



The Queen's Medical Research Institute

Medical School

Main Hospital

**Keeping your eye on the goal:
avoiding conflicts, agendas, emotions
and presumptions**

The example of endocrine disruptors



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MRC

Centre for
Reproductive
Health

Remember that nothing in science is ever quite as it may first appear



Evidence for 'endocrine disruption' is all around us

High and/or increasing incidence of:

- Male reproductive disorders
- Obesity, type II diabetes, cardiometabolic disorders
- Breast cancer
- PCOS
- Endometriosis

It has become increasingly ***presumed*** that endocrine disruptors play a causal role in some/all of these changes

Evidence for endocrine disruption is all around usor is it just my imagination?



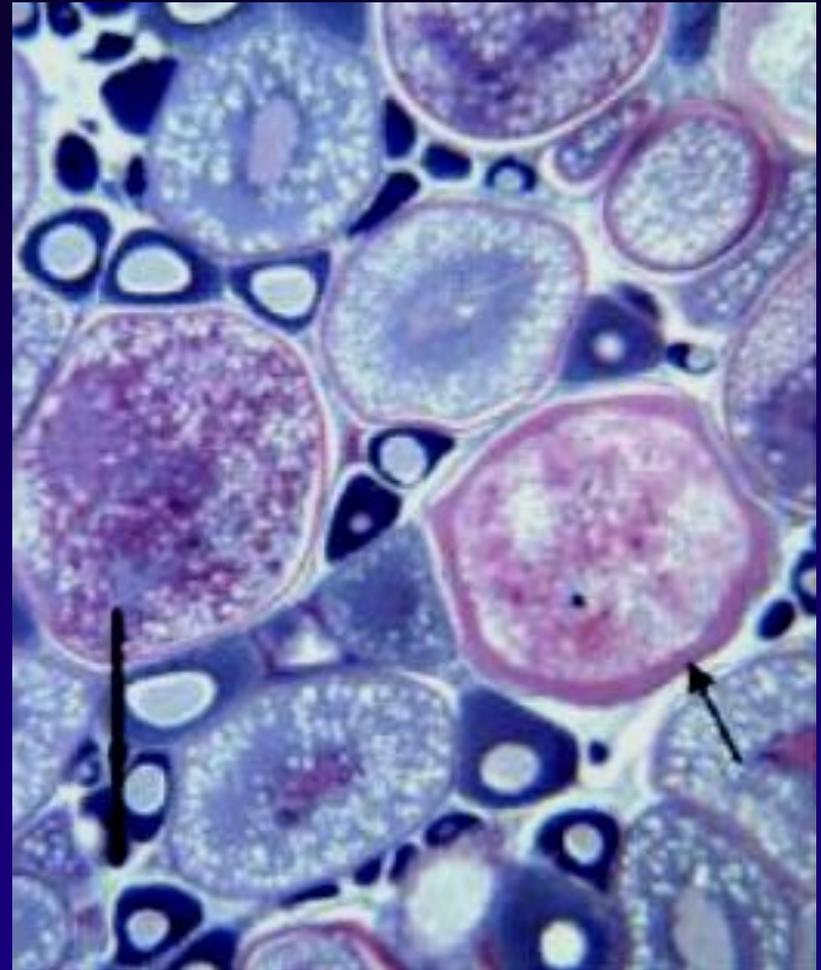
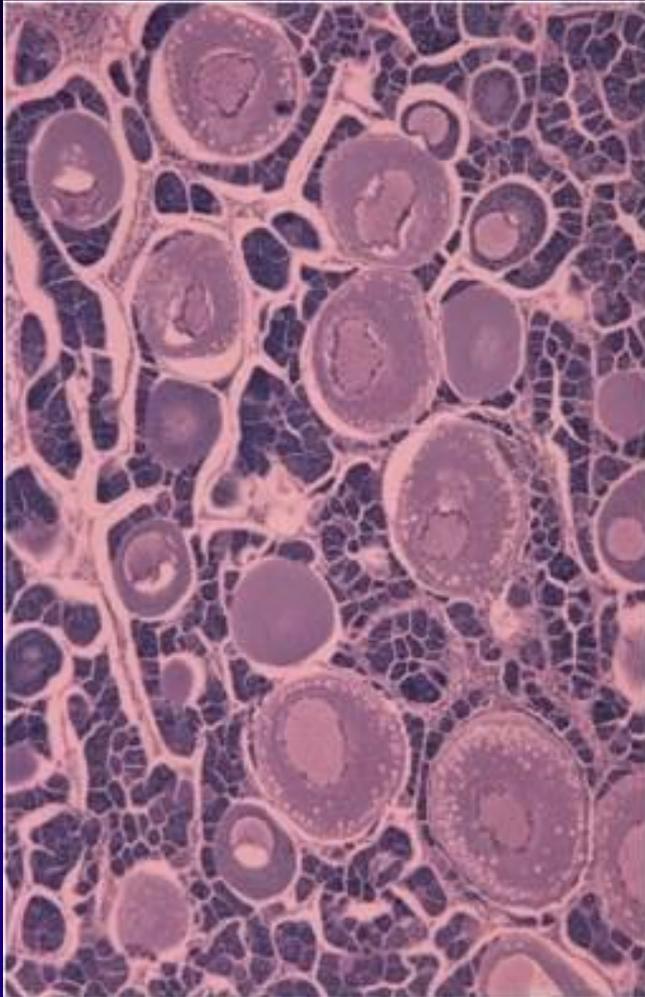
Some philosophy

Good judgement comes from
experience

Experience comes from
bad judgement

Widespread 'intersex' in freshwater fish

Clear evidence for induction by oestrogenic chemicals



Oocytes within the testes of 'male' fish

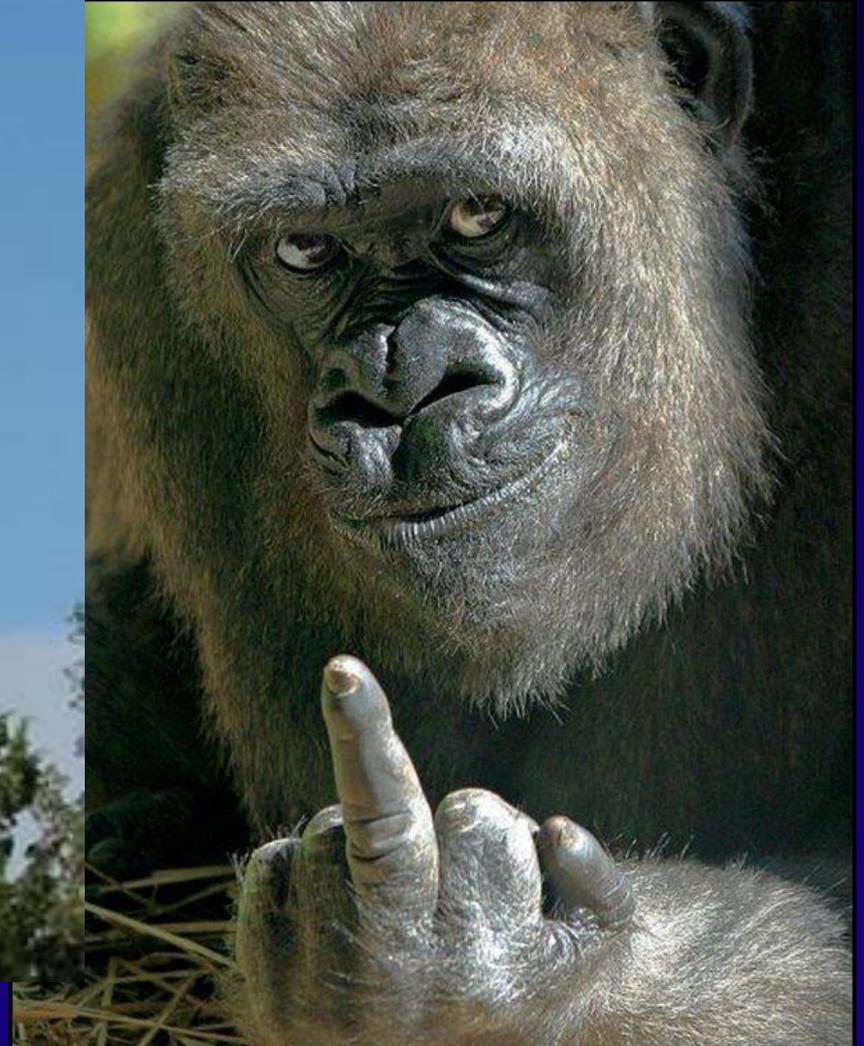
The prime suspect chemicals – surfactants

Alkylphenols shown to be oestrogenic in vitro and in vivo



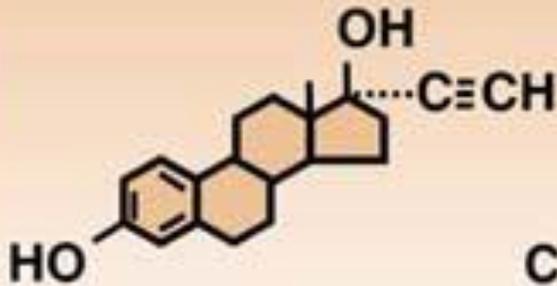
**PRESUMPTION
(although logical)**

Interpretation is no substitute for experimentation (to obtain evidence)

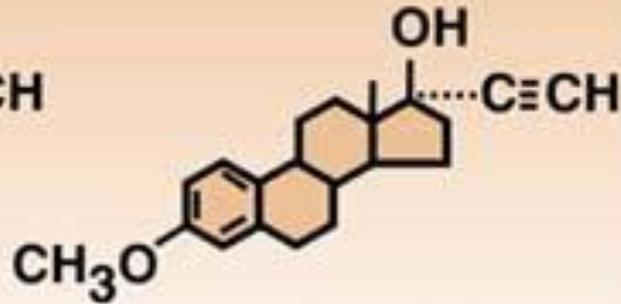


Final identification of the main culprit A pharmaceutical!

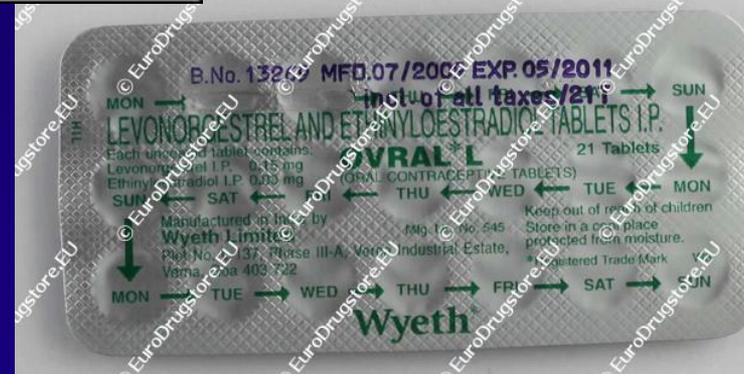
THE ORALLY ACTIVE 17α ETHINYL DERIVATIVES OF ESTRADIOL



17 α ETHINYLESTRADIOL



17 α ETHINYLESTRADIOL
3-METHYLETHER
(MESTRANOL)



Where it all started for me

Number of citations = 1826; new data = zero

HYPOTHESIS

Like most hypotheses it has
turned out to be
fundamentally wrong

Are oestrogens involved in falling sperm counts and disorders of the male reproductive tract?

RICHARD M. SHARPE NIELS E. SKAKKEBAEK

The incidence of disorders of development of the male reproductive tract has more than doubled in the past 30–50 years while sperm counts have declined by about half. Similar abnormalities occur in the sons of women exposed to diethylstilbestrol (DES) during pregnancy and can be induced in animals by brief exposure to exogenous oestrogen/DES during pregnancy. We argue that the increasing incidence of reproductive abnormalities in the human male may be related to increased oestrogen exposure in utero, and identify mechanisms by which this exposure could occur.

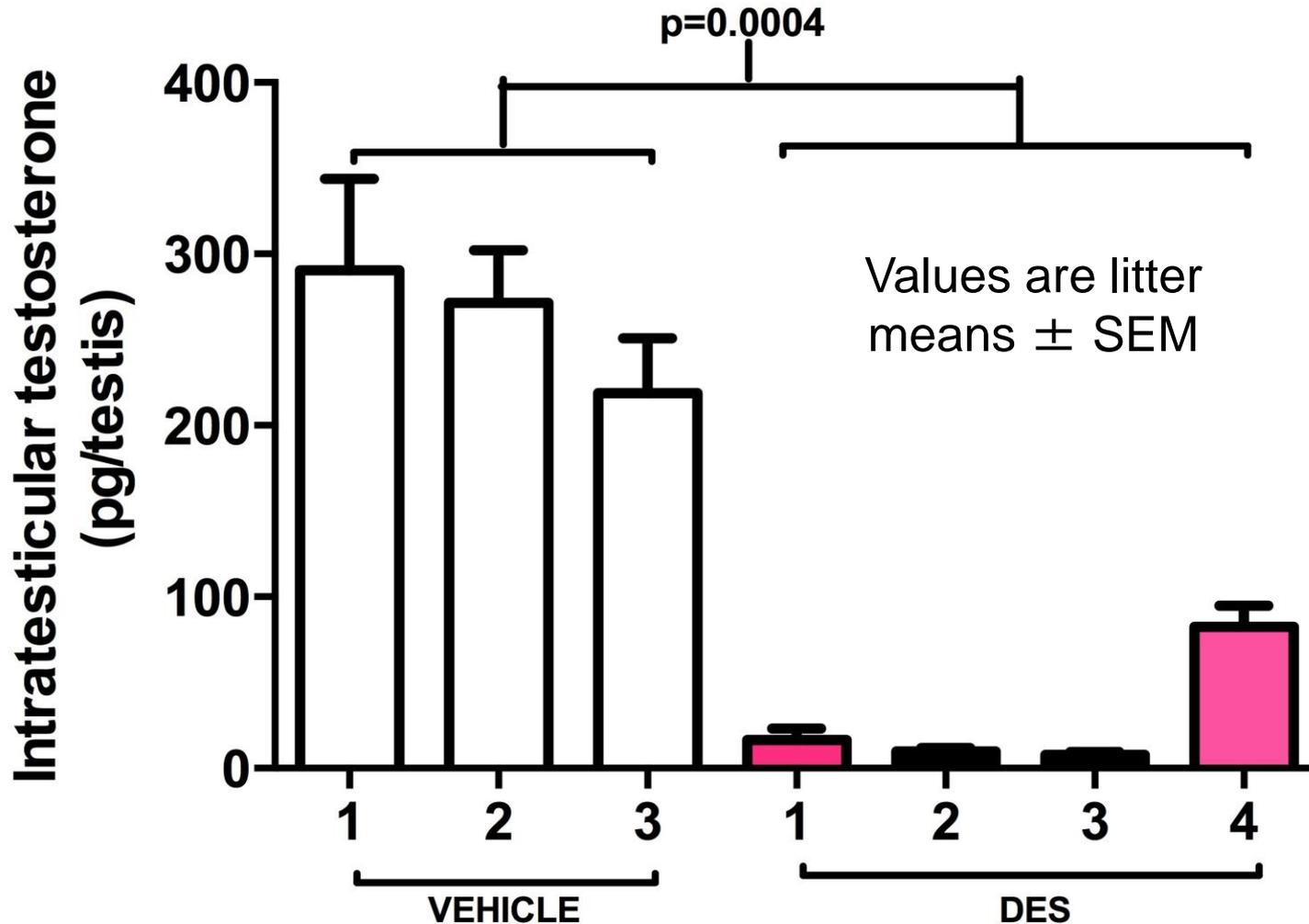
Lancet 1993; **341**: 1392–95.

adverse changes in male reproductive development and function.

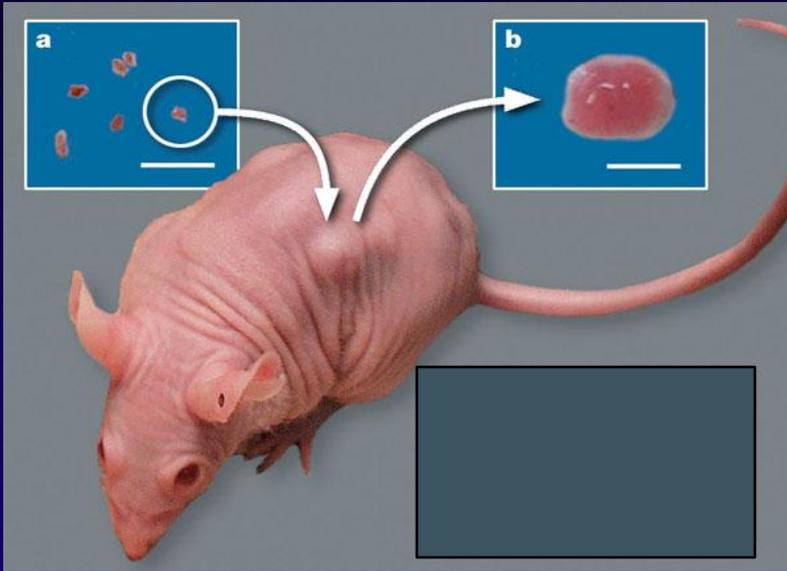
Alterations in oestrogen exposure and metabolism

The potential routes of human exposure to oestrogens are listed in the table, although there are few hard facts that enable the impact of each route to be evaluated. Perhaps the change in diet has had the greatest impact. It has been argued that the low incidence of breast cancer in Japan and China is related to their high-fibre low-fat diet,¹³ the key argument being that endogenous oestrogens (which are implicated in the aetiology of breast cancer) that are excreted via the bile are more readily metabolised and reabsorbed from the gut when the gut contains low amounts of fibre.

Profound inhibitory effect of DES on fetal rat testis T production – e21.5



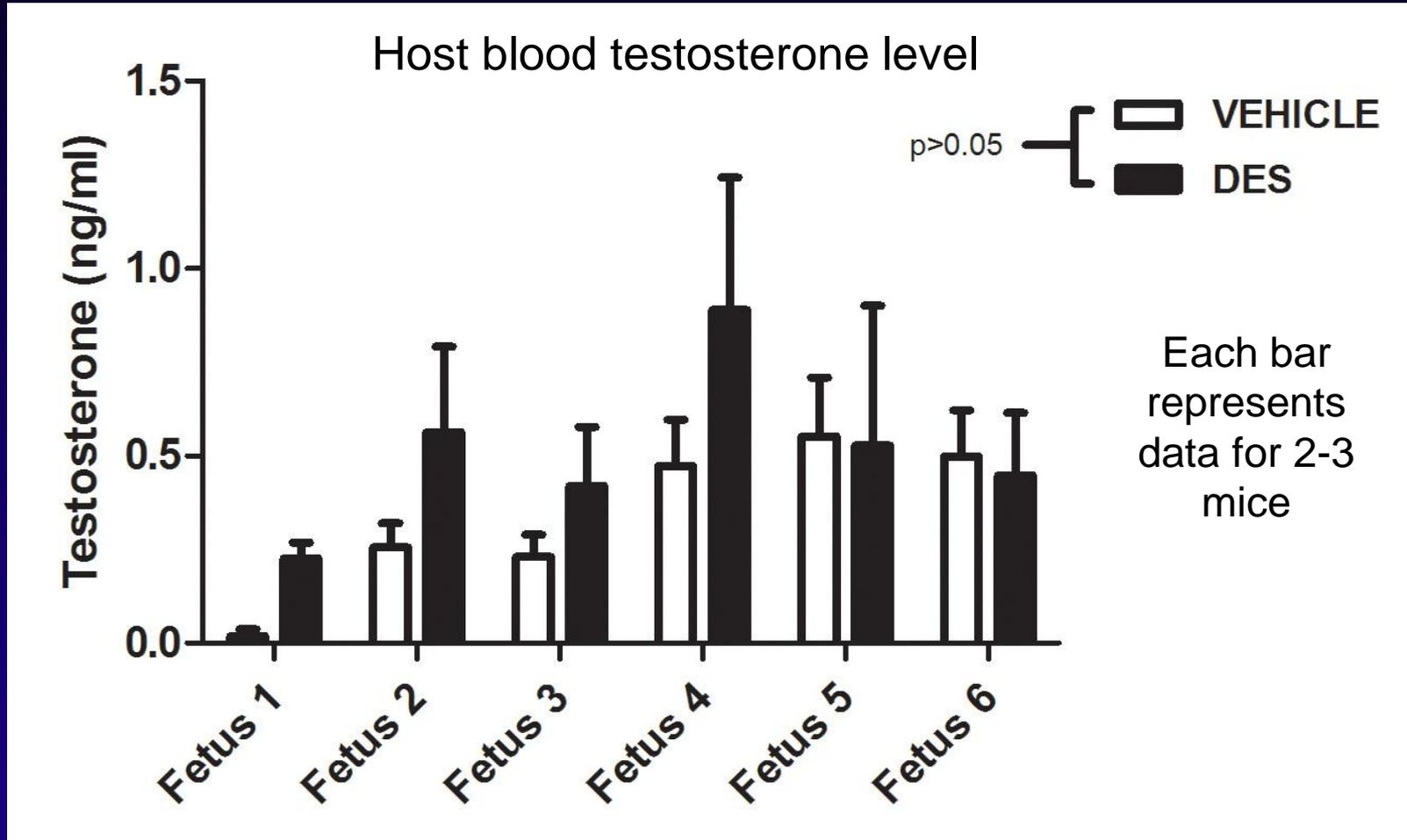
Fetal human testis xenografting into (castrate male) nude mice



- Grafts grow normally for 6+ weeks
- Treating the host is like experimentally exposing the real human fetal testis
- Can measure testosterone production by the grafts by (i) serum T , and (ii) Seminal vesicle weight in the hosts
- Have to treat hosts with hCG* to ensure T production and to mimic normal pregnancy

Mitchell *et al* (2010) *Hum
Reprod* 25: 2405-2414

Lack of effect of DES on fetal human testis T production after xenografting into castrate nude mice



Some more philosophy

No amount of experimentation can
ever prove me right; a single
experiment can prove me wrong

Albert Einstein

There is equal merit in a hypothesis being proved
wrong as in it being proved right – in either case,
scientific understanding is advanced

Presumption

Dictionary definition

An idea that is *taken to be true*, and often used as the basis for other ideas, although it is not known for certain

In science we only discover our presumptions in retrospect

Bisphenol A (BPA)

I have no vested interest in BPA –
in either proving it is safe or that it
is harmful.

I just look at the evidence (all of it)

Human diseases/impairments positively associated with (total) urinary BPA levels

Adults

- Obesity, waist circumference
 - Prediabetes & Type 2 diabetes
 - Cardiovascular disease
 - Impaired liver function, steatosis
- Altered oocyte development
 - IVF outcome/success
 - PCOS
 - Reduced adult male testosterone
 - Male libido/sexual function
 - Semen Quality
 - Mammary gland development/breast cancer

Fetus/Babies/Children

- Reduced fetal growth/birth outcomes
- Reduced anogenital distance
- Thyroid hormone levels
- Childhood obesity
- Kidney disease
- Behavioural disorders
- CpG methylation (girls)

BPA exposure is associated with obesity in children, adolescents and adults

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

Leonardo Trasande, MD, MPP

Teresa M. Attina, MD, PhD, MPH

Jan Blustein, MD, PhD

Context Bisphenol A (BPA), a manufactured chemical, is found in canned food, polycarbonate-bottled liquids, and other consumer products. In adults, elevated urinary BPA concentrations are associated with obesity and incident coronary artery disease. BPA exposure is plausibly linked to childhood obesity, but evidence is lacking to date.

Urinary bisphenol A and obesity: NHANES 2003–2006 ☆

Jenny L. Carwile^a, Karin B. Michels^{a,b,c,*}

^a Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115, USA

^b Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02116, USA

^c Division of Cancer Epidemiology, Comprehensive Cancer Center Freiburg, Freiburg University, Freiburg, Germany

BPA exposure is associated with increased risk of type 2 diabetes

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

ORIGINAL RESEARCH

Annals of Internal Medicine

Relationship of Urinary Bisphenol A Concentration to Risk for Prevalent Type 2 Diabetes in Chinese Adults

A Cross-sectional Analysis

Guang Ning, MD, PhD; Yufang Bi, MD; Tiange Wang, MD; Min Xu, MD; Yu Xu, MD; Yun Huang, MD; Mian Li, MD; Xiaoying Li, MD, PhD; Weiqing Wang, MD; Yuhong Chen, MD; Yaohua Wu, MM; Jianing Hou, MD; Aiyun Song, MD; Yu Liu, MD; and Shenghan Lai, MD, MPH

OPEN ACCESS Freely available online

 PLOS one

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

Monica K. Silver¹, Marie S. O'Neill^{1,2}, MaryFran R. Sowers^{2†}, Sung Kyun Park^{1,2*}

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

BPA exposure is associated with increased risk of obesity-related health disorders

JAMA[®]

Online article and related content
current as of January 12, 2010.

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

Iain A. Lang; Tamara S. Galloway; Alan Scarlett; et al.

JAMA. 2008;300(11):1303-1310 (doi:10.1001/jama.300.11.1303)

OPEN ACCESS Freely available online

PLoS one

Association of Urinary Bisphenol A Concentration with Heart Disease: Evidence from NHANES 2003/06

David Melzer^{1*}, Neil E. Rice¹, Ceri Lewis², William E. Henley³, Tamara S. Galloway²

¹Epidemiology and Public Health Group, Peninsula Medical School, University of Exeter, Exeter, United Kingdom, ²School of Biosciences, University of Exeter, Exeter, United Kingdom, ³School of Mathematics and Statistics, University of Plymouth, Plymouth, United Kingdom

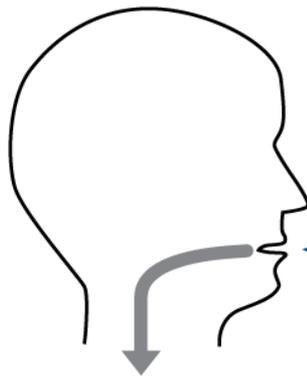
Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

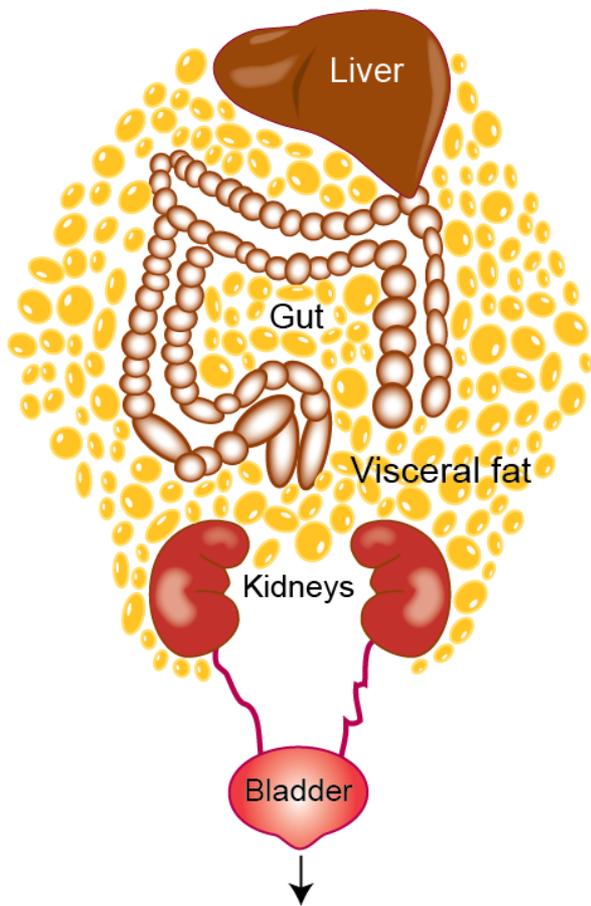
American Heart
Association[®] 
Learn and LiveSM

Urinary Bisphenol: A Concentration and Risk of Future Coronary Artery Disease in Apparently Healthy Men and Women

David Melzer, Nicholas J. Osborne, William E. Henley, Ricardo Cipelli, Anita Young,
Cathryn Money, Paul McCormack, Robert Luben, Kay-Tee Khaw, Nicholas J. Wareham
and Tamara S. Galloway



**Too much
Biphenol A (BPA)**



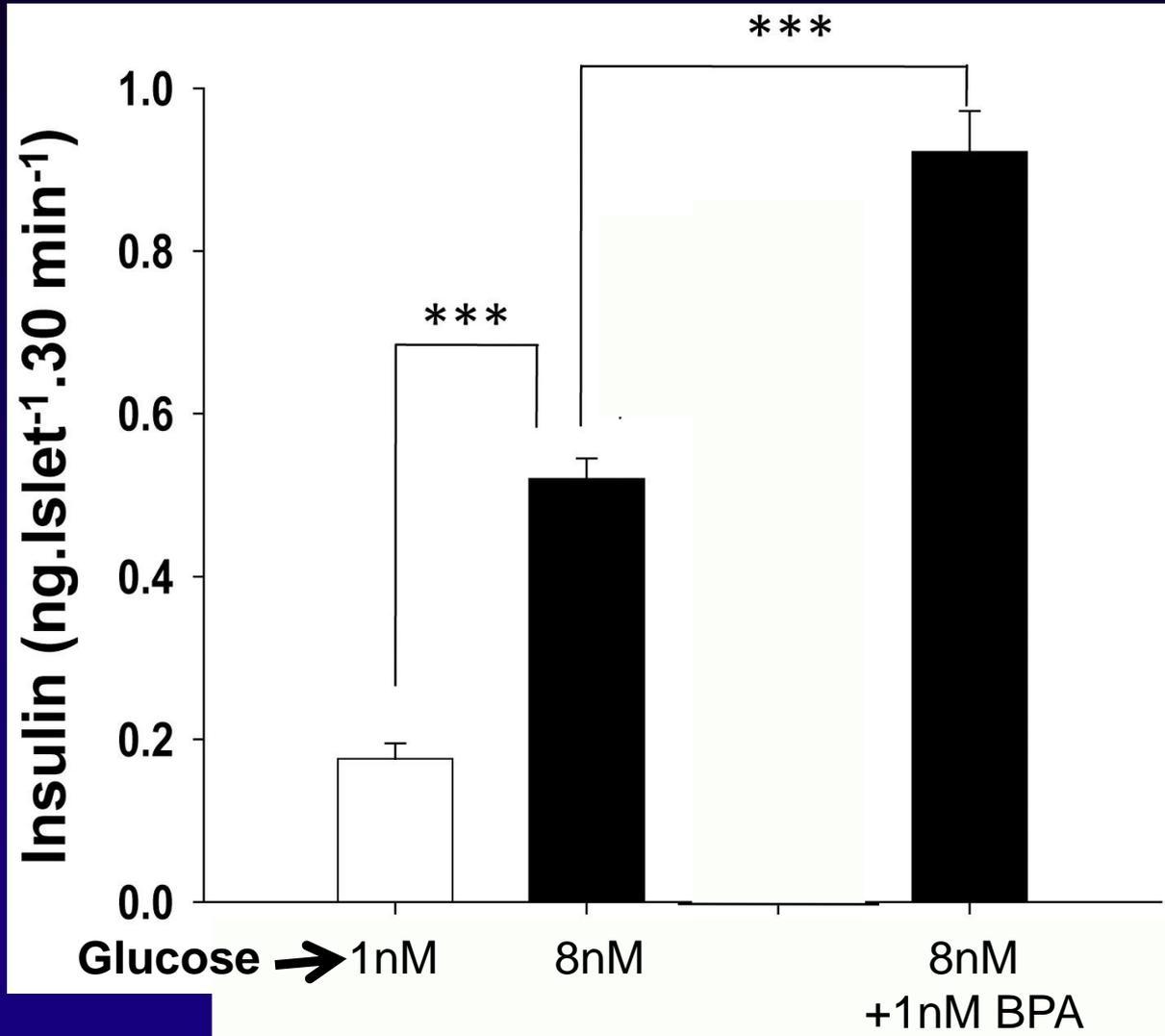
Western Disorders

- INCREASED WAISTLINE
- OBESITY
- FATTY LIVER DISEASE
- TYPE 2 DIABETES
- CARDIOVASCULAR/
HYPERTENSION DISORDERS

Enhancement by BPA of glucose-stimulated insulin secretion by isolated human islets of Langerhans

From: Soriano et al (2012)
PlosOne 7: e31109

Numerous other
pieces of mechanistic
in vitro or animal data
consistent with BPA
being able to affect
metabolic processes



Hence the 'obesogens' hypothesis

NEWS & VIEWS

OBESITY

Fat from plastics? Linking bisphenol A exposure and obesity

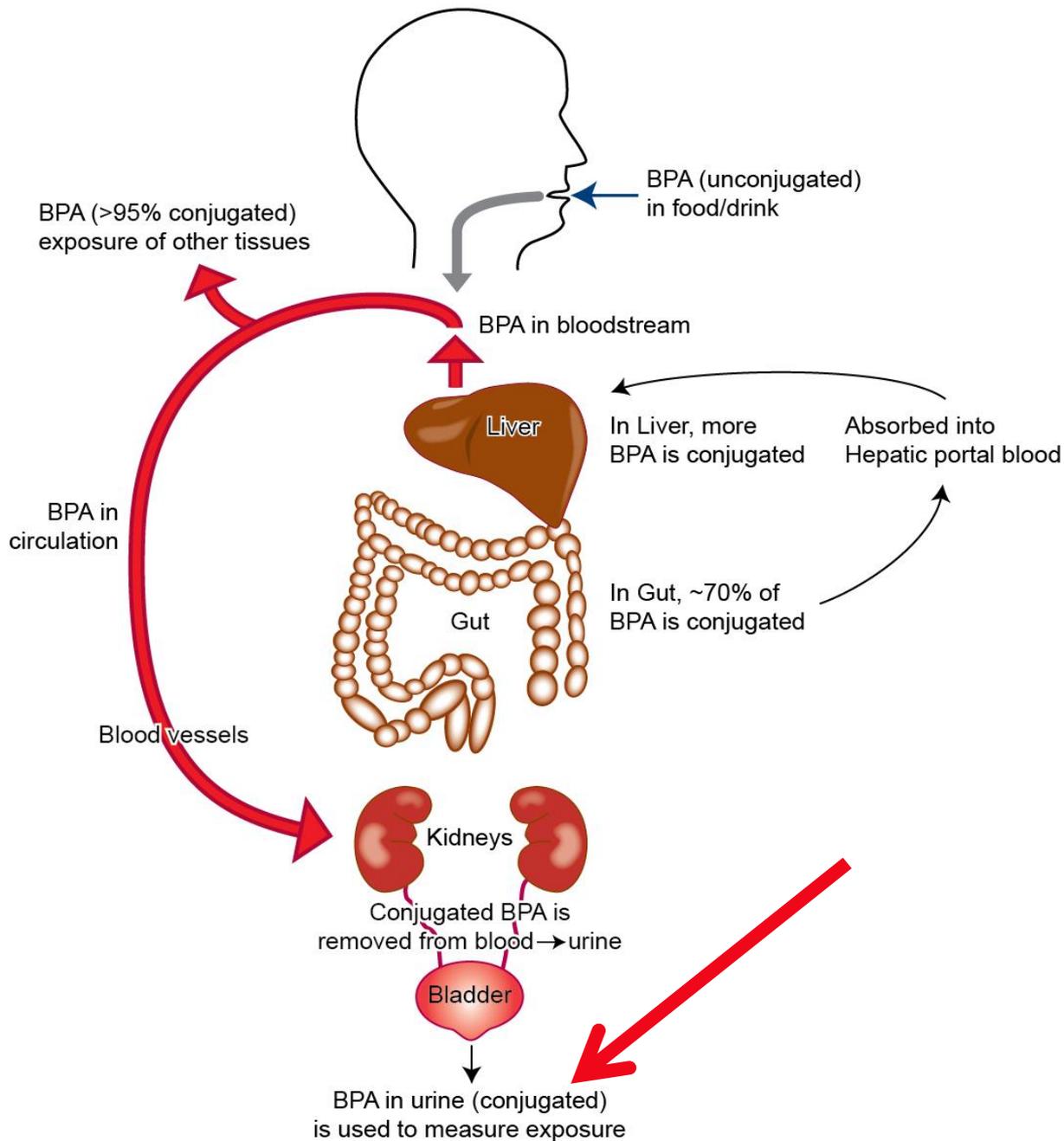
Angel Nadal

The weight of evidence indicates that bisphenol A (BPA), a widespread endocrine disruptor, might be an important risk factor for obesity and metabolic disorders. An epidemiological study shows an association between urinary BPA levels and increased body mass in children and adolescents.

Nadal, A. *Nat. Rev. Endocrinol.* **9**, 9–10 (2013); published online 13 November 2012;
[doi:10.1038/nrendo.2012.205](https://doi.org/10.1038/nrendo.2012.205)

Scottish scientist gets his hands on evidence that bisphenol A is feminizing soldiers in the UK army





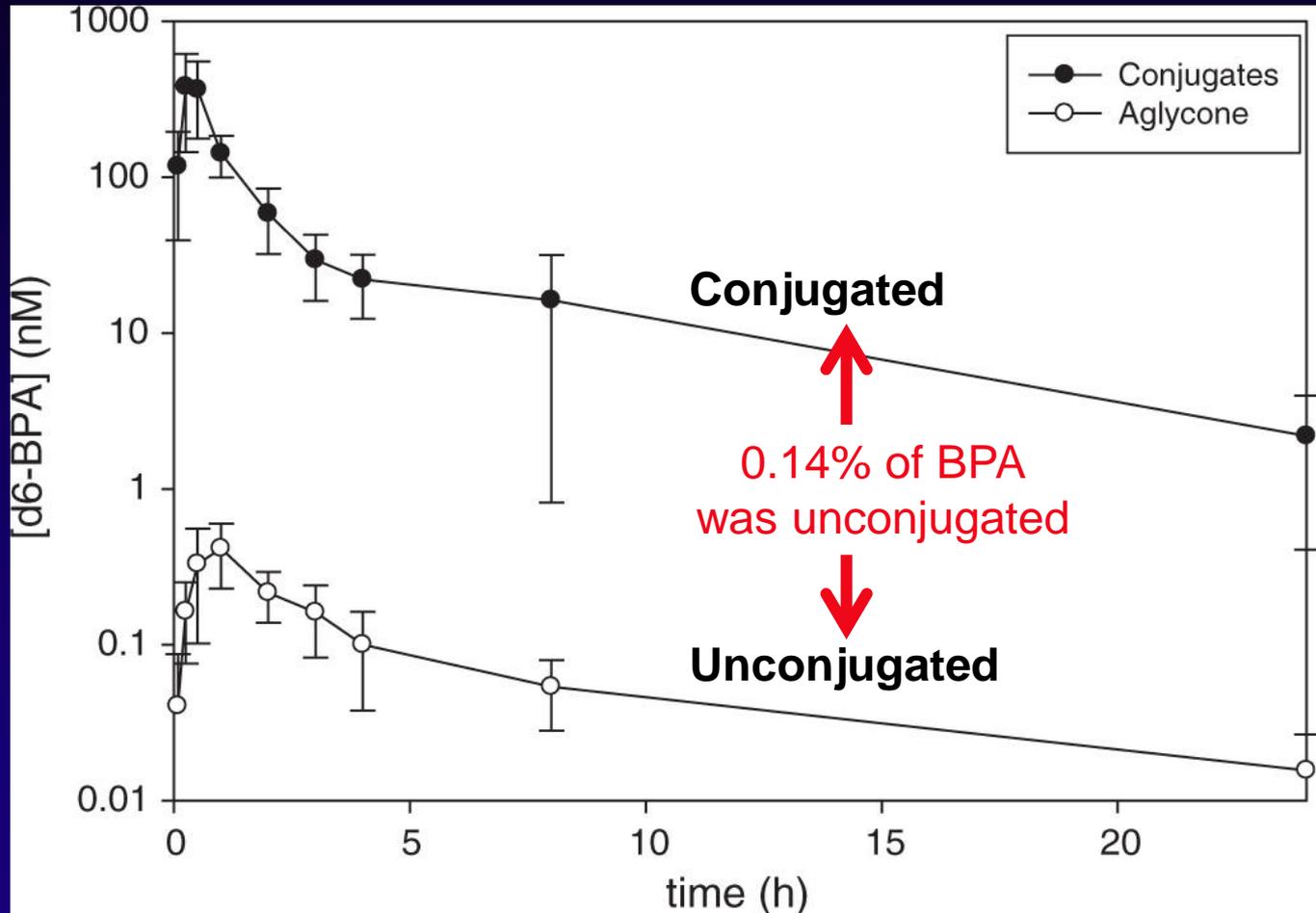
The reality of BPA exposure

Based on detailed pharmacokinetic studies in rats, mice, monkeys, fetuses, humans of various ages

BPA pharmacokinetics in pregnant Rhesus monkey

Serum profile after bolus oral dose of 100ug/kg d⁶-BPA

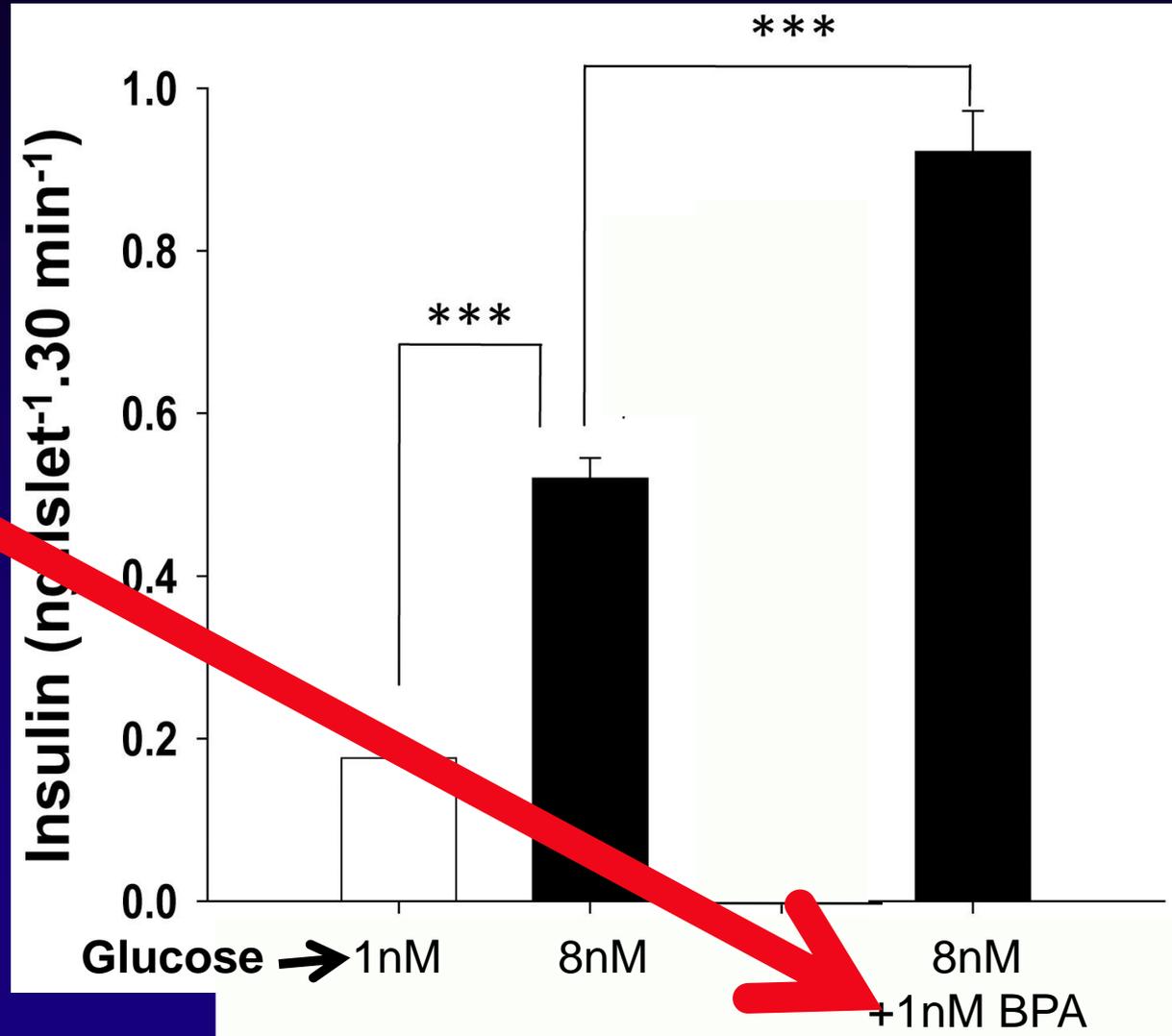
Note the logarithmic scale

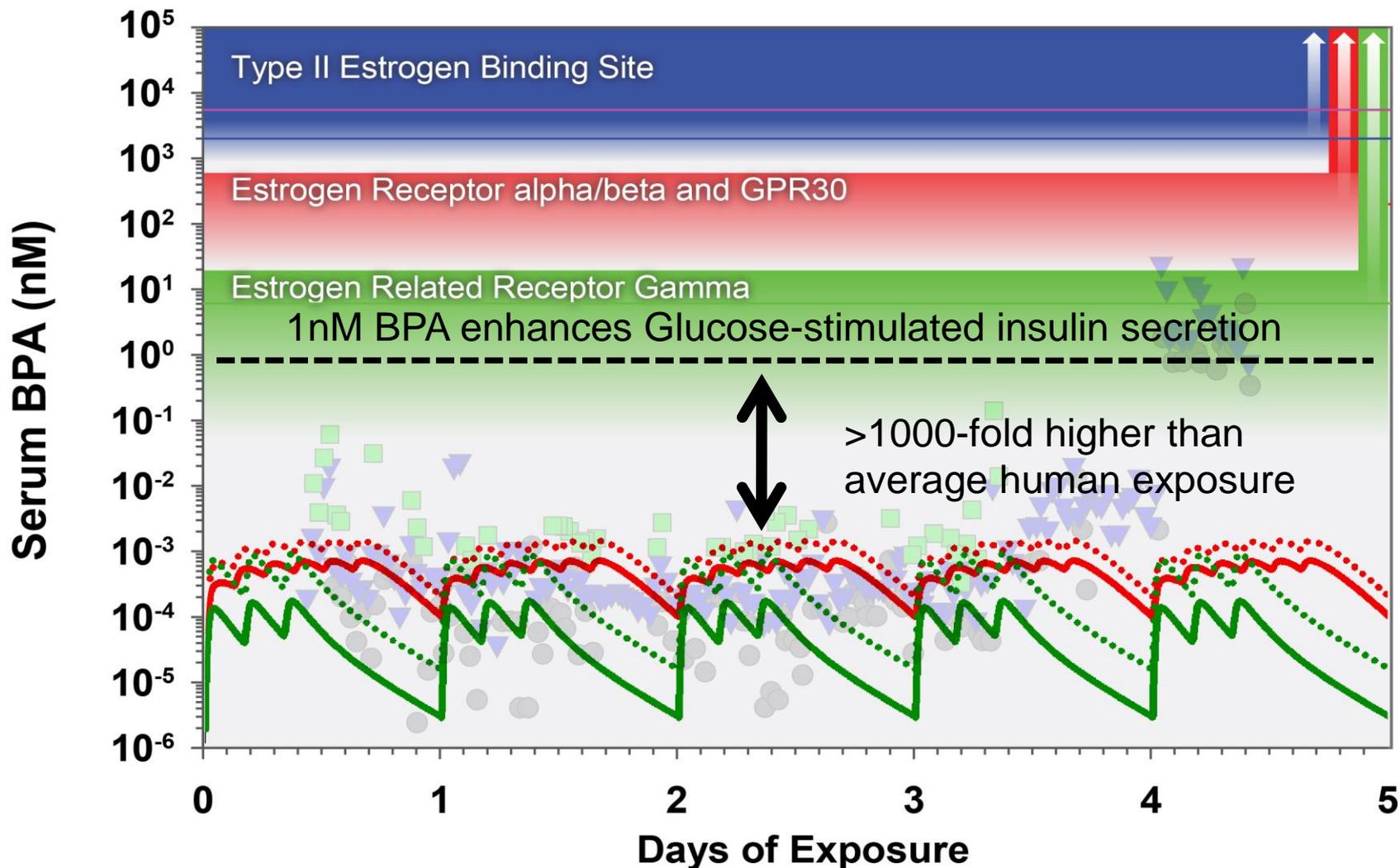


Enhancement by BPA of glucose-stimulated insulin secretion by isolated human islets of Langerhans

The 'dose'
1nM BPA

From: Soriano et al (2012)
PlosOne 7: e31109





- Infant Mean
- Infant 90th Percentile
- Women of Child Bearing Age Mean
- Women CB Age 95th Percentile

From Teeguarden et al (2013)
 Food Chem Toxicol S0278-6915(13)00536-X. doi

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Urinary bisphenol A and obesity: NHANES 2003–2006 ☆

Jenny L. Carwile^a, Karin B. Michels^{a,b,c,*}

^a Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115, USA

^b Obstetrics and Gynecology Epidemiology Center, Department of Obstetrics, Gynecology and Reproductive Biology, Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Avenue, Boston, MA 02116, USA

^c Division of Cancer Epidemiology, Comprehensive Cancer Center Freiburg, Freiburg University, Freiburg, Germany

So we have two sets of *evidence*
that simply do not agree (fit together)



In science there is always an answer – and very often
it is a simple answer

Obesity is absolutely dependent on eating too much (I hope we all agree on this)



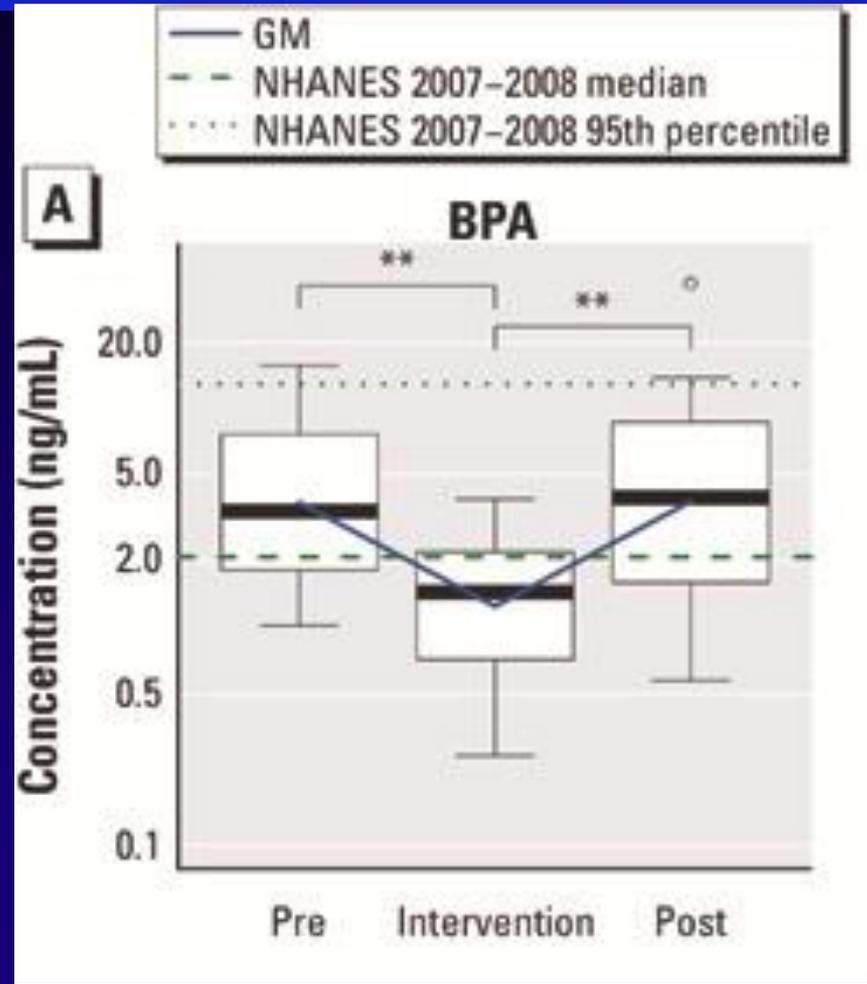
What does eating too much do to BPA exposure?

Effect of switching to a fresh food diet for 3 days on Bisphenol A exposure

So eating a modern Western style diet is associated with increased exposure to BPA.

Therefore, the more of such a diet you eat, the more BPA you're exposed to.

This is also associated with higher risk of obesity, type 2 diabetes, cardiovascular disease etc



From: Rudel et al (2011) Environ Health Perspect 119: 914

This is what we suggest as a hypothesis – which requires further investigation

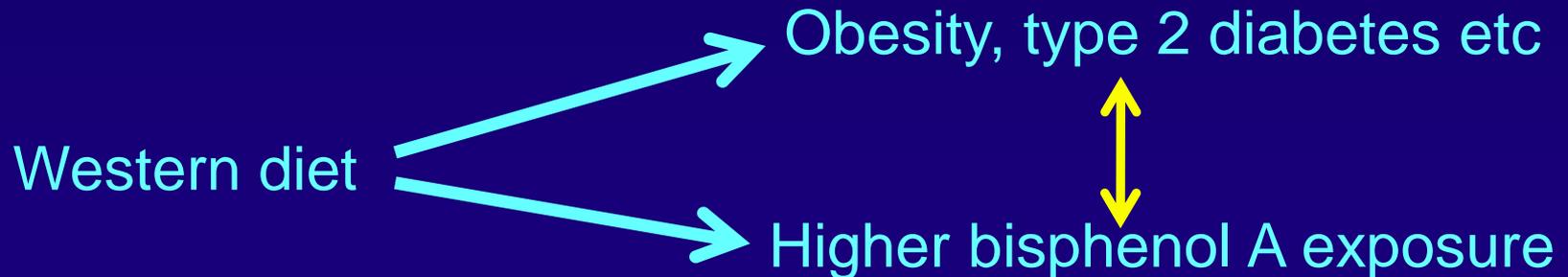
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Articles
COMMENTARY

Obesogens and Obesity—an Alternative View?

Richard M. Sharpe¹ and Amanda J. Drake²

Obesity



Human diseases/impairments positively associated with (total) urinary BPA levels

Adults

- Obesity, waist circumference ✓
- Prediabetes & Type 2 diabetes ✓
- Cardiovascular disease ✓
- Impaired liver function, steatosis ✓
- Altered oocyte development ✓
- IVF outcome/success ✓
- PCOS ✓
- Reduced adult male testosterone ✓
- Male libido/sexual function ✓
- Semen Quality ✓
- Mammary gland development/breast cancer ✓

Fetus/Babies/Children

- Reduced fetal growth/birth outcomes ✓
- Reduced anogenital distance ✓
- Thyroid hormone levels ✓
- Childhood obesity ✓
- Kidney disease ✓
- Behavioural disorders ✓
- CpG methylation (girls) ? ✓

✓ Association and/or causal evidence for dietary induction

Does this mean I consider that endocrine disruptors are unimportant?



Diet is inextricably linked to ED exposure*; diet has its own effects; ED has its own effects. We cannot focus just on one and ignore the other

*BPA, Phthalates, POPs etc

Some philosophy

With implications for scientific research

It is not truth, but opinion, that can
travel the world without passport

Sir Walter Raleigh 1614

English aristocrat, writer, poet, soldier, courtier, spy, and explorer

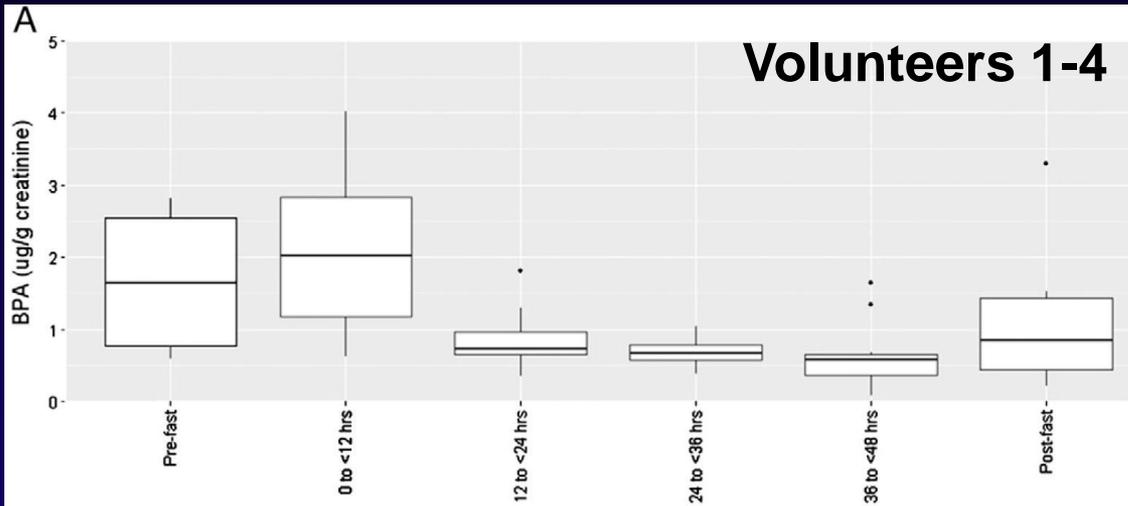
In science, opinion = interpretation (or beliefs)

The truth = the evidence

Opinion is fine, provided it is not presented as fact

Diet as the major source of BPA

Effect of fasting on urinary excretion of conjugated BPA



From
Christensen et al (2012)
Environ Internat 50: 7-14

My final piece of philosophy

Which I may have demonstrated in my talk!

Man armed with science is like a
baby with a box of matches

JBS Haldane 1892-1964

English geneticist and biometrician

Presumption example

- Eating too much food makes you fat
- Therefore, eating is bad for you

Only eating too much is bad
It's all about the 'dose'