ADVERSE HEALTH EFFECTS DUE TO EXPOSURE TO BISPHENOL A: EVIDENCE FROM ANIMAL EXPERIMENTS AND EPIDEMIOLOGICAL STUDIES

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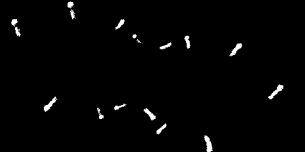
Bisphenol A



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National Institute of Environmental Health Sciences

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Reproductive Toxicology

www.elsevier.com/locate/reprotox

Chapel Hill bisphenol A expert panel consensus statement: Integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure

Human exposure to bisphenol A (BPA)☆

Laura N. Vandenberg[a,*], Russ Hauser[b], Michele Marcus[c], Nicolas Olea[d], Wade V. Welshons[e]

In vitro molecular mechanisms of bisphenol A action☆

Yelena B. Wetherill[a,b], Benson T. Akingbemi[c], Jun Kanno[d], John A. McLachlan[e], Angel Nadal[f], Carlos Sonnenschein[g], Cheryl S. Watson[h], R. Thomas Zoeller[i], Scott M. Belcher[j,*]

In vivo effects of bisphenol A in laboratory rodent studies☆

Catherine A. Richter[a,*], Linda S. Birnbaum[b], Francesca Farabollini[c], Retha R. Newbold[d], Beverly S. Rubin[e], Chris E. Talsness[f], John G. Vandenbergh[g], Debby R. Walser-Kuntz[h], Frederick S. vom Saal[i]

An evaluation of evidence for the carcinogenic activity of bisphenol A

Ruth A. Keri[a], Shuk-Mei Ho[b], Patricia A. Hunt[c], Karen E. Knudsen[d], Ana M. Soto[e], Gail S. Prins[f,*]

An ecological assessment of bisphenol-A: Evidence from comparative biology

D. Andrew Crain[a,*], Marcus Eriksen[b], Taisen Iguchi[c], Susan Jobling[d], Hans Laufer[e], Gerald A. LeBlanc[f], Louis J. Guillette Jr.[g]

Human Blood Levels of BPA

- Most humans are exposed to BPA.
- Unconjugated BPA in human serum is in the 0.1 to 10 ng/ml range.
- Mean levels in adults and fetuses are **1 - 3 ng/ml (4 - 13 nM)**.

BPA Expert Panel Consensus Statement
Reprod. Toxicol. 2007

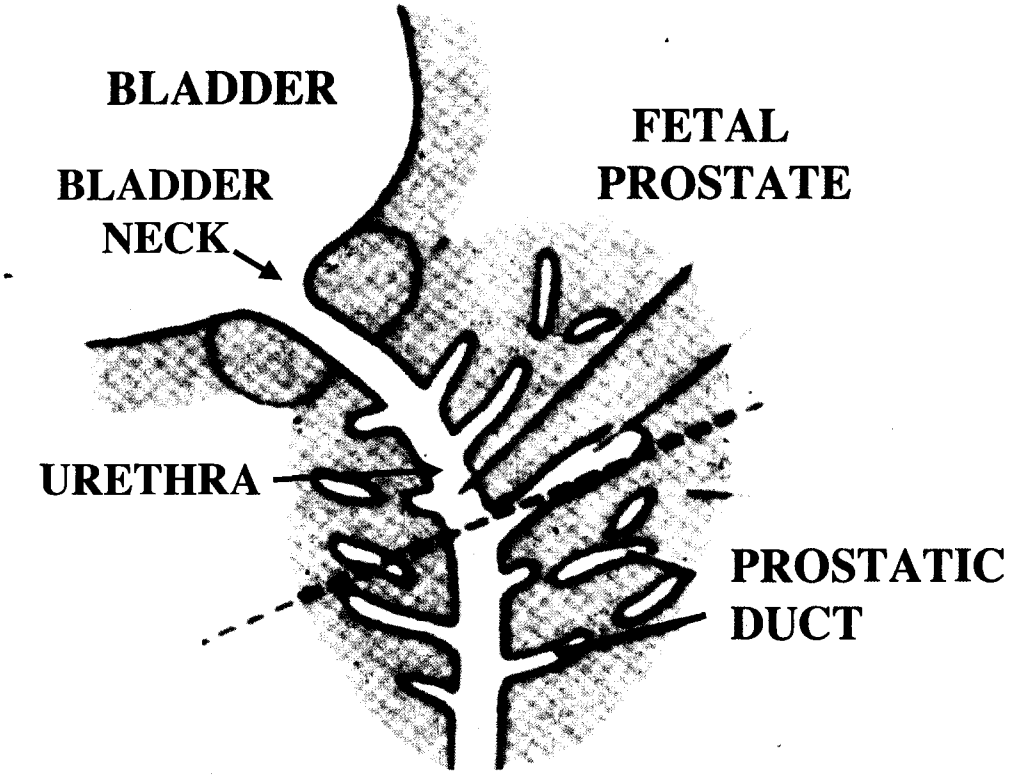
Vandenberg et al.
Reprod. Toxicol. 2007

IN VIVO DEVELOPMENTAL EFFECTS OF BPA:

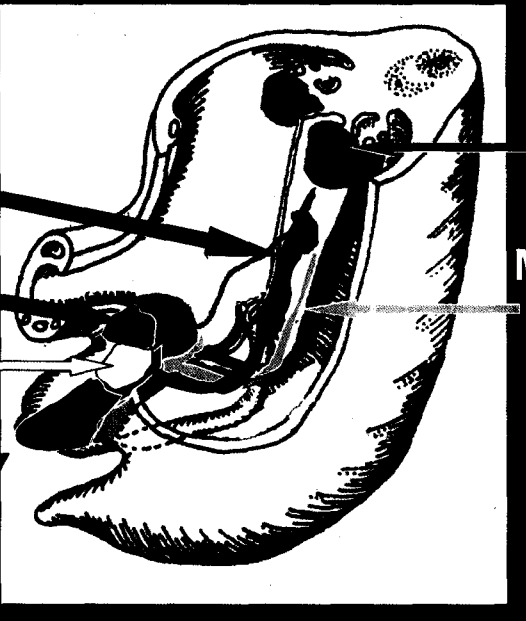
FINDINGS THAT BPA ALTERS PROSTATE DEVELOPMENT AS AN EXAMPLE OF STUDIES DISCARDED BY THE FDA

PUBLISHED FINDINGS SHOW

- ♦ Increase in Prostate Androgen Receptors
- ♦ Changes in Growth Factors
- ♦ Basal (stem) Cell Proliferation
- ♦ Prostate Cancer

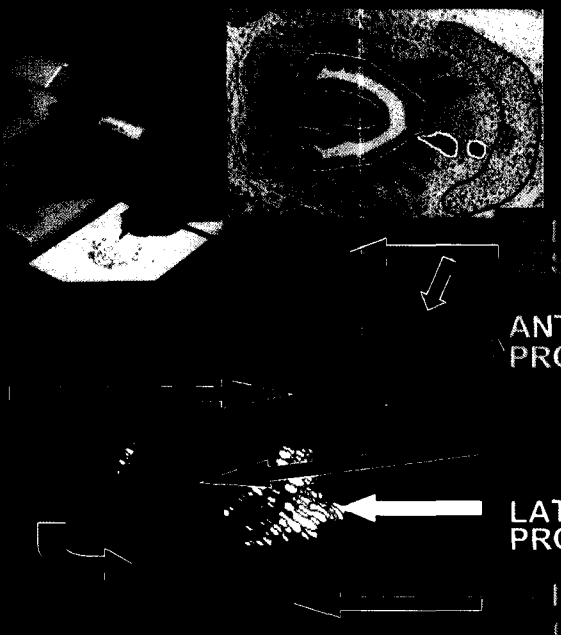


DUCTS THAT FORM THE REPRODUCTIVE ORGANS IN MOUSE FETUSUS



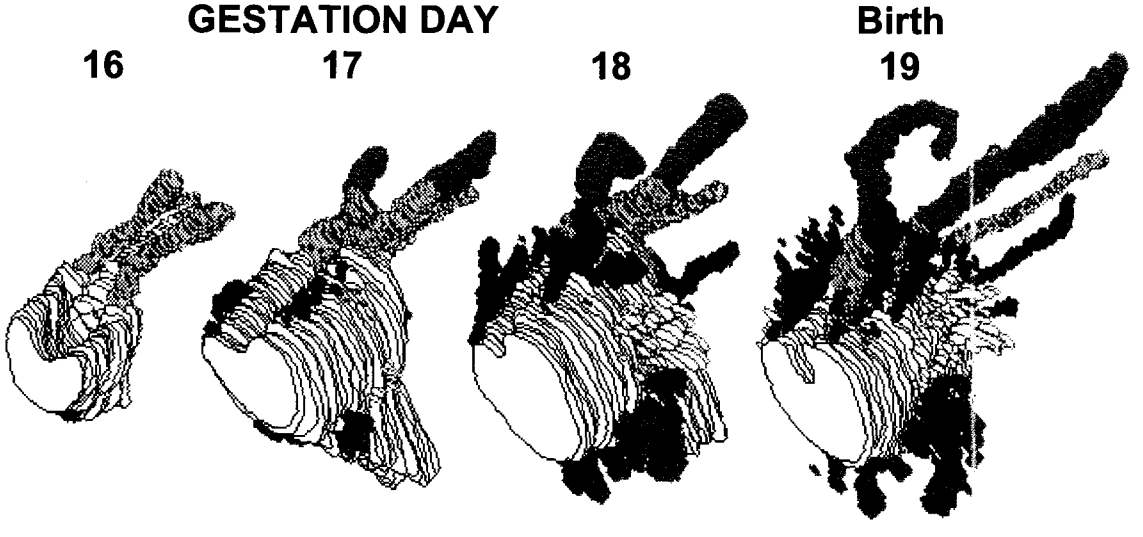
Computer Serial Section Reconstruction Gestation Day 18 or 19 Mouse Fetus

- Serial sections
- Trace sections



Barry Timms
Univ. South Dakota
Vermillion, SD, USA

PROSTATE DEVELOPMENT IN MOUSE FETUSES



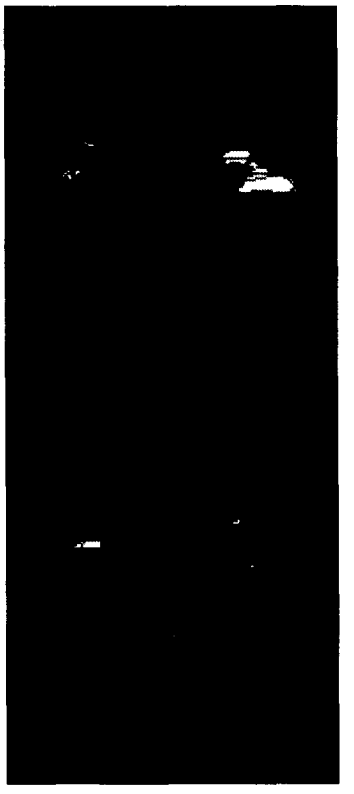
EFFECT OF ESTRADIOL ON MOUSE PROSTATE DEVELOPMENT
(Gestation Day 18)

Fetal Serum Free Estradiol Increase: 0.1 pg/ml (0.1 ppt)

40% increase in prostatic buds

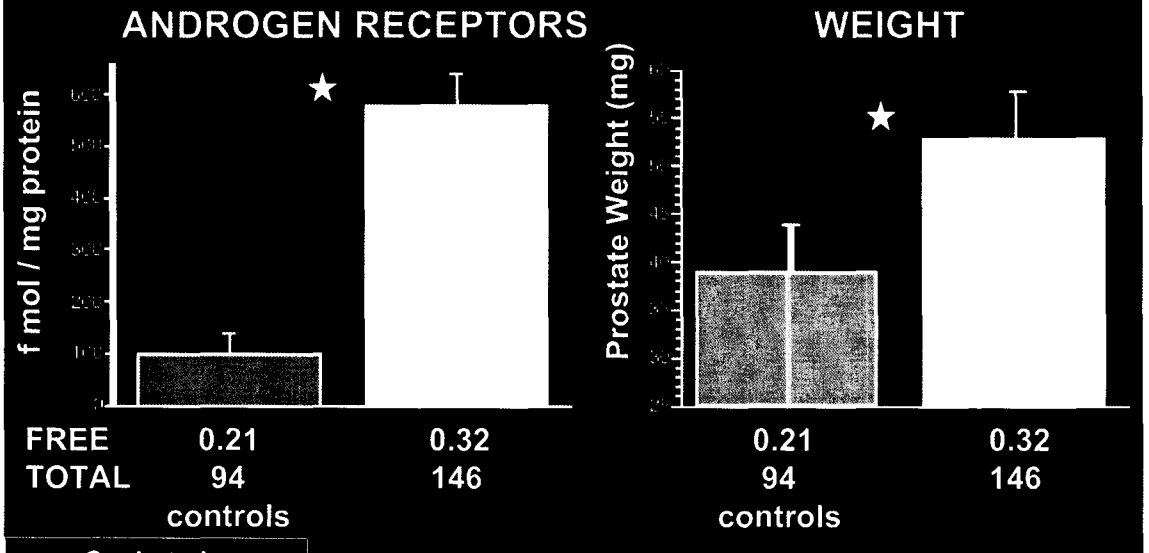
32% increase in prostate size

Control



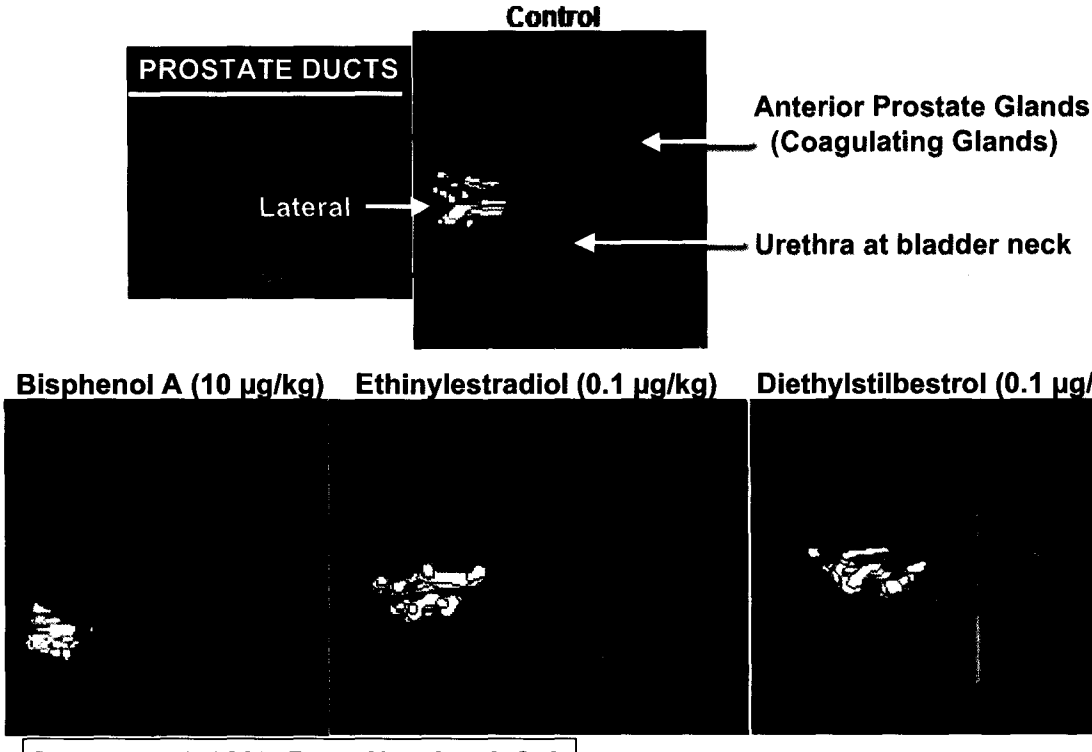
vom Saal et al., 1997
PNAS 94:2056

FETAL ESTRADIOL INCREASES PROSTATE SIZE IN 8-MONTH-OLD CF-1 MALE MICE (CASTRATED + T)



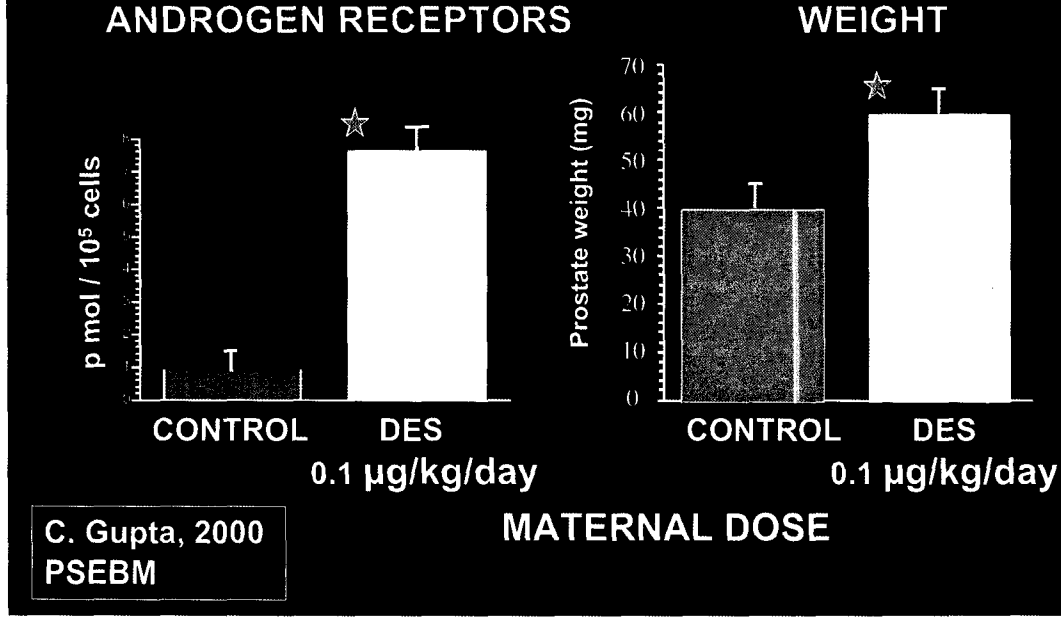
vom Saal et al.
Proc. Nat. Acad. Sci.
94:2056-2061, 1997

UROGENITAL SINUS FROM A GESTATION DAY 19 CD-1 MOUSE FETUS



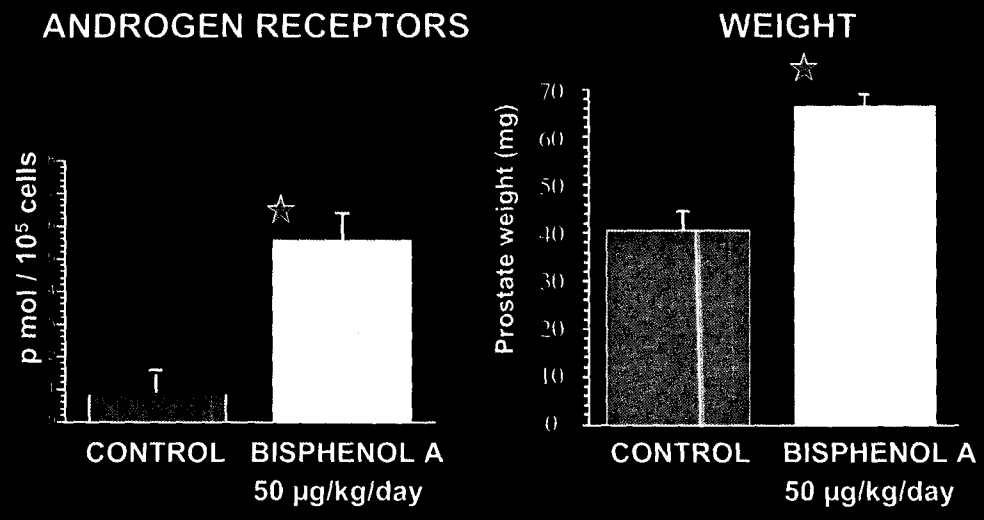
Timms et al. 2005, Proc. Nat. Acad. Sci.

EFFECT OF PRENATAL DES ON PROSATE WEIGHT AND ANDROGEN RECEPTORS IN 60-DAY-OLD CD-1 MALE MICE



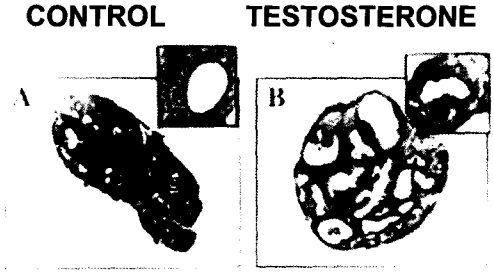
C. Gupta, 2000
PSEBM

EFFECT OF PRENATAL BISPHENOL A ON PROSATE WEIGHT AND ANDROGEN RECEPTORS IN 60-DAY-OLD CD-1 MALE MICE



C. Gupta, 2000
PSEBM

DES STIMULATES THE FETAL CD-1 MOUSE PROSTATE IN PRIMARY CULTURE



TESTOSTERONE +
DES 0.5 pg/ml (0.5 ppt)

C. Gupta,
PSEBM
224:61-68, 2000

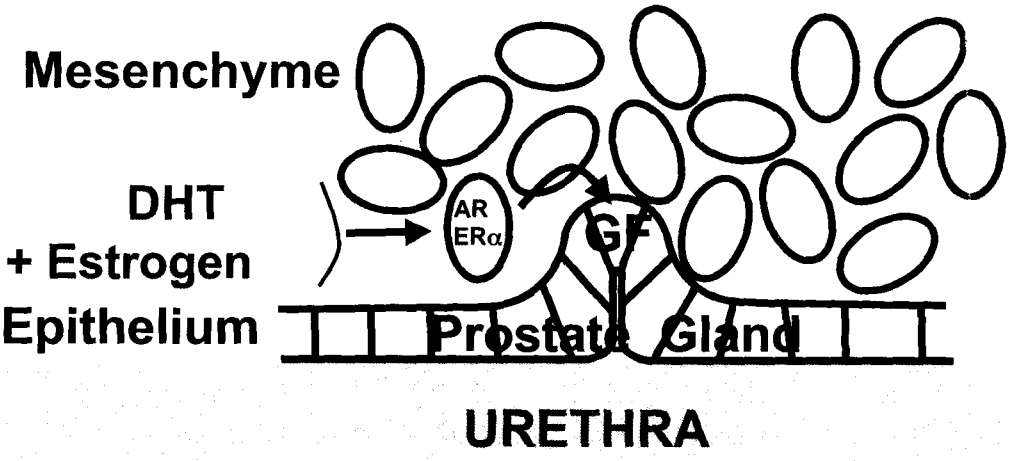
BISPHENOL A STIMULATES THE FETAL CD-1 MOUSE PROSTATE IN PRIMARY CULTURE

CONTROL | TESTOSTERONE | TESTOSTERONE + BISPHENOL A 50 pg/ml (50 ppt)

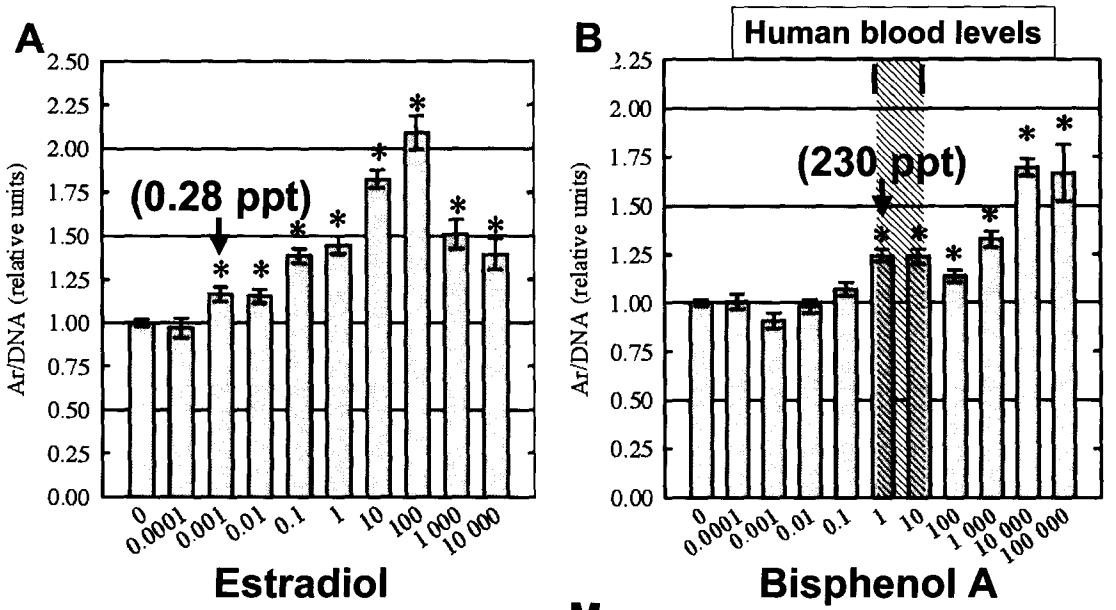
C. Gupta, 2000
PSEBM

NOEC = 5 ppt BPA

STUDIES IN PRIMARY CULTURE
MESENCHYME DIRECTS GROWTH AND DIFFERENTIATION OF PROSTATE GLAND UROGENITAL SINUS (UGS) EPITHELIUM

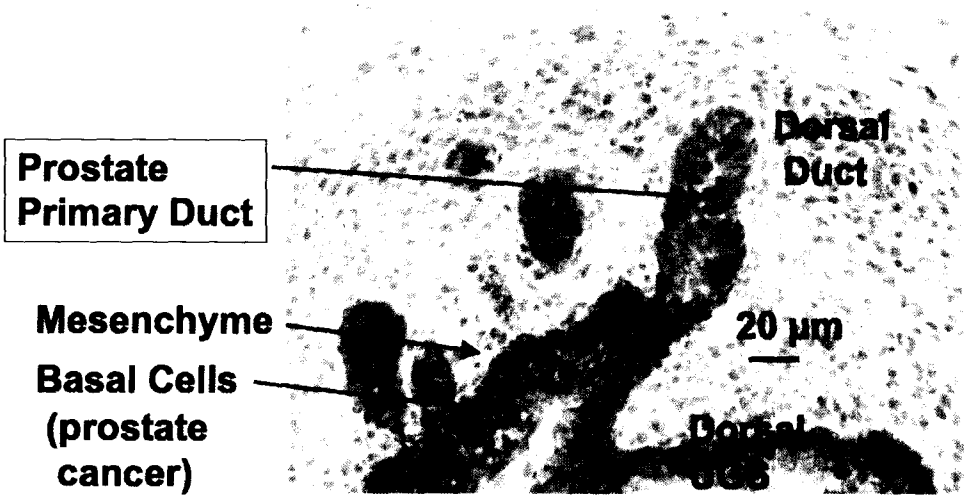


INDUCTION OF ANDROGEN RECEPTOR (Ar) mRNA BY ESTRADIOL AND BISPHENOL A IN CD-1 FETAL MOUSE PROSTATE MESENCHYME CELLS IN PRIMARY CULTURE



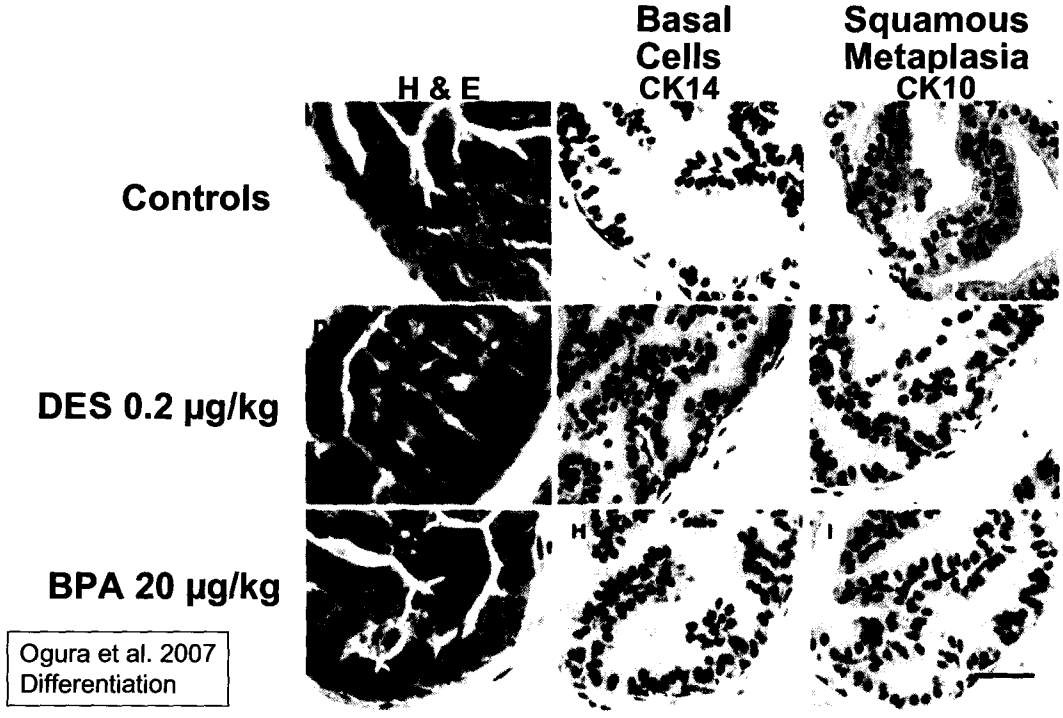
Richter, et al. 2007
Environ. Health Perspect.

BASAL CELL MK5 LABELING ASSOCIATED WITH TWO-FOLD INCREASE IN PCNA LABELING INDICATING A DOUBLING OF PROLIFERATION CAUSED BY BPA, DES OR ETHINYLESTRADIOL



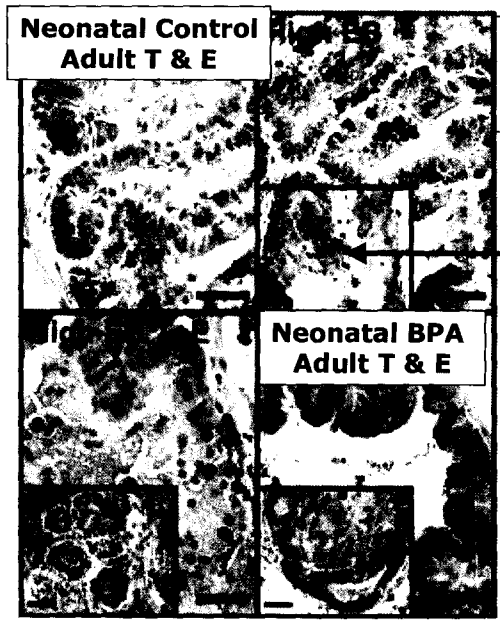
Timms et al. 2005
Proc. Nat. Acad. Sci.

CONVENTIONAL H & E STAINING OF PROSTATE SECTIONS DOES NOT SHOW PRENATAL EFFECTS OF OF DES AND BPA REVEALED BY OTHER MORE SOPHISTICATED TECHNIQUES



Ogura et al. 2007 Differentiation

Neonatal Exposure to 10 µg/kg/day BPA Causes Prostatic Intraepithelial Neoplasia (PIN; Early Stage Cancer) in Adult Rats

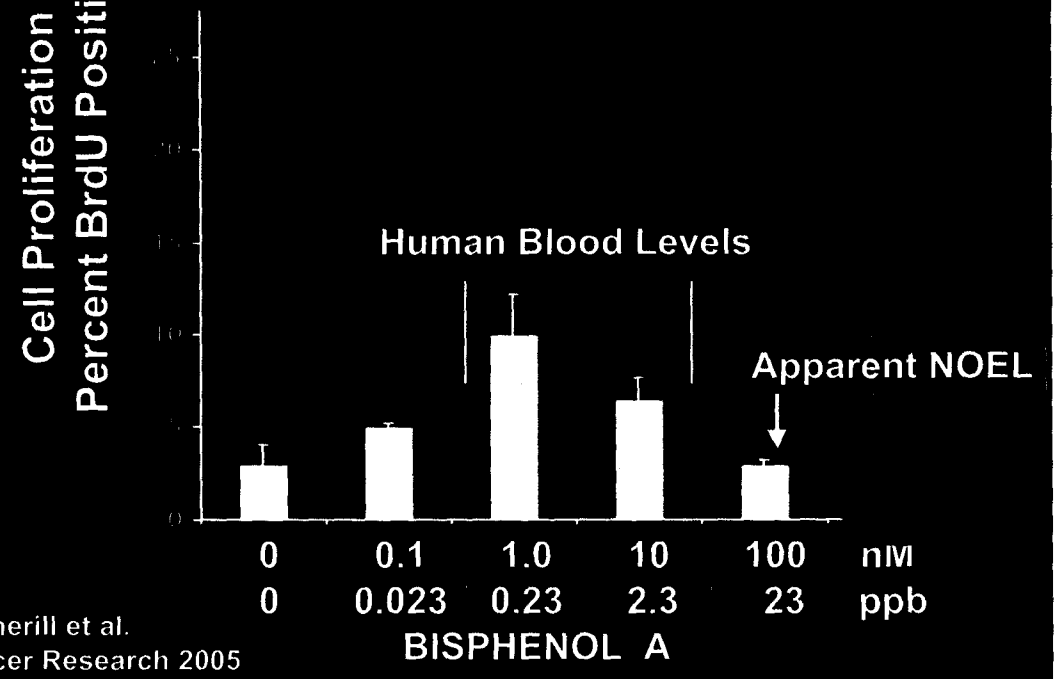


Proliferation identified by immunostaining with Ki 67

PIN Lesion

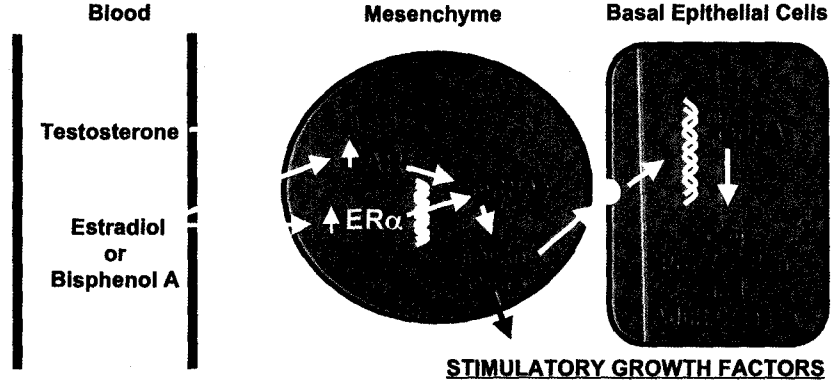
Ho et al. 2006 Cancer Res.

BISPHENOL A STIMULATES PROLIFERATION OF HUMAN PROSTATE CANCER CELLS (LNCaP)



Wetherill et al.
Cancer Research 2005
Mol. Cancer. Therapeut. 2002, 2006

ESTROGENS ALTER PROSTATE DEVELOPMENT LEADING TO PRE-CANCEROUS PROSTATE INTEREPITHELIAL NEOPLASIA ASSOCIATED WITH DIFFERENT METHYLATION OF GENES



INCREASE IN GENE ACTIVITY

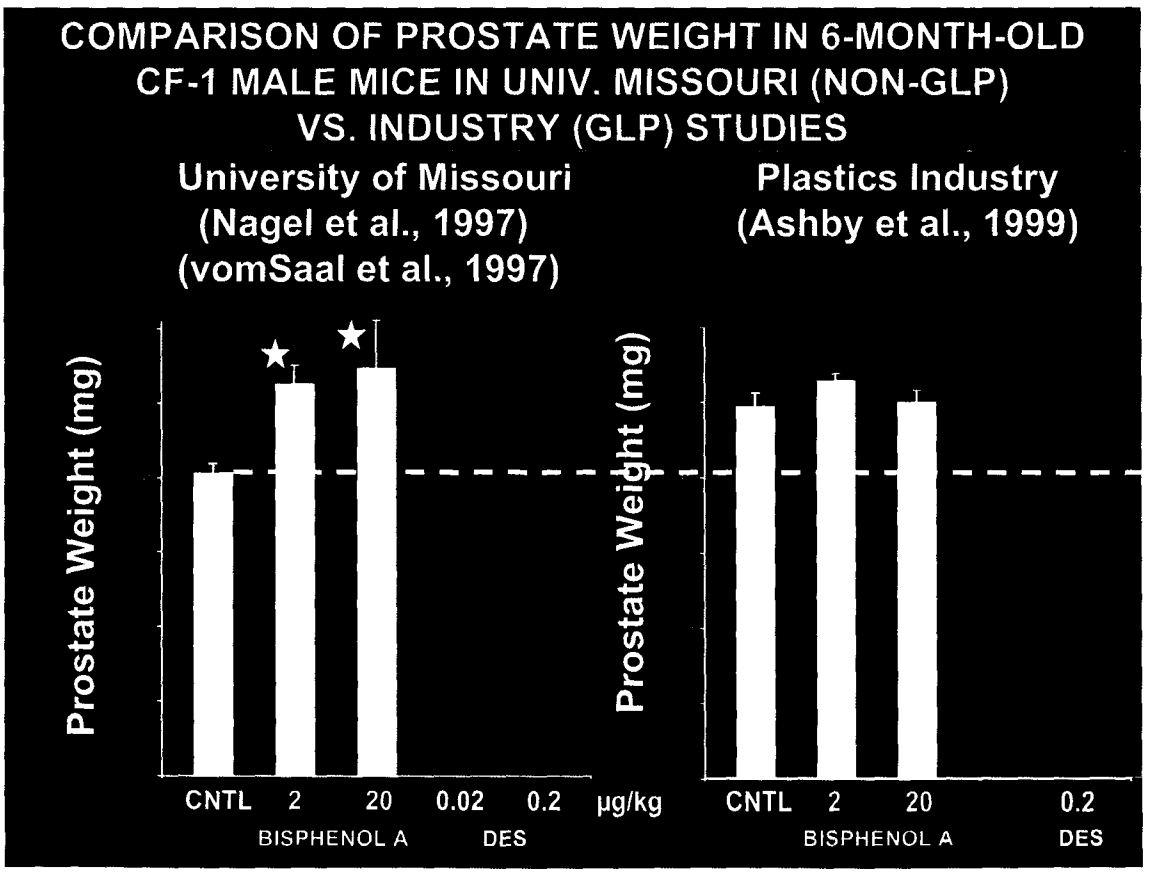
STIMULATORY GROWTH FACTORS
Fibroblast growth factor - 7 (FGF-7)
Fibroblast growth factor - 10 (FGF-10)
Insulin-like growth factor - 1 (IGF-1)

DECREASE IN GENE ACTIVITY

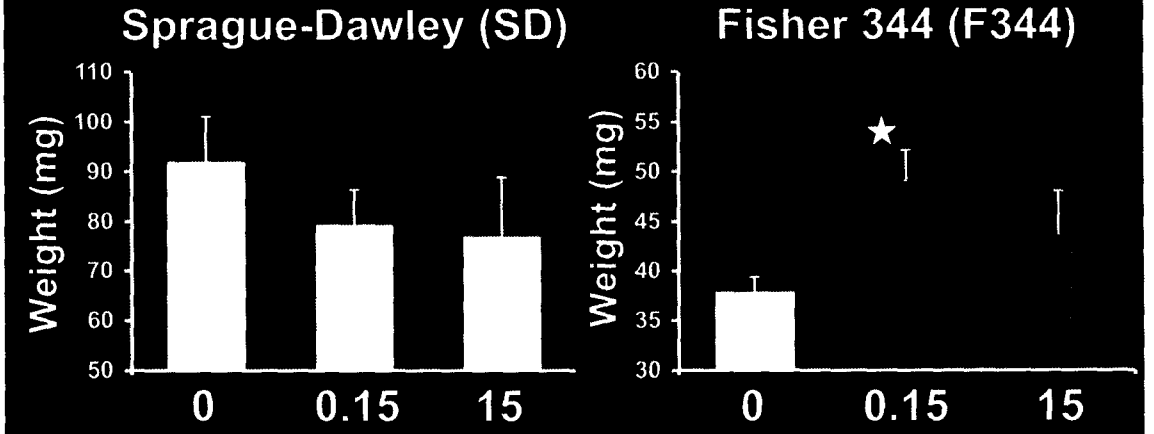
INHIBITORY GROWTH FACTORS
Bone morphogenic protein - 4 (BMP-4)
Transforming growth factor-ß (TGFß)

NON REPLICATION OF PROSTATE FINDINGS IN GLP STUDIES FUNDED BY THE CHEMICAL INDUSTRY

COMPARISON OF PROSTATE WEIGHT IN 6-MONTH-OLD CF-1 MALE MICE IN UNIV. MISSOURI (NON-GLP) VS. INDUSTRY (GLP) STUDIES



STRAIN DIFFERENCES IN THE EFFECTS OF NEONATAL ESTRADIOL BENZOATE ON DORSAL PROSTATE WEIGHT IN ADULT SD AND F344 RATS



Putz et al. 2001
Biol. Reprod.

IN VIVO BISPHENOL A STUDIES THAT USED THE CHARLES RIVER SPRAGUE-DAWLEY (CD-SD) OR THE LONG EVANS (LE) RAT

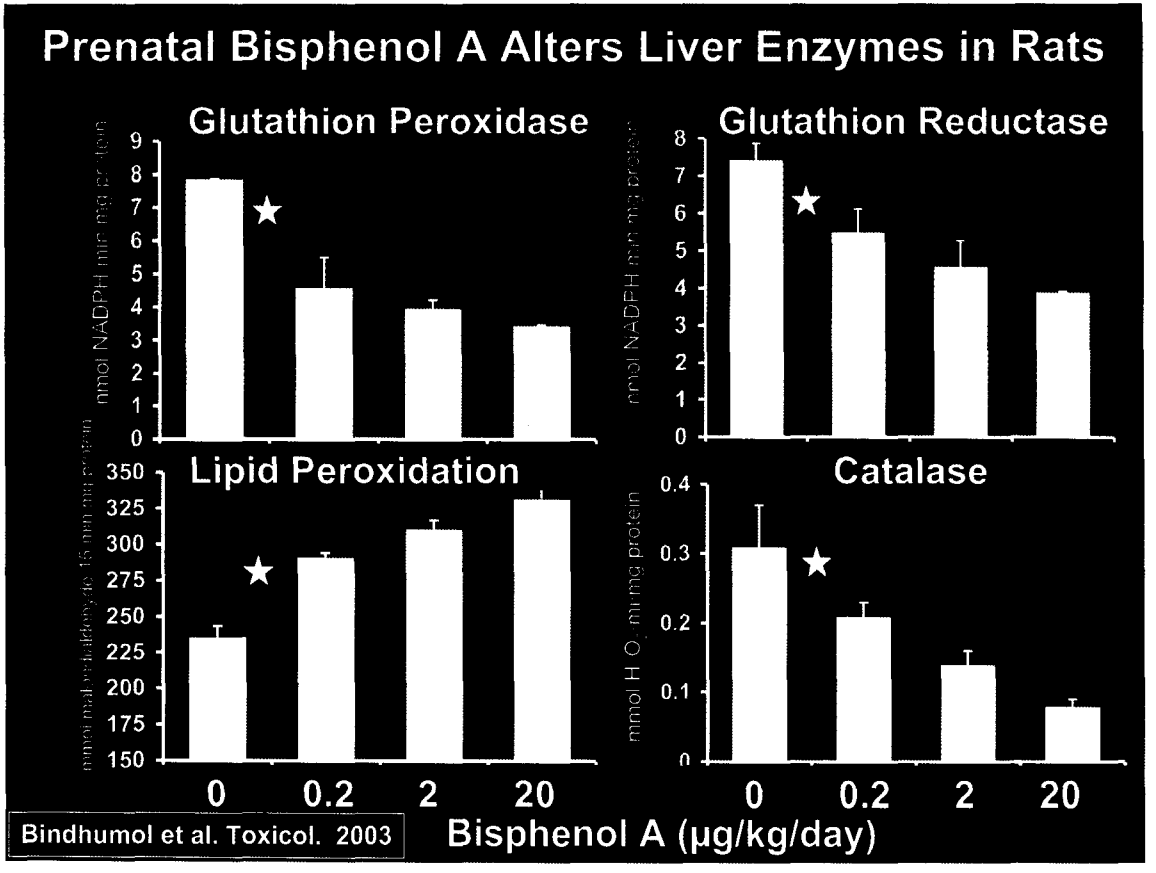
REPORTED STUDY OUTCOME

HARM	NO HARM	TOTAL
2 (12%)	15 (88%)	17

These rats do not respond to doses of the estrogenic drug ethinylestradiol (EE) in birth control pills (0.3 µg/kg/day) They require 5 - 50 µg/kg/day EE to show any gross effects.

vom Saal and Hughes, 2005
Environ. Health Perspect.

– Type 2 diabetes
– Cardiovascular disease



Mechanism: We consider the following <u>likely</u> but requiring confirmation

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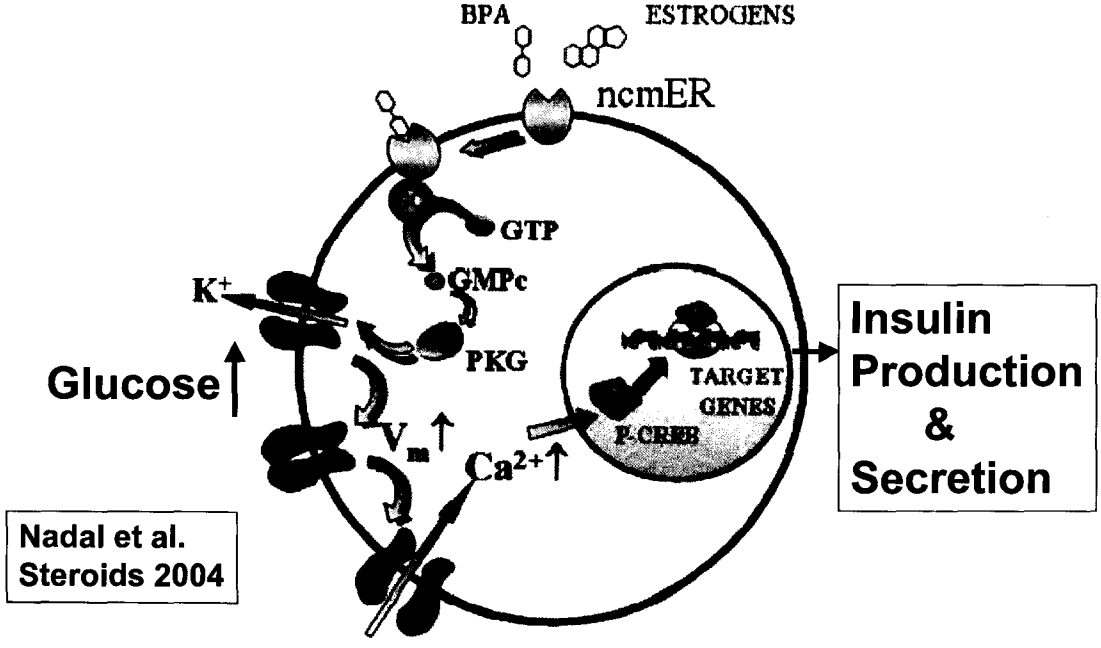
Estrogen Receptor (ER) action

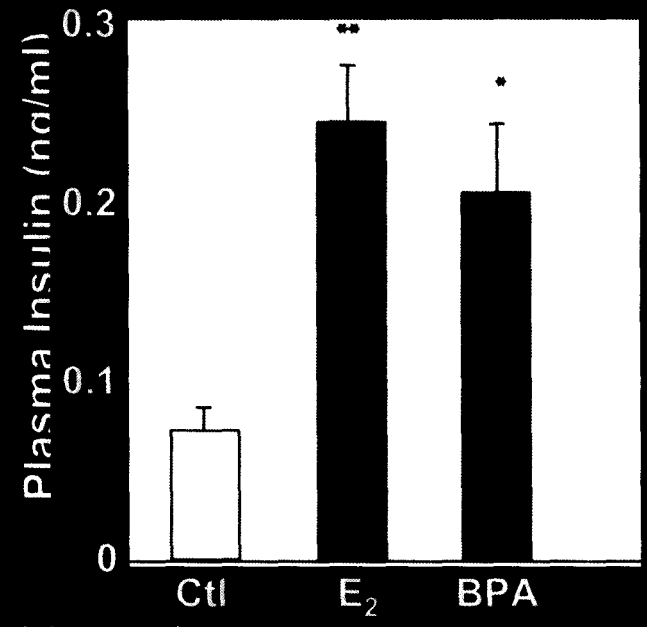
- <u>Receptor sub-type is important for biological outcome</u>
  - **Very low dose effects of BPA are likely mediated by rapid signaling systems activated by ERs**

BPA Expert Panel Consensus Statement
NIEHS/EPOA, November 2006

Bisphenol A Activates cAMP Responsive Element Binding Protein (CREB) in Mouse Pancreatic ß Cells Resulting in Insulin Secretion

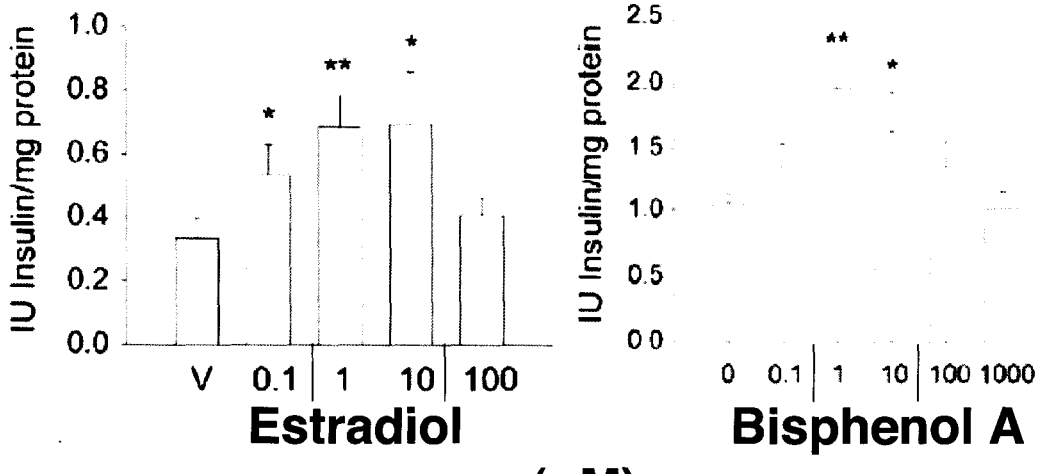


BISPHENOL A STIMULATES INSULIN SECRETION IN MICE



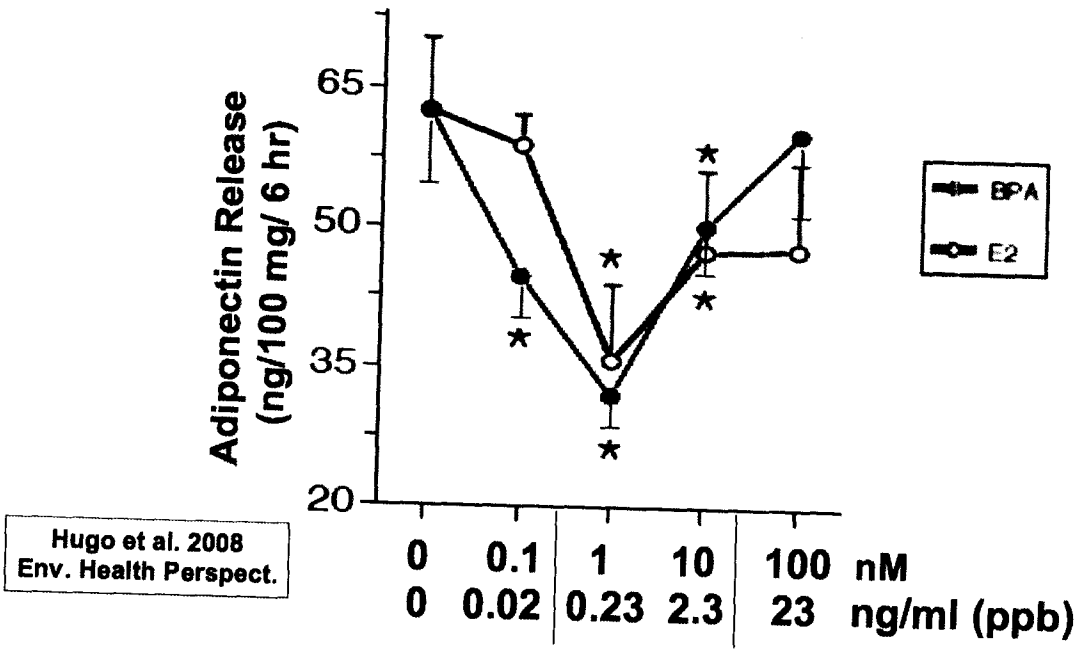
Alonso-Magdalena et al.
Env.Health Pers. 2006

ESTRADIOL AND BISPHENOL A STIMULATE INSULIN RELEASE FROM MOUSE PANCREATIC ß CELLS AT LOW DOSES



Alonso-Magdalena et al.
PLoS ONE, 2008

BISPHENOL A AND ESTRADIOL INHIBIT ADIPONECTIN RELEASE FROM HUMAN ABDOMINAL SUBCUTANEOUS FAT CELLS AT LOW BUT NOT HIGH DOSES



Hugo et al. 2008
Env. Health Perspect.

ESTROGENIC POTENCY OF BISPHENOL A

Production: about 7-billion pounds per year

ESTRADIOL AND BISPHENOL A ALTER:

- Human Fat Cells
- Human Prostate & Breast Cancer Cells
- Rat Brain cells
- Rat Pituitary Cells
- Mouse Pancreatic Cells
- Mouse Prostate Cells

Human Exposure

0.01	0.1	1	10	100	1	10	100	1	10	100	1	10	100	1.0
		(pg/ml)			(ng/ml)			(μg/ml)			(mg/ml)			
Parts Per trillion					billion			million			thousand			

Welshons et al. Endocrinology 147:S56, 2006

CONCERNS

- There is consensus that fetuses and infants are at greatest risk for harm due to exposure to very low doses of BPA.
- The sharp increase in metabolic diseases in children and adolescents has paralled the increase in the use of BPA in products targeted at infants and children.

DEVELOPMENTALEFFECTS IN MICE & RATS	HUMAN HEALTH TRENDS
Abnormal urethra ``` ``	Hypospadias
Prostate hyperplasia & cancer	Prostate cancer increase
Sperm count decrease	Sperm count decrease
Mammary hyperplasia & cancer	Breast cancer increase
Ovarian cysts / Uterine fibroids	PCOS / Uterine fibroids
Abnormal oocyte chromosomes	Miscarriage
Early puberty in females	Early sexual maturation
Hyperactivity / Impaired learning	ADHD
Body weight increase	Obesity increase

FDA CRITERION FOR DETERMINING THE SAFETY OF FOOD CONTACT MATERIALS

- "Safe means that there is reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use".
- The world's leading experts predicted in the Chapel Hill Consensus statement with a high level of confidence that at current levels of exposure, BPA posed a threat to human health.

CONCLUSIONS

- Good Laboratory Practices (GLP) has been misinterpreted by FDA as "good science" instead of good record keeping.
- The FDA has ignored hundreds of studies warning of the hazards of BPA.

UNIVERSITY OF MISSOURI ENDOCRINE DISRUPTORS WEB SITE

A document containing references and abstracts for studies on bisphenol A is updated periodically.

http://endocrinedisruptors.missouri.edu/vomsaal/vomsaal.html