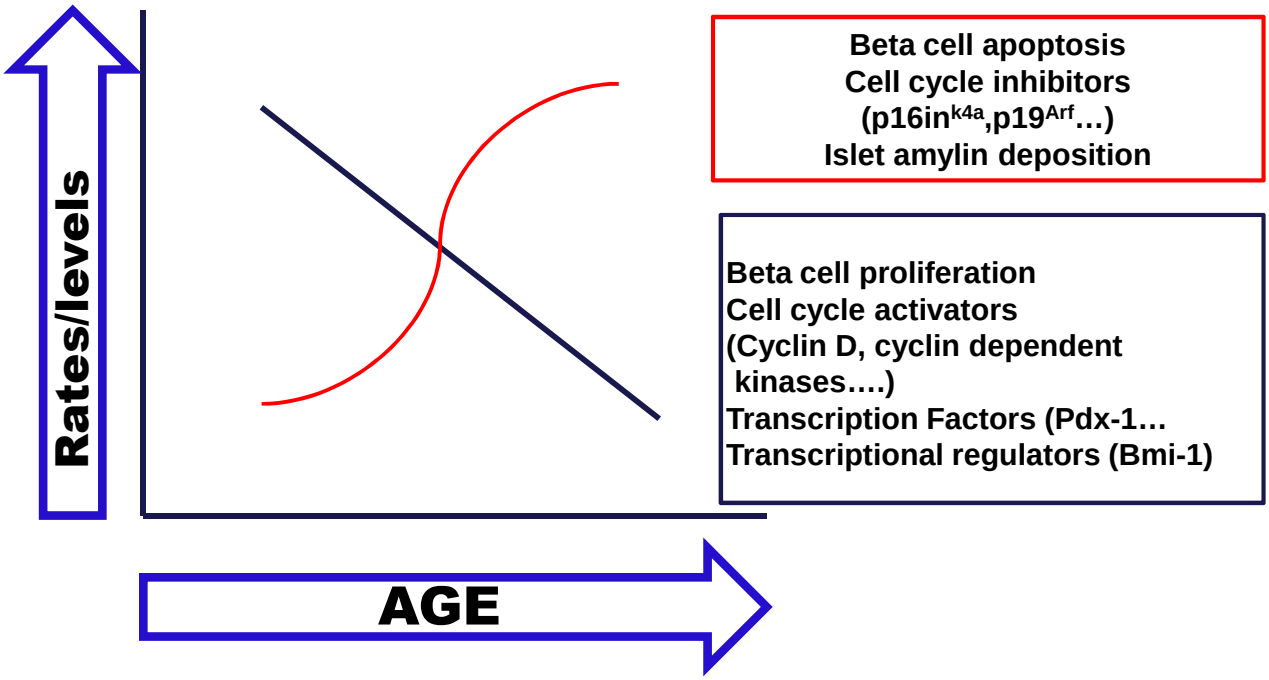




Alonso-Magdalena P. et al Endocrinology 2015

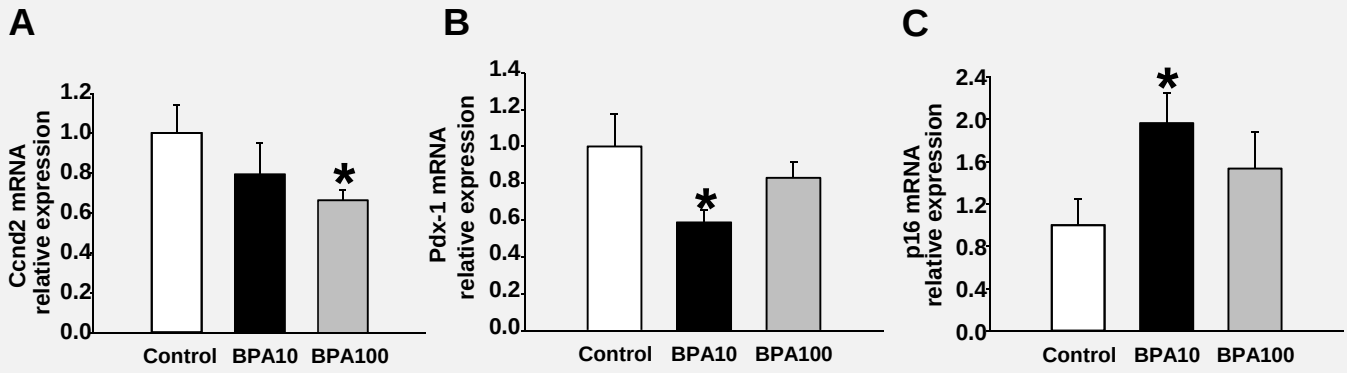
- **Decline of pancreatic β-cell function**
- **Reduced β-cell mass**
- **Decreased β-cell proliferation**
- **Increased β-cell apoptosis**

The aging pancreatic β-cell



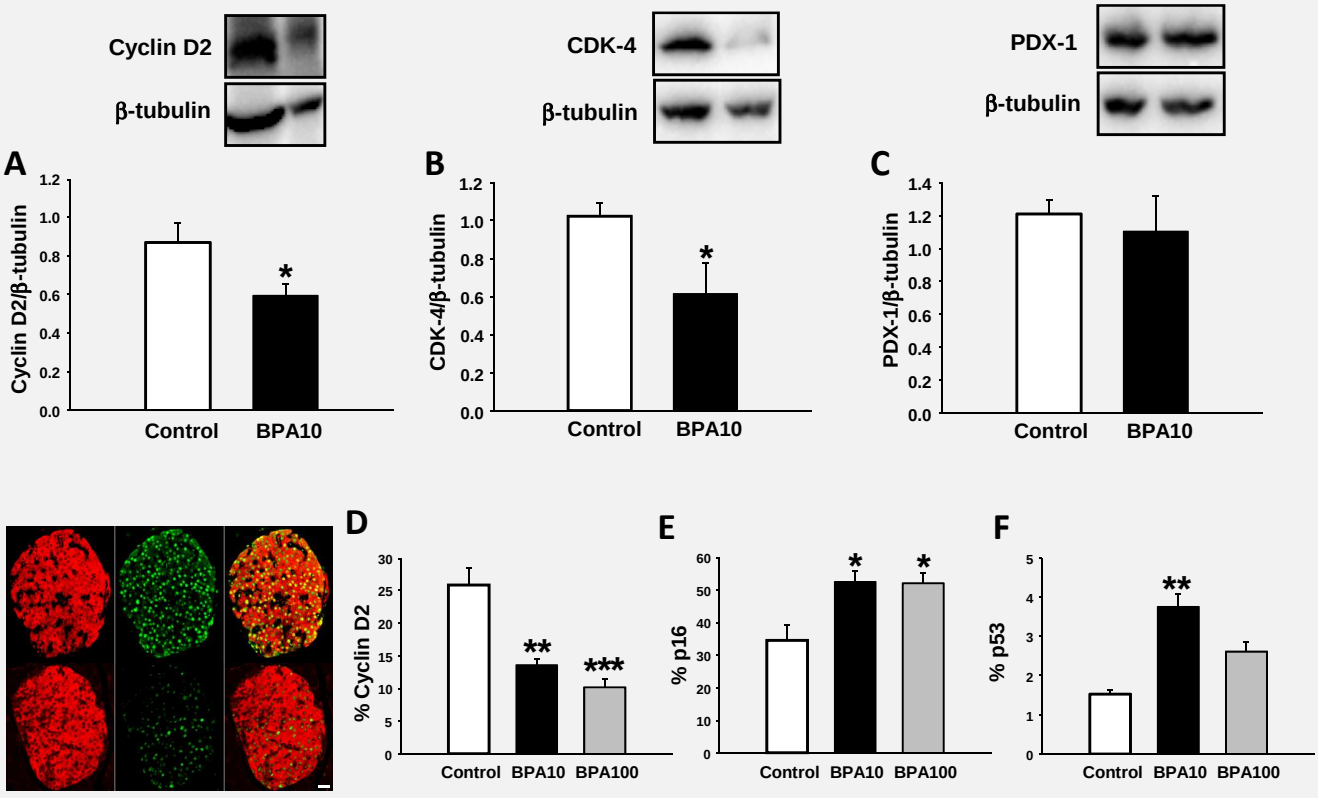
***Modified from Gunasekaran et al, Aging 2011*. Summary of the effects of age on various beta cell parameters. Multiple factors influence the beta cell as it ages.**

Altered gene expression of important cell cycle regulators in pancreatic β-cells seven months after labour



Alonso-Magdalena P. et al Endocrinology 2015

Altered protein expression of important cell cycle regulators in pancreatic β-cells seven months after labour



Alonso-Magdalena P. et al Endocrinology 2015

Levels of the 15 common contaminants found in human amniotic fluid

Phenolic compounds

- Bisphenol A (BPA) 0.2 $\cdot 10^{-8}$ M
- Triclosan **0.7** $\cdot 10^{-7}$ **M**
- Benzophenone-3 **0.9** $\cdot 10^{-7}$ **M**

Phthalates

- DBP **0.24** $\cdot 10^{-6}$**M**
- DEHP 10^{-7} **-10^{-6} M**

Organochlorine pesticides

- HCB **10^{-11} M**
- 4-4' DDE **10^{-9} M**

Polyaromatic hydrocarbons

- 2-Napthol 0.5 $\cdot 10^{-8}$ M

Perfluorinated compounds

- PFOS **0.8** 10^{-8} **M**
- PFOA **0.4** 10^{-8} **M**

Halogenated compounds

- PCB-153 0.2 $\cdot 10^{-8}$ M
- BDE-209 0.6 $\cdot 10^{-9}$ M
- Sodium perchlorate **10^{-8}M**

Heavy metals

- Methyl Mercury **10^{-7} M**
- Lead 0.2 $\cdot 10^{-9}$ M

Many of these compounds individually have been shown to behave as diabetogens, obesogens or both

J Clin Endocrin Metab. First published ahead of print November 16, 2011 as doi:10.1210/jc.2011-1989

JCEM ONLINE

Brief Report—Endocrine Research

Urinary Bisphenol A (BPA) Concentration Associates with Obesity and Insulin Resistance

Tiange Wang,* Mian Li,* Bing Chen, Min Xu, Yu Xu, Yun Huang, Jieli Lu, Yuhong Chen, Weiqing Wang, Xiaoying Li, Yu Liu, Yufang Bi, Shenghan Lai, and Guang Ning

TABLE 2. Association between urinary bisphenol A concentration and obesity, insulin resistance

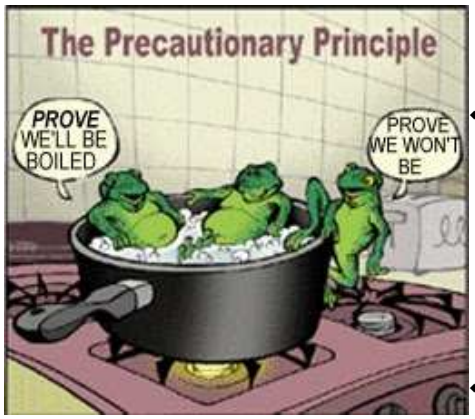
	BPA quartiles (ng/ml)			
	Quartile 1 (≤0.47)	Quartile 2 (0.48–0.81)	Quartile 3 (0.82–1.43)	Quartile 4 (>1.43)
Generalized overweight[a]				
Cases/participants	329/707	354/698	345/702	344/666
Age-, sex-, and urinary creatinine-adjusted OR (95% CI)	1.00	1.20 (0.97–1.48)	1.15 (0.93–1.43)	1.29 (1.04–1.61)
Multivariate adjusted OR (95% CI)[b]	1.00	1.23 (0.97–1.57)	1.28 (1.01–1.63)	1.24 (0.97–1.59)
Generalized obesity				
Cases/participants	144/851	150/848	145/847	178/844
Age-, sex-, and urinary creatinine-adjusted OR (95% CI)	1.00	1.15 (0.89–1.48)	1.16 (0.89–1.50)	1.57 (1.22–2.01)
Multivariate adjusted OR (95% CI)[b]	1.00	1.14 (0.87–1.50)	1.19 (0.90–1.57)	1.50 (1.15–1.97)
Abdominal obesity				
Cases/participants	389/851	417/848	394/847	407/844
Age-, sex-, and urinary creatinine-adjusted OR (95% CI)	1.00	1.29 (1.06–1.57)	1.25 (1.03–1.53)	1.43 (1.17–1.74)
Multivariate adjusted OR (95% CI)[b]	1.00	1.26 (1.02–1.57)	1.28 (1.03–1.59)	1.28 (1.03–1.60)
Insulin resistance				
Cases/participants	248/851	268/848	250/847	282/844
Age-, sex-, and urinary creatinine-adjusted OR (95% CI)	1.00	1.27 (1.02–1.57)	1.20 (0.97–1.50)	1.56 (1.26–1.94)
Multivariate adjusted OR (95% CI)[c]	1.00	1.18 (0.92–1.52)	1.09 (0.85–1.42)	1.37 (1.06–1.77)
Insulin resistance in participants with BMI <24 kg/m^2 (n = 1401)				
Cases/participants	47/331	58/344	45/357	53/322
Age-, sex-, and urinary creatinine adjusted OR (95% CI)	1.00	1.75 (1.14–2.68)	1.31 (0.83–2.06)	2.00 (1.28–3.13)
Multivariate adjusted OR (95% CI)[c]	1.00	1.55 (0.97–2.46)	1.04 (0.64–1.70)	1.94 (1.20–3.14)
Insulin resistance in participants with BMI ≥24 kg/m^2 (n = 1989)				
Cases/participants	201/473	210/504	205/490	229/522
Age-, sex- ,and urinary creatinine-adjusted OR (95% CI)	1.00	1.03 (0.79–1.35)	1.09 (0.84–1.43)	1.26 (0.97–1.65)
Multivariate adjusted OR (95% CI)[c]	1.00	1.06 (0.78–1.43)	1.11 (0.81–1.51)	1.21 (0.89–1.64)

[a] For the risk of generalized overweight, we defined participants with a BMI less than 24 as 0 (n = 1401) and generalized overweight as 1 (n = 1372), excluding obesity participants (n = 617) from the analysis.

[b] The OR (95% CI) were adjusted for age, sex, urinary creatinine concentration, smoking, alcohol drinking, education levels, systolic blood pressure, HDL-C, LDL-C, TC, TG, hs-CRP, fasting plasma glucose, fasting serum insulin, and serum ALT and GTT.

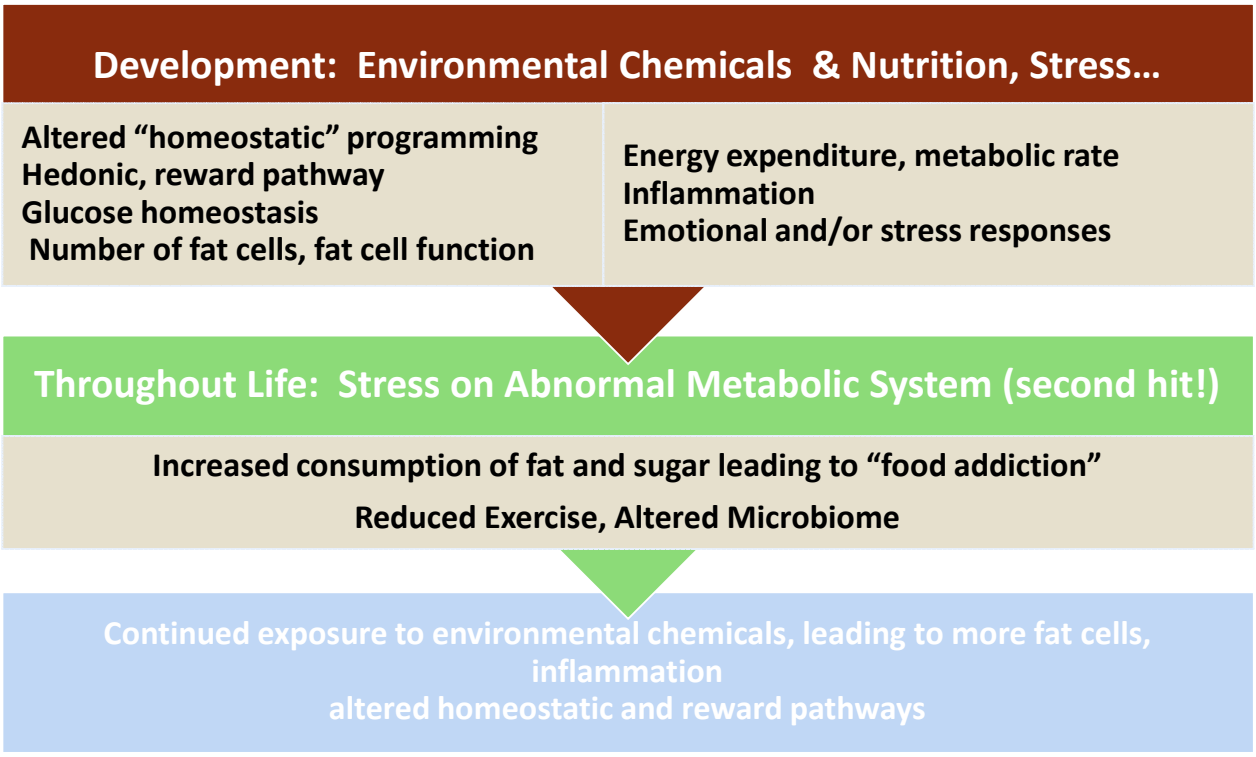
[c] The OR (95% CI) were further adjusted for BMI based on the adjustment indicated in *footnote b*.

PRECAUTIONARY PRINCIPLE



- **General practitioners, endocrinologists, pediatricians and obstetricians should consider advising patients on the exposure to those EDCs that may be risk factors for type 2 diabetes.**
- **This precaution would be particularly useful during the most sensitive periods of life, such as infancy and pregnancy.**
- **Public health policy should be readdressed for those EDCs, such as BPA, for which use is still unrestricted.**

The Perfect Storm for Diabetes and Obesity



Epidemic of Obesity and Metabolic Diseases

The Perfect Storm for Diabetes and Obesity

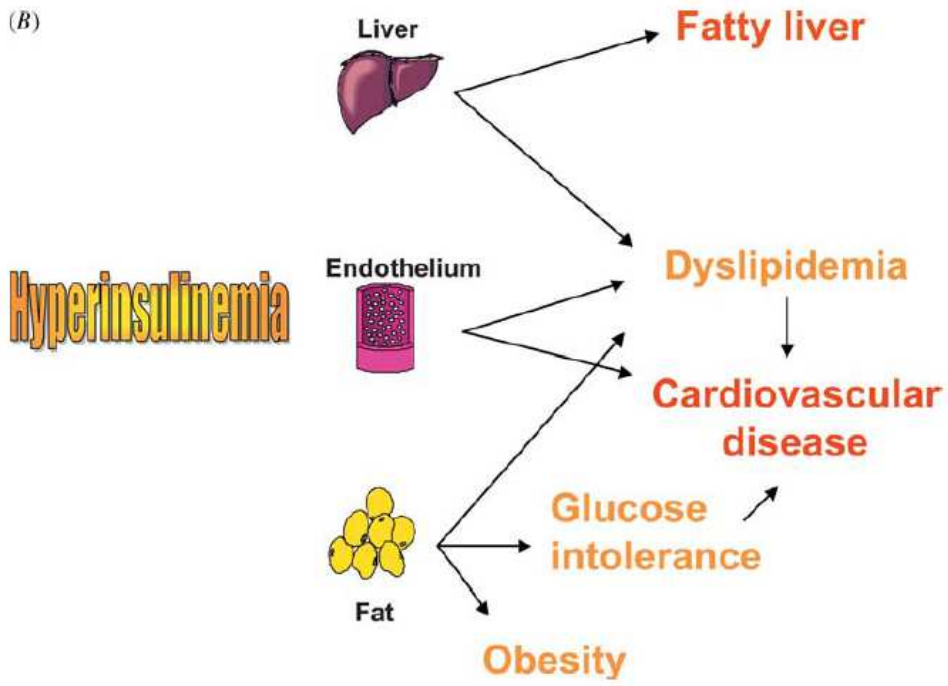
Development: Environmental Chemicals & Nutrition, Stress…

- Altered "programming" of components of the homeostatic system
- Hedonic, reward pathway
- Glucose homeostasis
- Fat cells
- Energy expenditure
- Inflammation/inflammatory responses

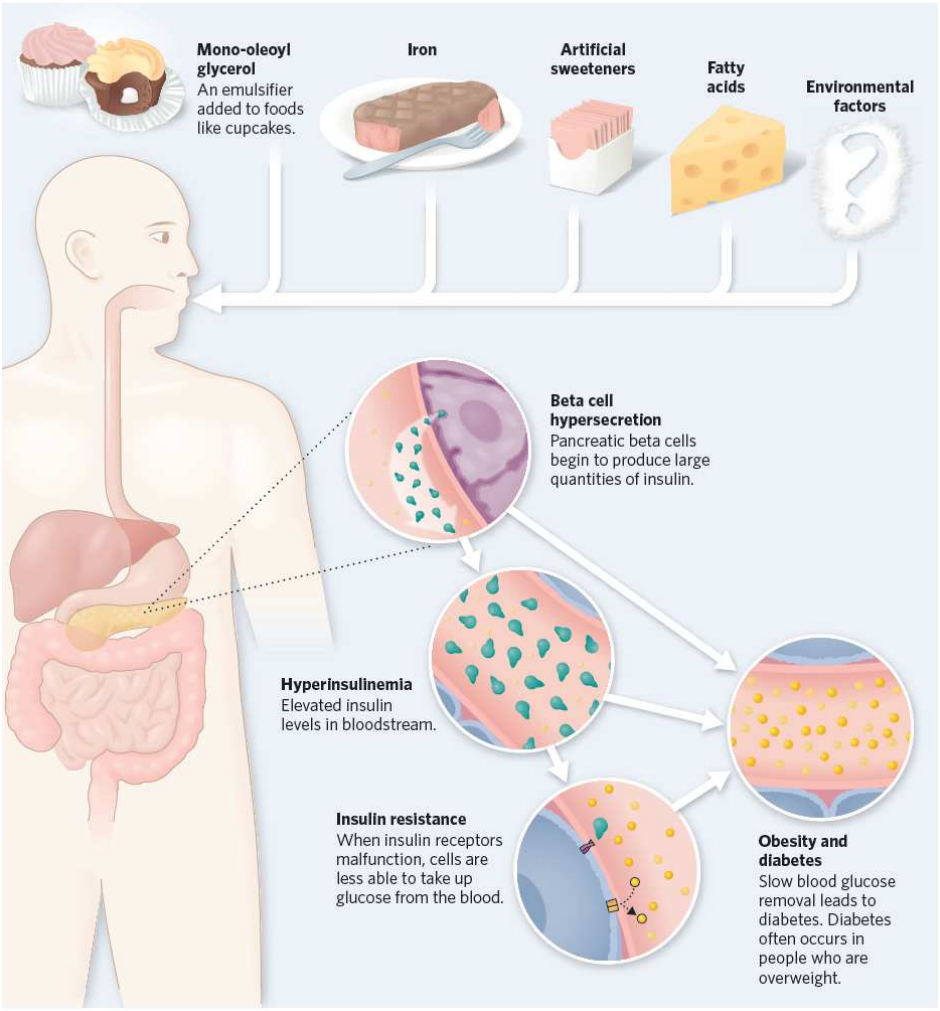
Throughout Life: Continued Stress on Abnormal Metabolic System (second hit!)

Continued exposure to environmental chemicals, leading to altered homeostatic and reward pathways, altered insulin signaling signaling, more fat cells, inflammation

Two different manners of understanding the etiology of diabetes…..



Sudha B. Biddinger1,2 and C. Ronald Kahn
Annu. Rev. Physiol. 2006. 68:123–58



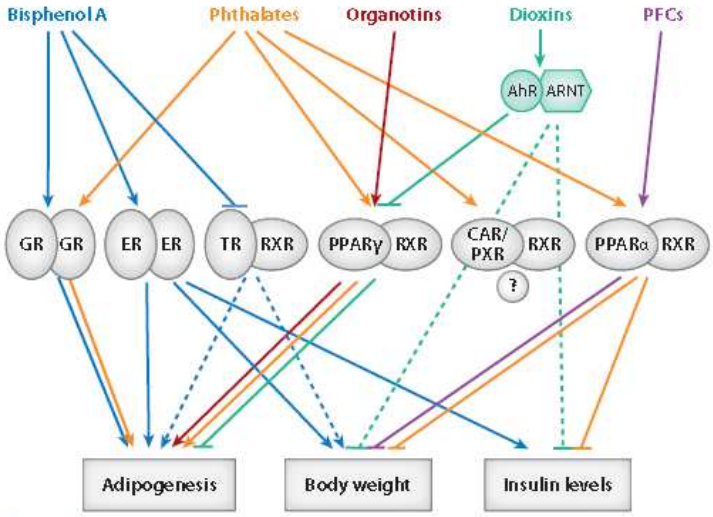
Why we are fat?
Bostonia Winter-Spring 2012

Hyperinsulinemia the cause of the problem

Corkey, Diabetes 2012
Alonso-Magdalena et al, EHP 2006
Nadal et al, Mol Cell Endocrinol 2009

Around the Home

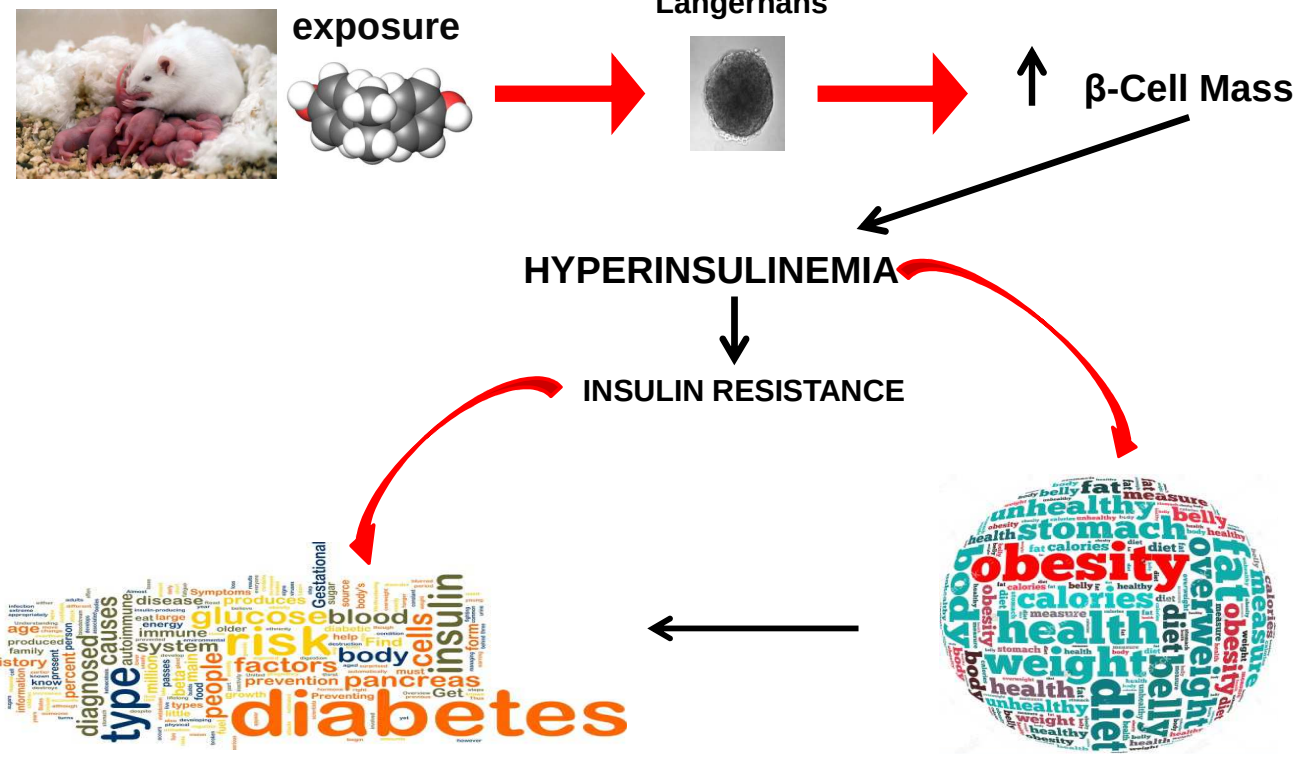
- ✓ For those with a submersible pump in their well who notice an oily film or fuel odor in their well water, check to see if the pump has failed and, if so, replace it. Contact your local Department of Public Health for information on how to clean the well
- ✓ Old fluorescent bulbs and deteriorating construction materials from older buildings should be replaced and discarded safely. Contact your local Department of Public Health
- ✓ Don't burn wood or trash
- ✓ Use hand-powered or electric lawn care equipment instead of gas-powered alternatives
- ✓ Forbid smoking indoors and advocate for measures to make public spaces tobacco-free
- ✓ Clean your floors regularly and remove dust from your home with a damp cloth.
- ✓ Plant trees, which filter out airborne gases and particulate matter

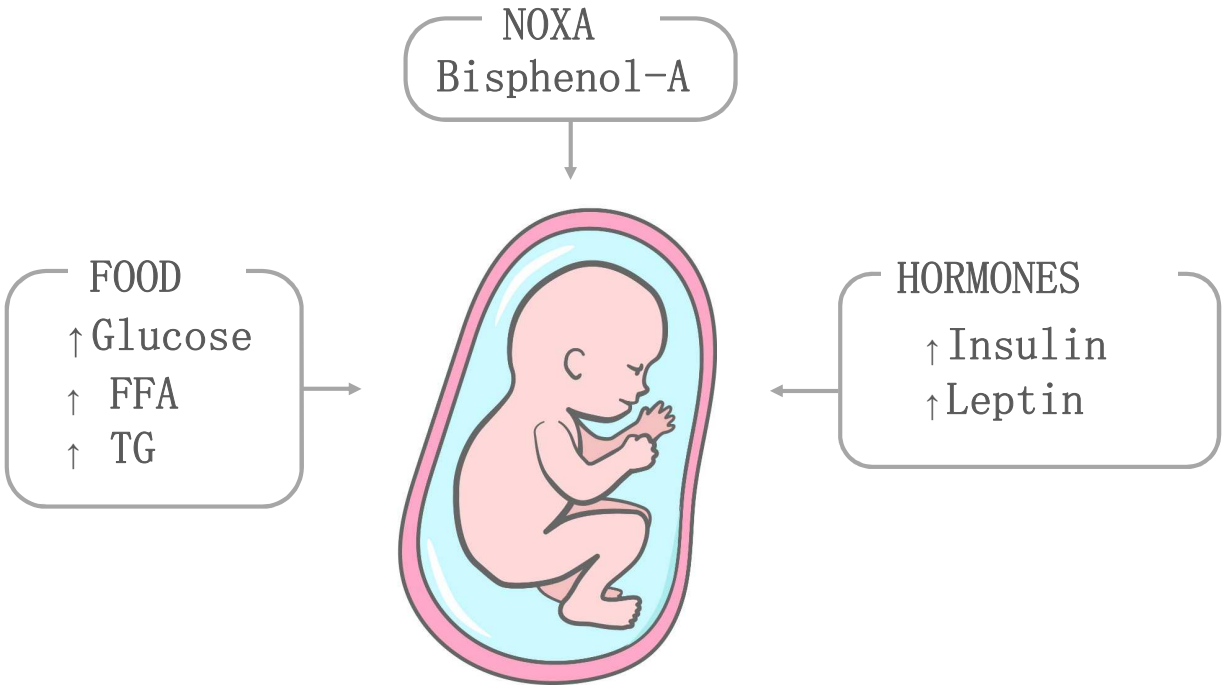


Endocrine Disruptors: From Endocrine to Metabolic Disruption

Cristina Casals-Casas and Béatrice Desvergne

TAKEN THE ETIOLOGY OF TYPE-2 DIABETES AND OBESITY FROM ANOTHER POINT OF VIEW

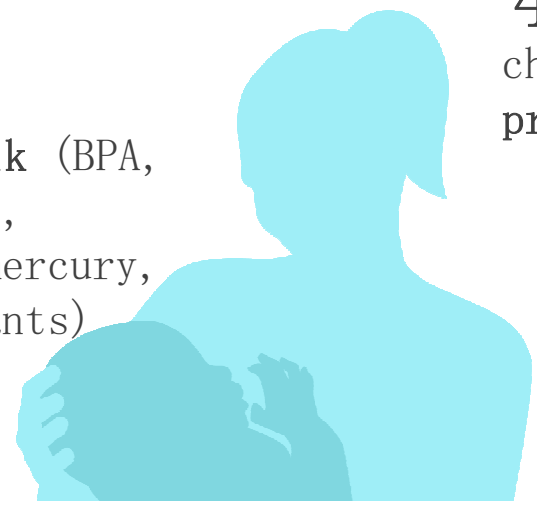




Diabetic mother's environment confers risks for T2D in mothers and offspring

We all carry a Chemical Body Burden

287 chemicals in **cord blood**



In **breast milk** (BPA, PCBs, dioxins, pesticides, mercury, flame retardants)

47 chemicals in every **pregnant woman** tested

The presence of **chemicals in the womb**
does not mean that they are causing harm.

However, every pregnant woman has a body burden
of chemicals without her knowledge
…with the **potential of harm.**

ANIMAL MODELS

EXPOSURE DURING ADULTHOOD

ADULT MALE MICE

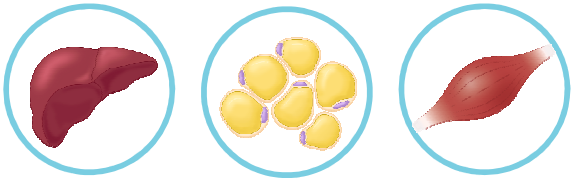
Bisphenol - A
100 µg/kg/day

LONG EVANS TOKUSHIMA FATTY RATS

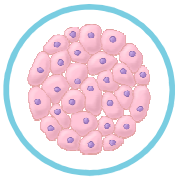
Accelerates onset of glucose intolerance and hyperinsulinemia

Yang et al, Toxicol Environ Health Sci 2014

INSULIN RESISTANCE



GLUCOSE INTOLERANCE

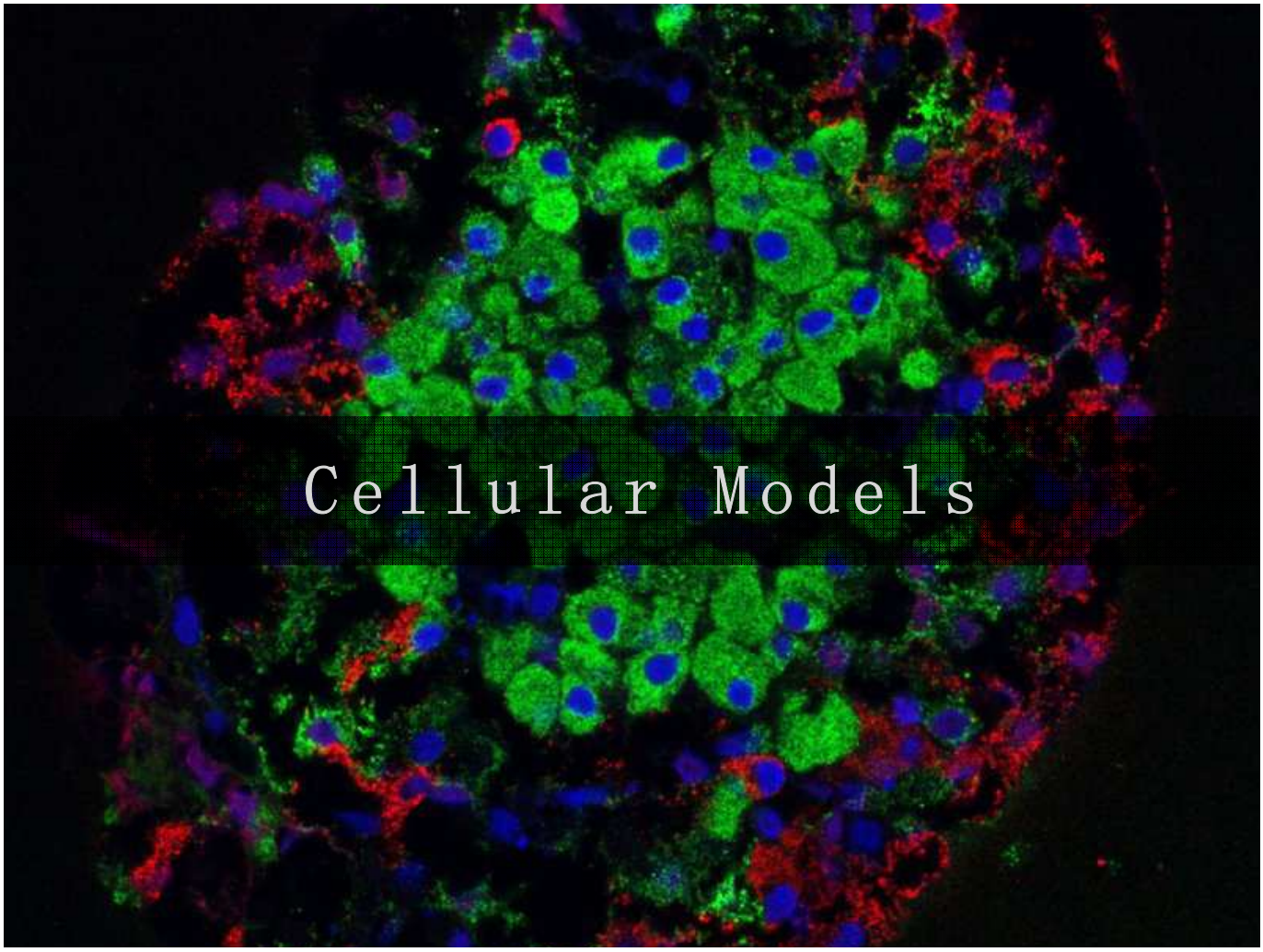


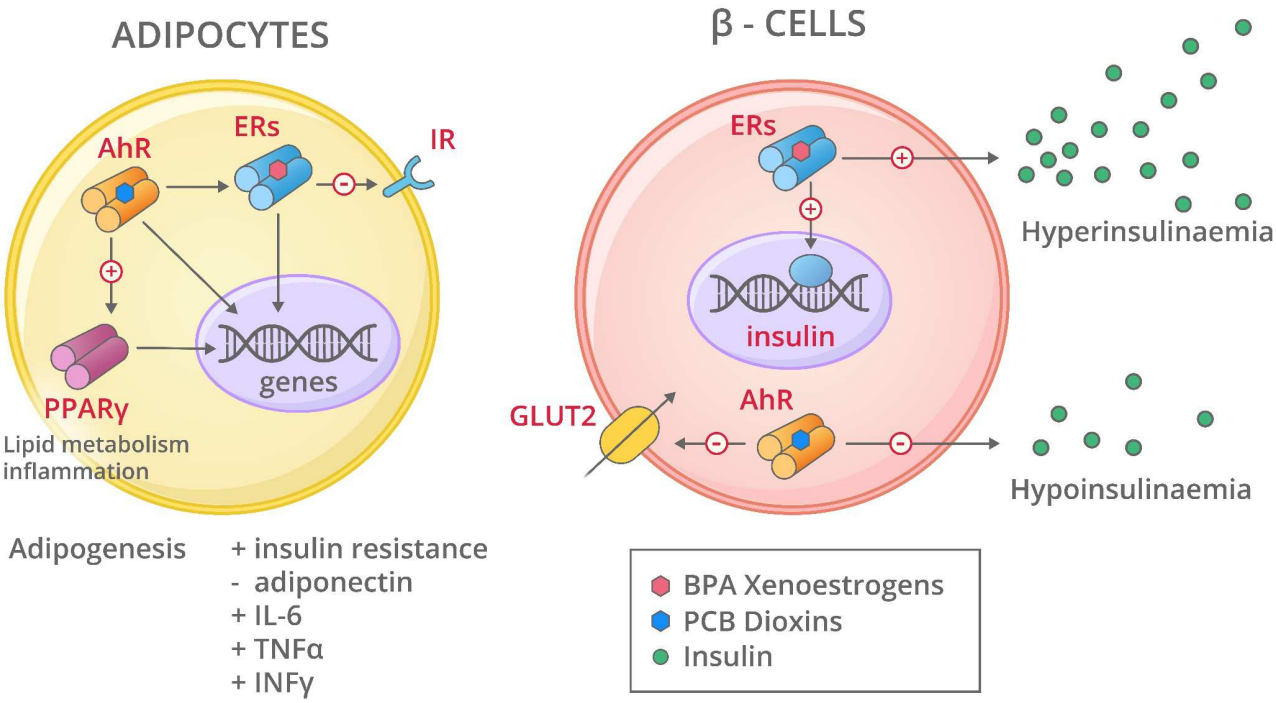
Alteration of insulin release
HYPERINSULINAEMIA

↓ Food intake
↓ Body Temperature
↓ Locmotor Activity

Alonso-Magdalena et al, EHP2006
Batista et al, Plos One 2012

Safe dose US-EPA: 50 mg/kg/day
Safe dose EFSA-EU: 4 mg/kg/day


Cellular Models



Adipogenesis
+ insulin resistance
- adiponectin
+ IL-6
+ TNFα
+ INFγ

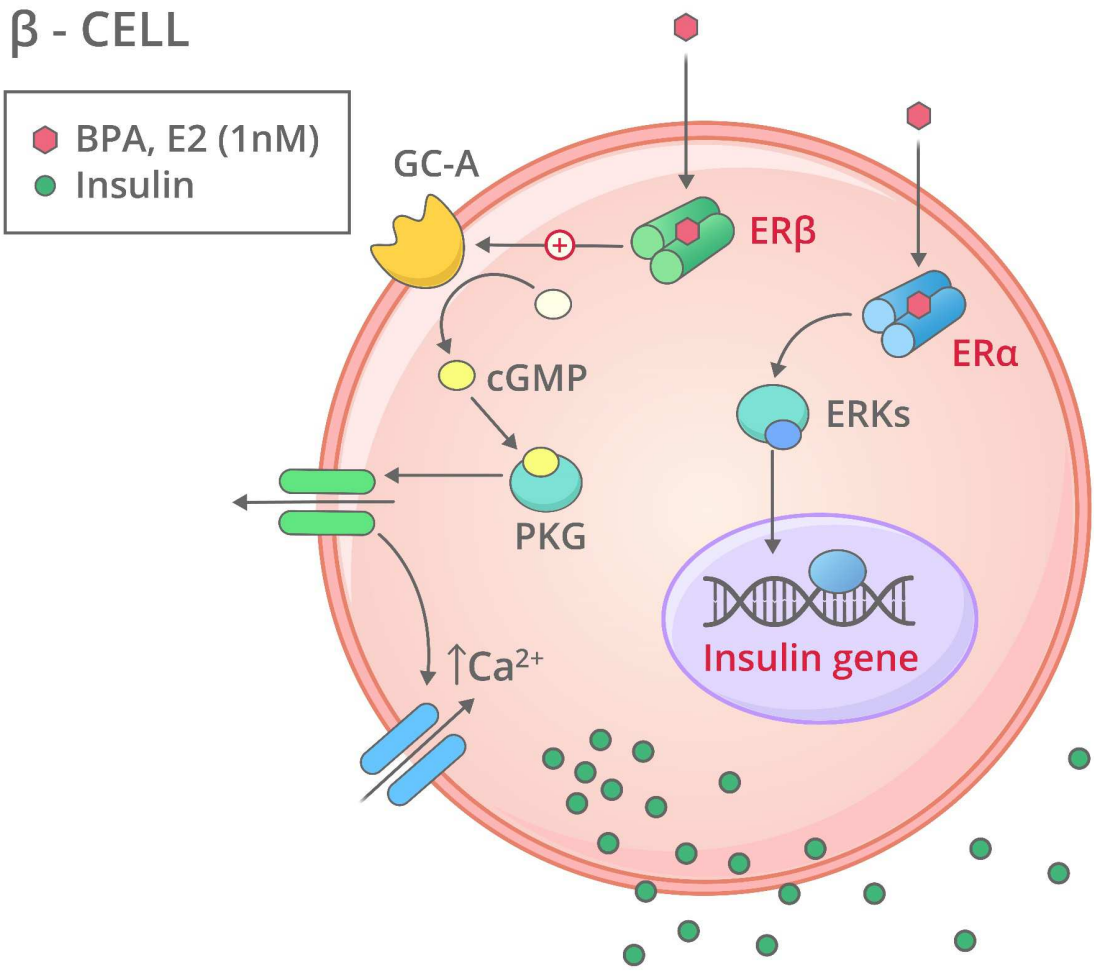
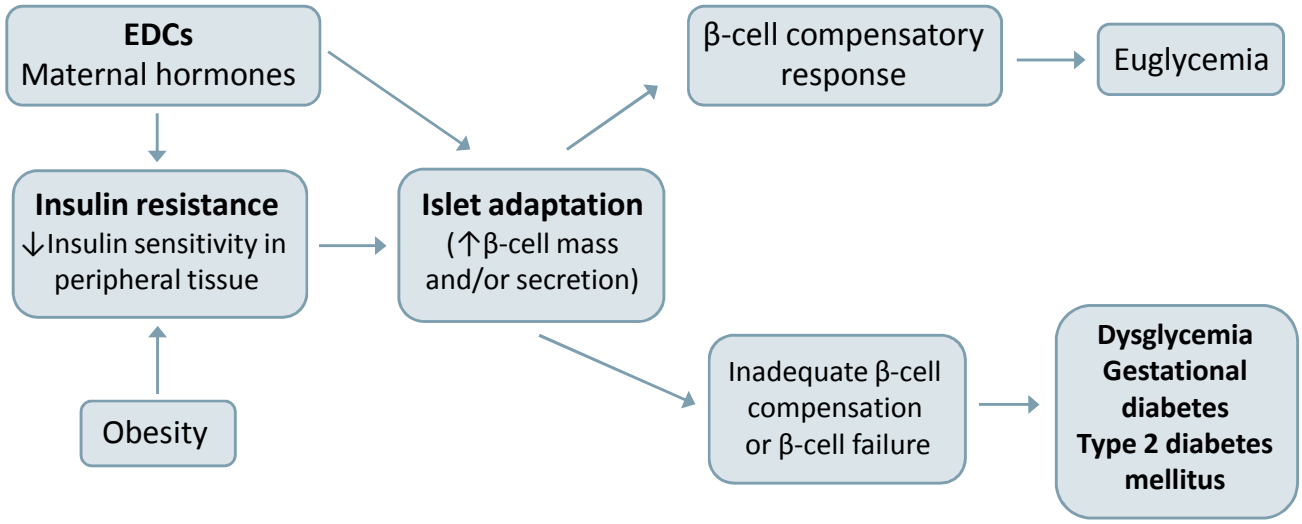

β - CELL
BPA, E2 (1nM)
Insulin
GC-A
ERβ
ERα
cGMP
ERKs
PKG
↑Ca2+
Insulin gene

Figure 1. Pregnancy-like actions of endocrine disrupting chemicals on islet function and glucose homeostasis



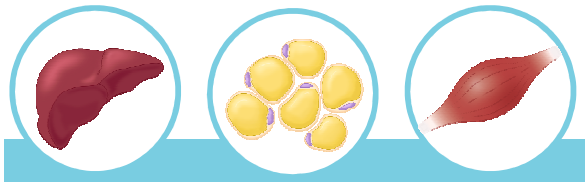
Alonso-Magdalena, P. *et al.* (2011) Endocrine disruptors in the etiology of type 2 diabetes mellitus *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2011.56

nature REVIEWS ENDOCRINOLOGY

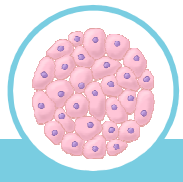
http://lameva.barcelona.cat/bcnmetropolis/es/editorial/descontaminar-el-cos-dels-habitants-de-les-ciutats/

http://lameva.barcelona.cat/bcnmetropolis/es/calaixera/reports/accions-individuals-per-protegir-se-dels-disruptors-endocrins/

The **etiology** of type 2 diabetes is based on

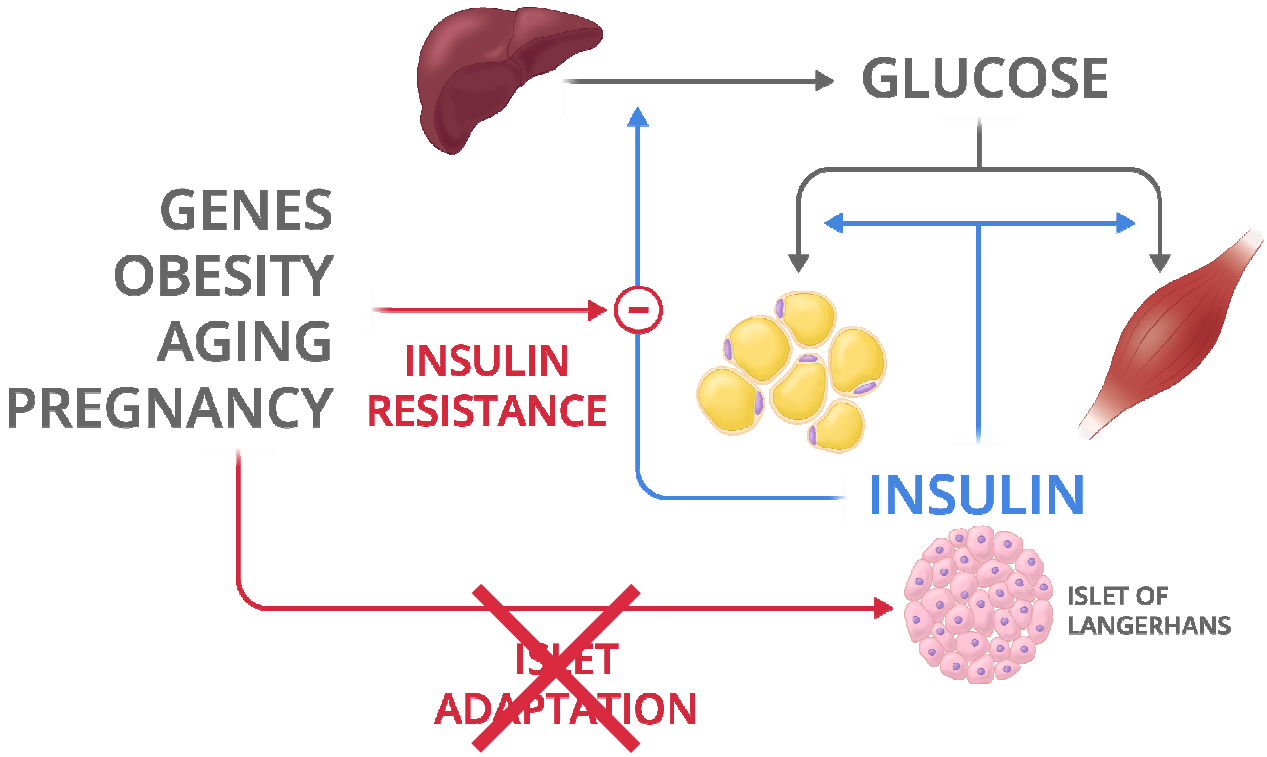


The induction of insulin resistance



Disruption of beta cell function

Genetic predisposition and **environmental factors** play key roles



1. ↑ Glucose-stimulated insulin secretion
2. ↑ Insulin biosynthesis
3. ↑ Beta-cell proliferation and islet volume

PREVENCION, DIAGNÓSTICO Y TRATAMIENTO DE LA OBESIDAD. POSICIONAMIENTO DE LA SOCIEDAD ESPAÑOLA PARA EL ESTUDIO DE LA OBESIDAD DE 2016.

PREVENTION, DIAGNOSIS AND TREATMENT OF OBESITY. 2016 POSITION STATEMENT OF THE SPANISH SOCIETY FOR THE STUDY OF OBESITY.

Autores: Lecube A [1*], Monereo S [2*], Rubio MA [3], Martínez-de-Icaya P [4], Marti A [5], Salvador J [6], Masmiquel L [7], Goday A [8], Bellido D [9], Lurbe E [10], García-Almeida JM [11], Tinahones FJ [12], García-Luna PP [13], Palacio E [14], Gargallo M [15], Breton I [16], Morales-Conde S [17], Caixàs A [18], Menéndez E [19], Puig-Domingo M [20], Casanueva FF [21].

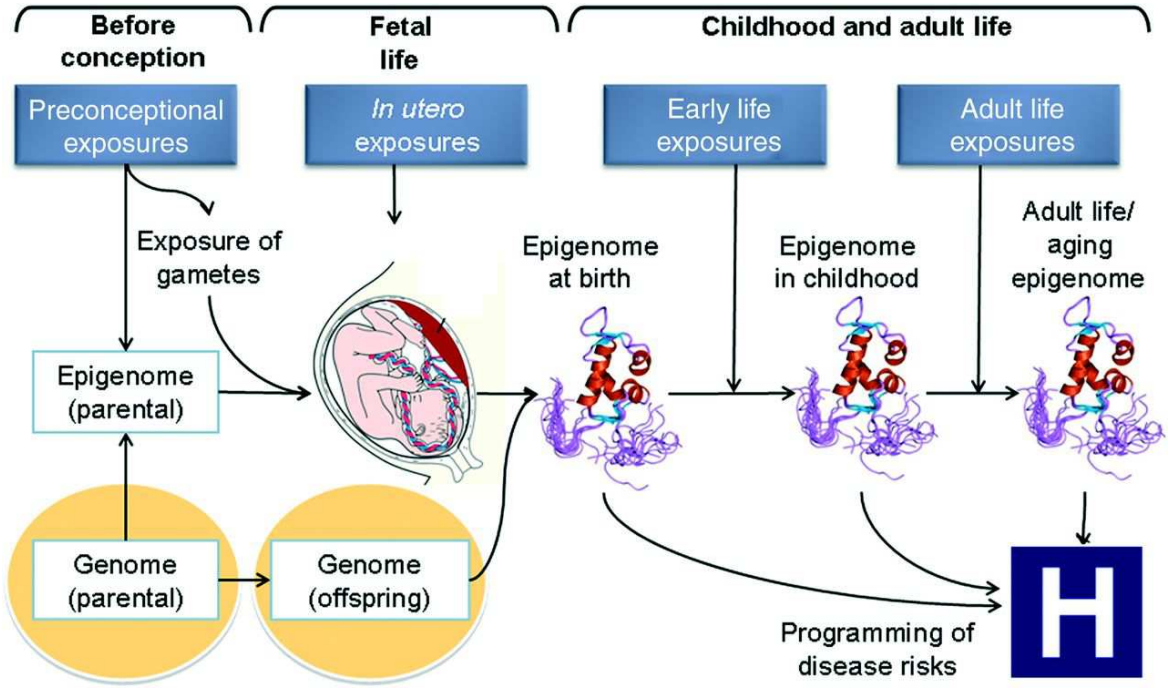
* Comparten primer autor.

Disruptores endocrinos: Los disruptores endocrinos son compuestos químicos exógenos con capacidad para alterar funciones hormonales de las personas expuestas. Estudios experimentales y epidemiológicos han mostrado como sustancias como bisfenol A, ftalatos, pesticidas órgano-fosforados, insecticidas como DDT o dioxinas pueden interferir distintas funciones hormonales, participando en alteraciones de la reproducción y la etiopatogenia del cáncer, pero también en la homeostasis metabólica, especialmente en el desarrollo de diabetes y, con menos evidencia, en la promoción de la obesidad [24,25]. Por ejemplo, tanto estudios

Applications of phthalates

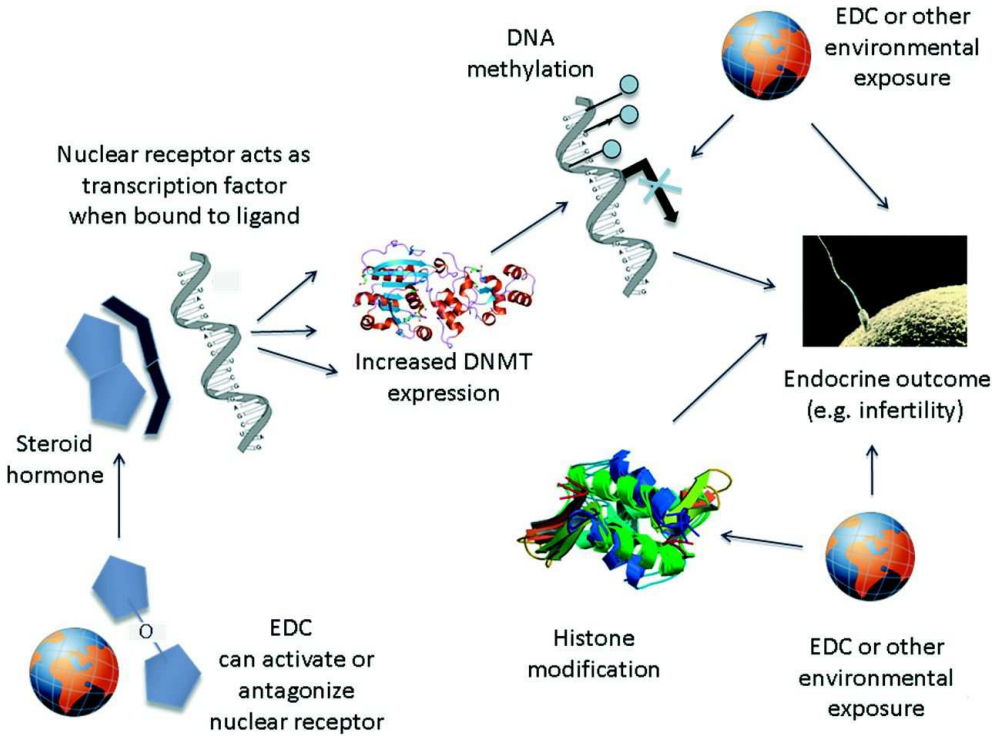
DEHP daily exposure 3-30 µg/kg/d
Urinary concentration of the DEHP metabolite MEHP is 1.5 µg/l
The reference dose of DEHP is 20 µg/kg of body weight per day

Figure 2 Exposures that occur preconceptionally, in utero, in early life and in adult life may result in epigenetic dysregulation.



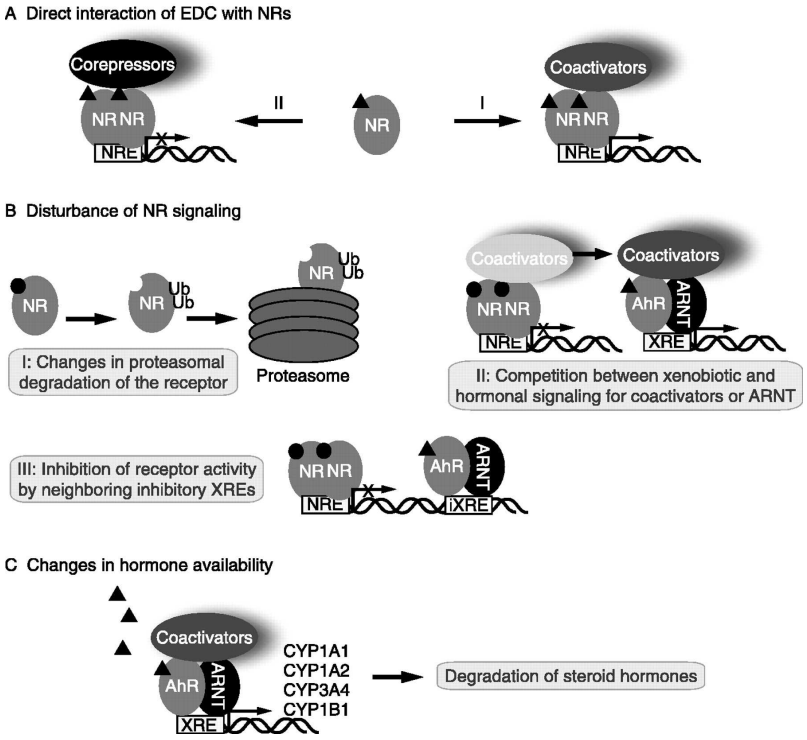
Abby F Fleisch et al. J Mol Endocrinol 2012;49:R61-R67

Figure 3 There are multiple potential causal pathways through which an environmental exposure may lead to epigenetic modifications, which may, in turn, impact clinical outcomes.



Abby F Fleisch et al. J Mol Endocrinol 2012;49:R61-R67

Figure 2 Mechanisms of endocrine disruption.



Elin Swedenborg et al. J Mol Endocrinol 2009;43:1-10

ENDOCRINE DISRUPTING CHEMICALS

HERBICIDES

2,4,-D
2,4,5,-T
Alachlor
Amitrole
Atrazine
Linuron
Metribuzin
Nitrofen
Trifluralin

FUNGICIDES

Benomyl
Ethylene thiourea
Fenarimol
Hexachlorobenzene
Mancozeb
Maneb
Metiram - complex
Tri-butyl-tin
Vinclozolin
Zineb

INSECTICIDES

Aldicarb
beta-HCH
Carbaryl
Chlordane
Chlordecone
DBCP
Dicofol
Dieldrin
DDT and metabolites
Endosulfan
Heptachlor / H-epoxide
Lindane (gamma-HCH)
Malathion
Methomyl
Methoxychlor
Oxychlordane
Parathion
Synthetic pyrethroids
Transnonachlor
Toxaphene

INDUSTRIAL CHEMICALS

Bisphenol - A
Polycarbonates
Butylhydroxyanisole (BHA)
Cadmium
Chloro- & Bromo-diphenyl ether
Dioxin (2,3,7,8-TCDD)
Furans
Lead
Manganese
Methyl mercury
Nonylphenol
Octylphenol
PBDEs
PCBs
Pentachlorophenol
Penta- to Nonylphenols
p-tert-Pentylphenol
Phthalates
Styrene

ENDOCRINE DISRUPTING CHEMICALS

HERBICIDES
2,4,-D
2,4,5,-T
Alachlor
Amitrole
Atrazine
Linuron
Metribuzin
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FUNGICIDES
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Ethylene thiourea
Fenarimol
Hexachlorobenzene
Mancozeb
Maneb
Metiram - complex
Tri-butyl-tin
Vinclozolin
Zineb

INSECTICIDES
Aldicarb
beta-HCH
Carbaryl
Chlordane
Chlordecone
DBCP
Dicofol
Dieldrin
DDT and metabolites
Endosulfan
Heptachlor / H-epoxide
Lindane (gamma-HCH)
Malathion
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Oxychlordane
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INDUSTRIAL CHEMICALS
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Nonylphenol
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PBDEs
PCBs
Pentachlorophenol
Penta- to Nonylphenols
p-tert-Pentylphenol
Phthalates
Styrene

Testosterone synthesis inhibitor
Thyroid hormone transport inhibitor

Estrogen receptor agonist
Androgen receptor antagonist

Exposures to Endocrine Disruptors Are Ubiquitous

Agricultural Chemicals
(pesticides/herbicides/fungicides),
Food Additives

Industrial Chemicals and By-Products
(Air Pollutants, solvents, PCBs)

Waste Products
(Dioxin, PAHs)

Some bioaccumulate and/or are persistent

Pharmaceutical Products
Phytochemicals

Personal Care Products, Flame Retardants,
Water Proof Coatings, packaging
(BPA, phthalates, parabens, PFOA/PFOS)

Graphics by Paul Volden

Bisphenol A (BPA)

What is BPA?

- BPA, is a chemical widely used to make polycarbonate plastics & epoxy resins

Where is BPA found?

- food & drink packaging, CDs, thermal paper products, impact-resistant safety equipment



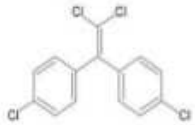



- The major human exposure route to BPA is → **DIET**
- Found in 93% of children and adults tested in 2003–04 (NHANES)

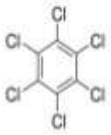
ENDOCRINE DISRUPTOR:
Estrogen, may also interfere with androgens, thyroid hormones, & glucocorticoid receptors

Persistent Organic Pollutants - POPs

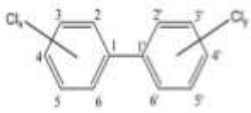
DDE

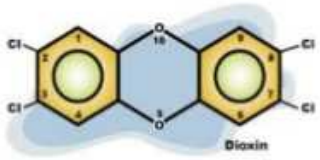


HCB



PCBs





Chemical stability

+

Resistance to degradation

+

Long half lives

+

Lipophilic properties

- **Persist** in the environment
- **Bioaccumulate** through the **food chain**
- **Endocrine disruptors**

Exposure through diet

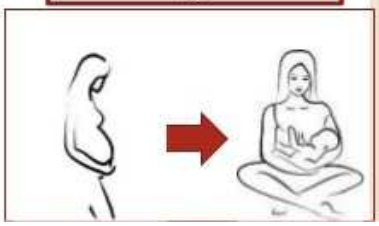
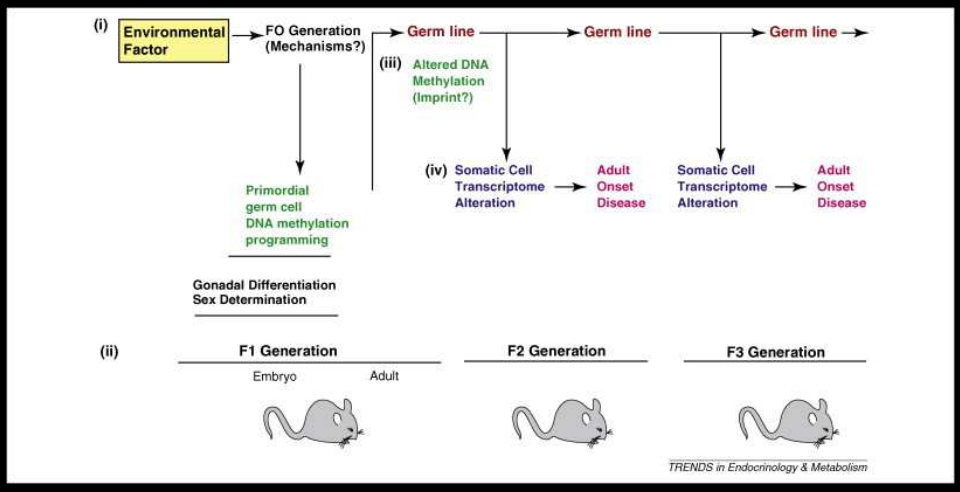


Figure 2



Trends in Endocrinology & Metabolism 2010 21, 214-222DOI: (10.1016/j.tem.2009.12.007)

Transgenerational Inheritance

In the case of an exposed female mouse, if she is pregnant, the fetus can be affected in utero (F1), as can the germline of the fetus (the future F2)

- considered to be parental effects, leading to intergenerational epigenetic inheritance
- Only F3 individuals can be considered as true transgenerational inheritance

Does it exist in humans?

Heard and Martienssen (2014) Cell

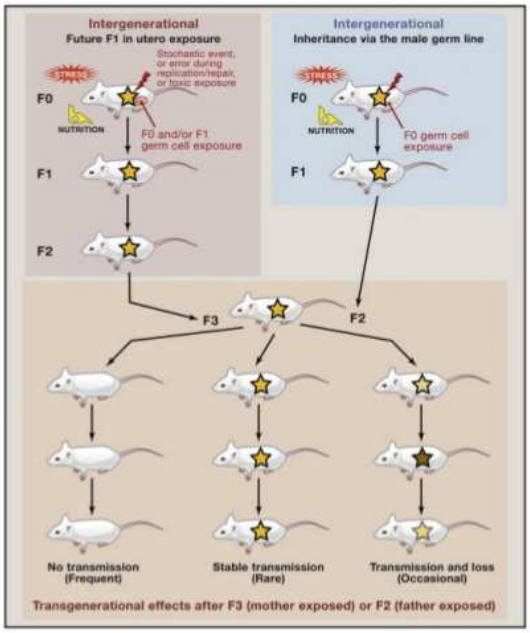
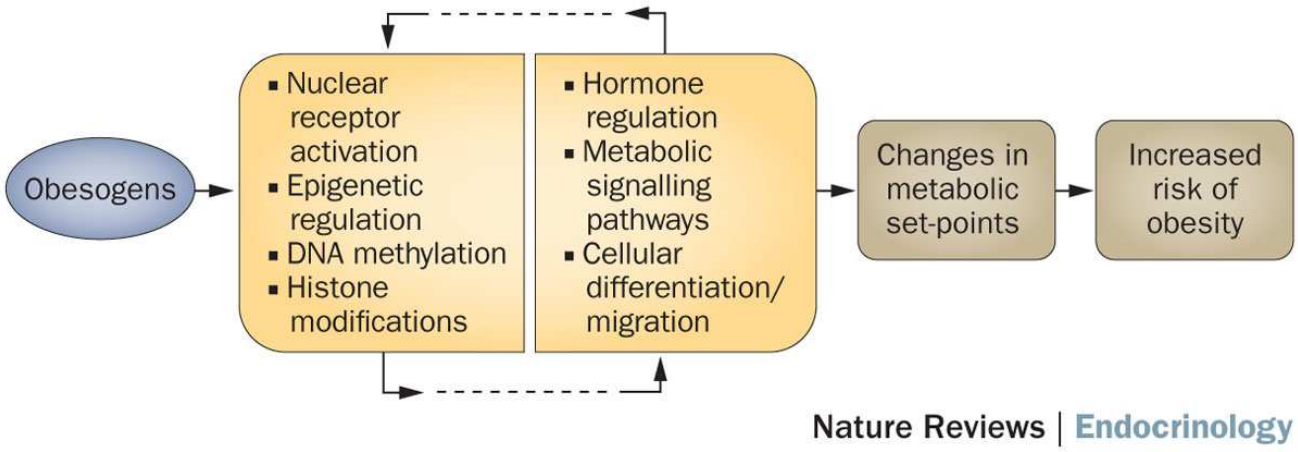
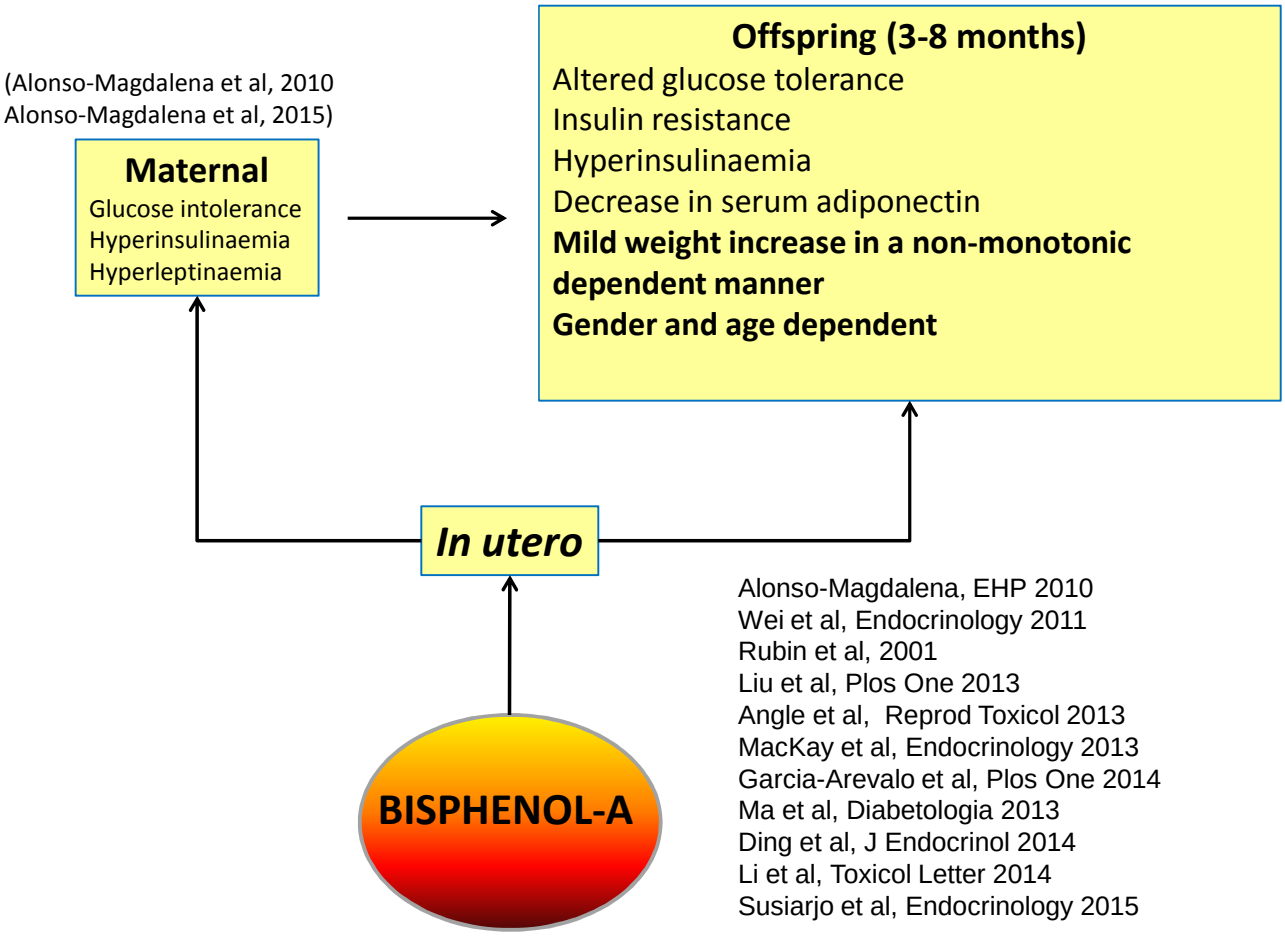
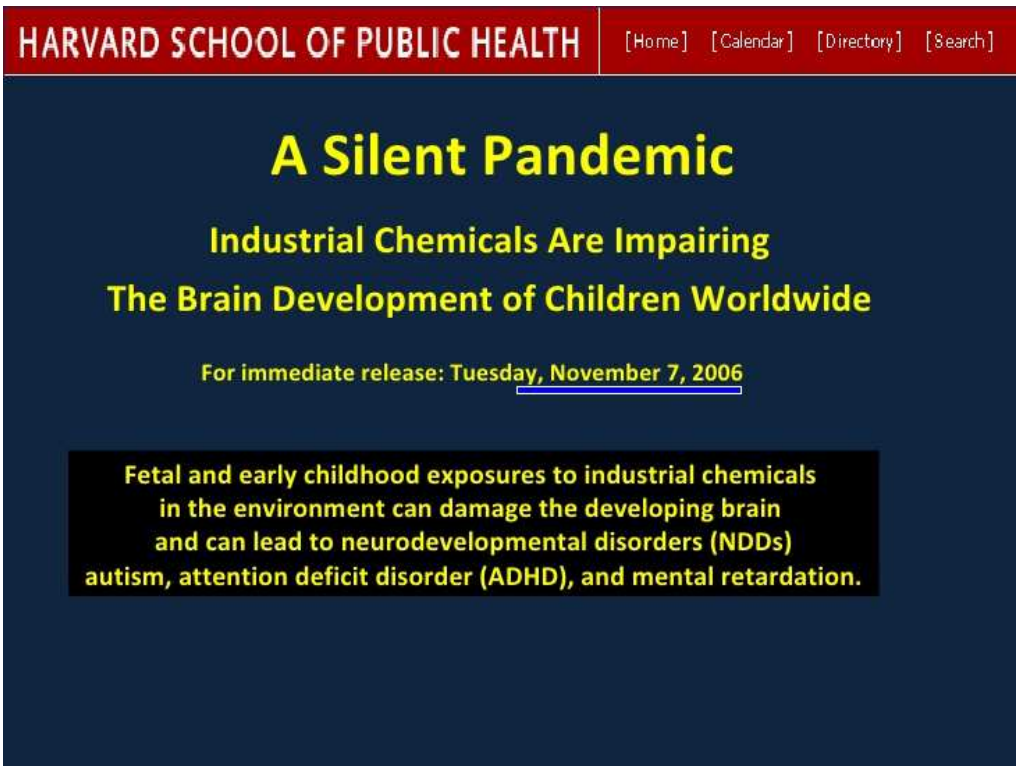


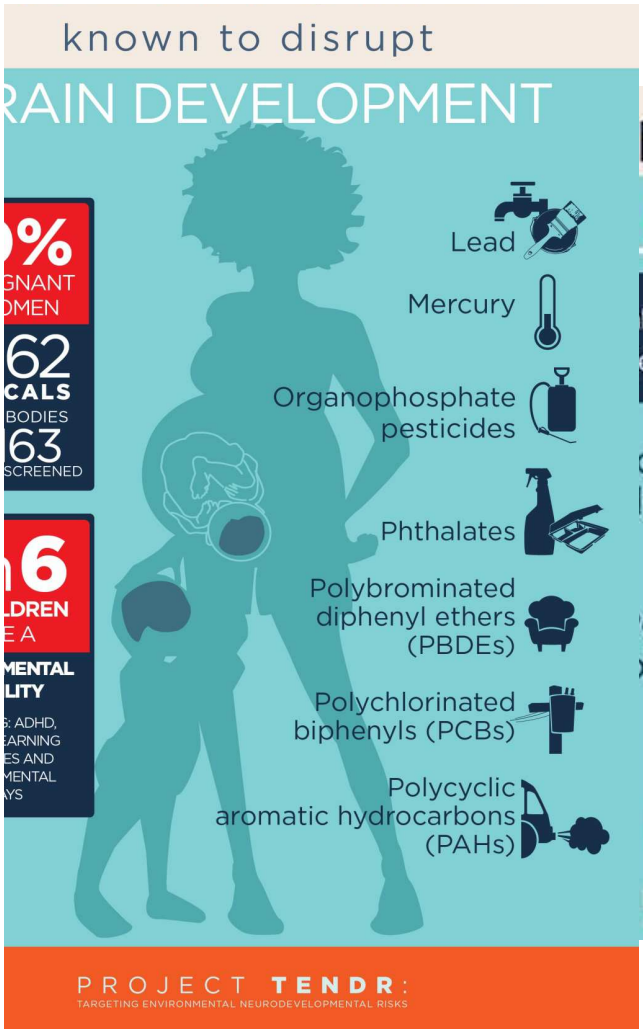
Figure 2 Potential mechanisms of obesogen action that alter metabolic set-points and increase the risk of obesity

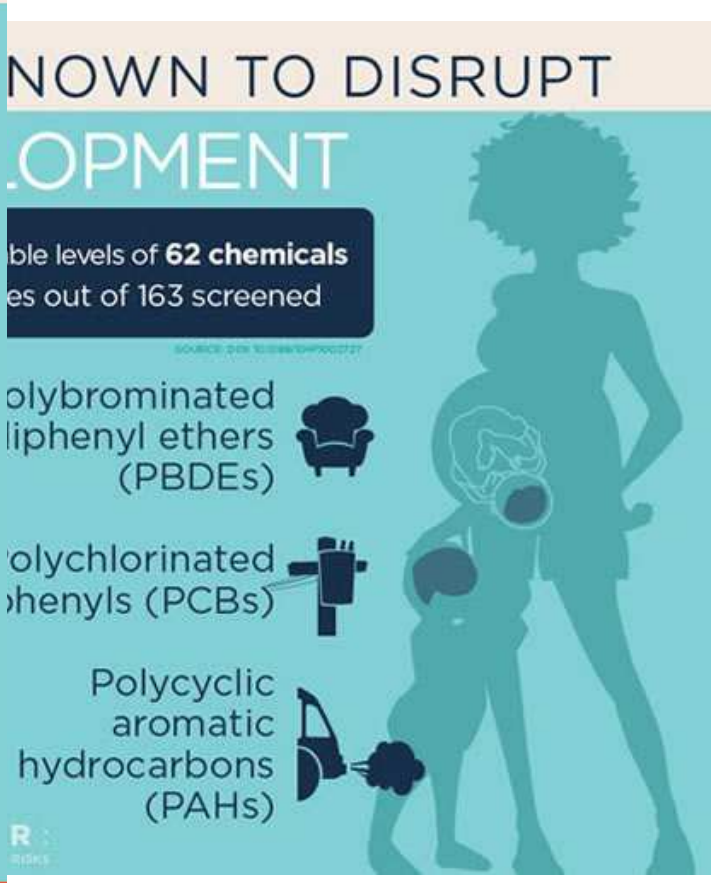


Heindel, J. J. *et al.* (2015) Endocrine disruptors and obesity
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2015.163


(Alonso-Magdalena et al, 2010
Alonso-Magdalena et al, 2015)
Maternal
Glucose intolerance
Hyperinsulinaemia
Hyperleptinaemia
Offspring (3-8 months)
Altered glucose tolerance
Insulin resistance
Hyperinsulinaemia
Decrease in serum adiponectin
Mild weight increase in a non-monotonic dependent manner
Gender and age dependent
In utero
BISPHENOL-A
Alonso-Magdalena, EHP 2010
Wei et al, Endocrinology 2011
Rubin et al, 2001
Liu et al, Plos One 2013
Angle et al, Reprod Toxicol 2013
MacKay et al, Endocrinology 2013
Garcia-Arevalo et al, Plos One 2014
Ma et al, Diabetologia 2013
Ding et al, J Endocrinol 2014
Li et al, Toxicol Letter 2014
Susiarjo et al, Endocrinology 2015


HARVARD SCHOOL OF PUBLIC HEALTH
[Home] [Calendar] [Directory] [Search]
A Silent Pandemic
Industrial Chemicals Are Impairing
The Brain Development of Children Worldwide
For immediate release: Tuesday, November 7, 2006
Fetal and early childhood exposures to industrial chemicals
in the environment can damage the developing brain
and can lead to neurodevelopmental disorders (NDDs)
autism, attention deficit disorder (ADHD), and mental retardation.


known to disrupt
RAIN DEVELOPMENT
%
GNANT
OMEN
62
CALS
BODIES
63
SCREENED
6
LDREN
E A
MENTAL
LITY
: ADHD,
EARNING
ES AND
MENTAL
AYS
Lead
Mercury
Organophosphate pesticides
Phthalates
Polybrominated diphenyl ethers (PBDEs)
Polychlorinated biphenyls (PCBs)
Polycyclic aromatic hydrocarbons (PAHs)
PROJECT TENDR:
TARGETING ENVIRONMENTAL NEURODEVELOPMENTAL RISKS


NOWN TO DISRUPT
OPMENT
ble levels of 62 chemicals
es out of 163 screened
olybrominated
iphenyl ethers
(PBDEs)
olychlorinated
henyls (PCBs)
Polycyclic
aromatic
hydrocarbons
(PAHs)

SOLUCIÓN GLOBAL DEL PROBLEMA

Corto Plazo: cambios en las normativas
para reducir la exposición

Medio y Largo Plazo:
Tenemos que ir más allá del Reducir, Reutilizar y Reciclar.
Hacía la cuarta R: REDISEÑAR

La OCDE define la **QUIMICA VERDE** como: “el diseño, la fabricación y uso de productos y procesos químicos eficientes, eficaces, seguros y más respetuosos con el medio ambiente”

Riesgo= Peligro x Exposición

Tradicionalmente:

↓Riesgo ↓Exposición

Química Verde:

↓Riesgo ↓Peligro

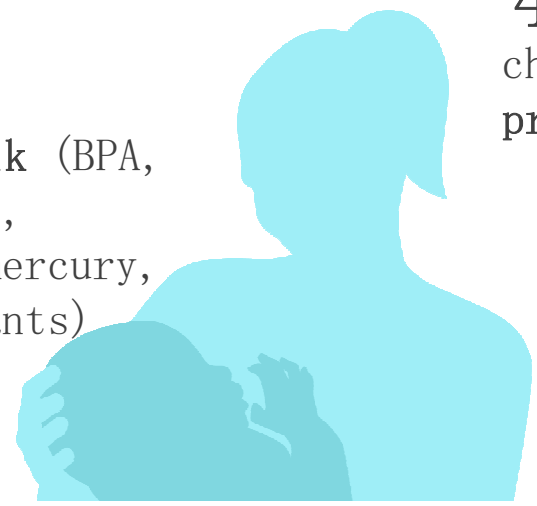
Hill et al, The Chemist 86: 24-31, 2013

AND MEANWHILE.....

We all carry a Chemical Body Burden

287 chemicals in **cord blood**

47 chemicals in every **pregnant woman** tested



In **breast milk** (BPA, PCBs, dioxins, pesticides, mercury, flame retardants)

The presence of **chemicals in the womb**
does not mean that they are causing harm.

However, every pregnant woman has a body burden
of chemicals without her knowledge
…with the **potential of harm.**